Pregnancy outcome in women with polycystic ovary syndrome: a retrospective study on the influence of clomiphene stimulation versus laparoscopic ovarian drilling after clomiphene resistance

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ABSTRACT

Purpose: We aimed to retrospectively evaluate adverse outcomes of singleton pregnancies in women with polycystic ovary syndrome (PCOS) after clomiphene (CC) stimulation versus laparoscopic ovarian drilling (LOD) after CC resistance.

Methods: This retrospective study included 67 PCOS women who had conceived naturally within 12 months after LOD and 67 matched pregnant women who had conceived after CC stimulation. In addition, 134 matched non-PCOS controls who had conceived naturally were included.

Results: The controls had higher rates of pregnancy complications than the PCOS cases. Neither CC responsiveness nor CC resistance was associated with any higher risk of pregnancy complications such as gestational diabetes mellitus (46.3% vs. 38.3%, p=0.485), pregnancy-induced hypertension (23.9% vs. 28.4%, p=0.694), preeclampsia/HELLP syndrome (10.4% vs. 16.4%, p=0.448), or preterm delivery (20.9% vs. 14.9%, p=0.500).

Conclusion: Singleton pregnancies in PCOS women do not carry higher risks after LOD for CC resistance compared with pregnancies after successful CC stimulation.

KEYWORDS

Pregnancy complications, polycystic ovary syndrome, ovarian drilling, clomiphene citrate.

Introduction

As demonstrated in a recent meta-analysis performed by Yu et al. [1], women with polycystic ovary syndrome (PCOS) are more likely to develop pregnancy complications, including gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preeclampsia, and preterm delivery. However, evidence on the impact of different artificial reproductive techniques that lead to pregnancies in women with PCOS is scarce, according to Bahri Khomami et al. [2]. Ott et al. [3] demonstrated that in metformin-treated PCOS women, clomiphene citrate (CC) stimulation might increase the overall risk of pregnancy complications compared with laparoscopic ovarian drilling (LOD). However, this analysis was limited by the small sample size and poor matching. From a clinical perspective, it would be interesting to know the risks associated with specific PCOS treatment modalities. Moreover, according to Ellakwa et al. [4], CC-responding and CC-resistant women reveal different characteristics that could also explain differences in their pregnancy-associated risk profiles. In view of these considerations, we aimed to retrospectively evaluate pregnancy complications in singleton pregnancies of PCOS women, also comparing those who conceived after CC stimulation with those who conceived after LOD for CC resistance.

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Materials and methods

This study included 67 PCOS women who had conceived naturally within 12 months after undergoing LOD for CC resistance and delivered at ≥23+0 weeks at the Medical University of Vienna (January 2010 - December 2016). These women were matched 1:1 for age (±0.5 years), body mass index (BMI; ±1.0 kg/m^2), metformin use before pregnancy, and parity with 67 PCOS women who had conceived after CC stimulation. Thus, 134 PCOS women were included. These were matched for age (±0.5 years), BMI (±1.0 kg/m^2), and parity with 134 non-PCOS controls who had conceived naturally. The revised Rotterdam criteria were applied for PCOS definition; all the women in the study sample showed polycystic ovaries on ultrasound [5].

CC was the first-line tool for ovulation induction, while LOD was recommended in cases of CC resistance, i.e., after three to six CC cycles that had failed to induce ovulation. Bilateral standard electrocoagulation LOD was performed with five to eight incisions in accordance with previous reports [3].

Data on risk were acquired using the PIA Fetal Database (GE-Viewpoint, Wessling, Germany) and SAP-based AKIM software. Using common definitions as Ott et al. [3] did, we focused on: the development of GDM, diagnosed using the 75g, 2h oral glucose tolerance test (OGTT), routinely performed in the third trimester. Patients were diagnosed with GDM if one of the following parameters reached or exceeded the 97.5th percentile: fasting venous blood glucose concentration (4.5mmol/l), at 1h (9.1mmol/l) and 2h (7.9mmol/l).

The indications for performing the OGTT in the second trimester were as follows: glucose in any of the monthly urine samples; GDM in a previous pregnancy; diabetes in the immediate family; and fetal macrosomy (>2 standard deviations); insulin-dependent GDM (IGDM); PIH, defined as gestational hypertension (blood pressure >140/90 mmHg without proteinuria at a gestational age >20 weeks on two or more occasions at least 6 h apart); preeclampsia, defined as blood pressure >140/90 mmHg in combination with proteinuria >0.3 g/24 h after 20 weeks' gestation; the HELLP syndrome, defined as hemolysis, elevated liver enzymes (serum lactate dehydrogenase, LDH ≥ 600 IU/L or total bilirubin ≥ 1.2 mg/dL), and low platelet count (≤ 100.000 cells/μL); premature delivery, defined as delivery between the 22nd and 37th week of gestation.

In addition, we evaluated general patient-, PCOS-, and pregnancy-related characteristics, including basal testosterone, anti-Mullerian hormone (AMH), luteinizing- (LH), and follicle-stimulating hormone (FSH) levels on days 2-5 of the first CC cycle. Insulin resistance was defined as a homeostasis model assessment, HOMA index (= fasting insulin x fasting glucose / 22.5x18) ≥2.5.

Variables are reported as numbers (frequencies) or mean values ± standard deviation. Differences between groups were tested using the Welch test and Fisher's exact test. A binary logistic regression model was performed to test the impact of patient characteristics on the development of IGDM. For this analysis, odds ratios (OR) with 95% confidence intervals (95%CI) and p-values of the likelihood ratio tests are provided. Statistical analysis was performed using SPSS 24.0 (SPSS Inc., 1989–2017). P-values< 0.05 were considered significant. The study was approved by the Institutional Review Board (number: 2203/2016).

Results

The controls and PCOS patients did not differ in terms of age (31.6 ± 4.8 versus 31.6 ± 4.8 years, respectively; p= 0.922), BMI (26.8 ± 4.9 versus 26.8 ± 4.9 kg/m^2, respectively; p=0.947), or parity (0.1 ± 0.3 versus 0.1 ± 0.3, respectively; p=1.000). With regard to pregnancy complications, the PCOS women revealed higher rates of GDM (57/134, 42.5% versus 12/134, 8.9%, respectively; p< 0.001), IGDM (38/134, 28.4% versus 8/134, 6.0%, respectively; p< 0.001), PIH (35/134, 26.1% versus 15/134, 11.2%, respectively; p=0.003), preeclampsia/HELLP syndrome (18/134, 13.4% versus 5/134, 3.7%, respectively; p=0.008), and preterm delivery (24/134, 17.9% versus 5/134, 3.7%, respectively; p> 0.001). No differences between PCOS patients and controls were found for preterm premature rupture of the membranes (5/134, 3.7% versus 2/134, 1.5%, respectively; p=0.447), cervical insufficiency/preterm labor (13/134, 9.7% versus 9/134, 6.7%, respectively; p=0.505), or intrauterine growth retardation (6/134, 4.5% versus 9/134, 6.7%, respectively; p=0.597). While birth weight was the same in both groups (PCOS patients: 3139.0 ± 906.4 g versus controls: 3242.0 ± 613.2 g, p=0.278), gestational age at delivery was higher in the controls (PCOS patients: 37.5 ± 4.3 weeks versus controls: 38.5 ± 2.6 weeks, p=0.029).

Table I shows the basic characteristics of the PCOS patients divided by final PCOS treatment. CC-resistant women who underwent LOD revealed higher baseline LH and AMH levels, LH:FSH ratios, and amenorrhea rates.

In a subsequent step, a multivariate binary logistic regression model for the prediction of IGDM was calculated. A higher age (OR: 1.226, 95%CI: 1.206,1.464; p=0.025) and a higher presence of insulin resistance as indicated by the HOMA index during diagnostic evaluation of PCOS (OR: 29.542, 95%CI: 5.727,152.393; p<0.001) were associated with development of IGDM during pregnancy, while primary versus secondary sterility (OR: 1.601, 95%CI: 0.323,7.937, p=0.564), LOD for CC resistance (OR: 3.182, 95%CI: 0.579,17.490, p=0.183), BMI (OR: 1.159, 95%CI: 0.974,1.379, p=0.096), parity (OR: 1.158; 95%CI: 0.079,16.881, p=0.915), LH:FSH ratio (OR: 1.068, 95%CI: 0.614,1.857; p=0.815), total testosterone (OR: 1.296, 95%CI: 0.074,22.569; p=0.859), and AMH (OR: 0.915, 95%CI: 0.797,1.1050; p=0.206) were not.

Discussion

In our retrospective dataset, PCOS women revealed higher rates of GDM, IGDM, PIH, preeclampsia/HELLP syndrome, and preterm delivery. These data are in line with previous reports summarized in a recent meta-analysis [1]. However, the main focus of our study was differences in rates of complications in singleton pregnancies after successful CC stimulation versus LOD for CC resistance.

On comparing these two PCOS groups, it became evident that the CC-resistant women had higher baseline LH and AMH levels, LH:FSH ratio and amenorrhea rates than the CC responders. This is in line with previous publications, like that of Ellakwa et al. [4]. It can be assumed that these findings reflect the more severe clinical state of CC-resistant PCOS patients. However, as regards pregnancy outcome, in our dataset of age-, BMI-, and parity-matched PCOS women, neither CC responsiveness nor CC resistance was associated with higher risk of any pregnancy complication (Table I).

Thus, it seems reasonable to assume that pregnancy risks in the PCOS population are affected by basic patient characteristics, such as obesity, age, and insulin resistance, as stated by Bahri Khomami et al. [2], rather than by CC stimulation or LOD. We were able to prove this in relation to the risk of developing

Table 1 Patient characteristics and pregnancy complications in women who achieved singleton pregnancy after CC stimulation or after LOD.

	SUCCESSFUL CC STIMULATION (N=67)	LOD (N=67)	P
Patient characteristics			
Age (years)*	31.6±4.8	31.6±4.8	0.974
Pre-pregnancy BMI (kg/m^2)*	27.0±5.0	26.6±4.8	0.679
Parity*	0.1±0.3	0.1±0.3	1.000
Secondary sterility#	29 (43.3)	21 (31.3)	0.211
Amenorrhea#	15 (22.4)	27 (40.3)	0.040
Number of CC cycles*	2.3±0.9	3.4±0.7	<0.001
LH (IU/l)*	8.8±4.7	14.3±9.4	<0.001
Maximum CC dose 50mg	55 (82.1)	0	
100mg	10 (14.9)	42 (62.7)	<0.001
150mg	2 (3.0)	25 (37.3)	
LH/FSH ratio*	1.6±1.1	2.6±1.5	<0.001
Testosterone (ng/ml)*	0.44±0.18	0.47±027	0.565
AMH (ng/ml)*	7.1±5.3	9.7±6.0	0.010
Insulin resistance#	16 (23.9)	18 (26.9)	0.843
Metformin treatment#	18 (26.9)	17 (25.4)	1.000
Pregnancy complications			
GDM#	31 (46.3)	26 (38.3)	0.485
Insulin-dependent GDM#	20 (29.9)	18 (26.9)	0.848
PIH#	16 (23.9)	19 (28.4)	0.694
Preeclampsia/HELLP#	7 (10.4)	11 (16.4)	0.448
Preterm premature rupture of membranes#	2 (3.0)	3 (4.5)	1.000
Cervical insufficiency/preterm labor#	8 (11.9)	5 (7.5)	0.561
Intrauterine growth retardation#	3 (4.5)	3 (4.5)	1.000
Preterm delivery#	14 (20.9)	10 (14.9)	0.500
Birth weight (g)*	3136.8±1038.7	3141.3±759.4	0.977
Gestational age at delivery (completed weeks)*	37.2±4.7	37.9±3.8	0.355

*Data are provided as *mean values ± standard deviation or # numbers (frequencies). Differences between groups were calculated using the Welch-test and the Fisher's exact test.*

IGDM. In our multivariate analysis, a higher patient age and an abnormal pre-pregnancy HOMA index significantly increased this risk, whereas the type of fertility treatment that led to pregnancy did not. Notably, about one fourth of the patients in our study were insulin resistant; the patients' mean BMI was about 27 kg/m^2, and thus within the range indicating overweight. The first of these findings seemed to have particular relevance for the observed rates of GDM and IGDM (42.5% and 28.4%, respectively), although more women developed GDM than had been considered insulin resistant based on the HOMA index before pregnancy.

However, in a previous study these surrogate indices were found to be of limited accuracy in identifying insulin resistance. In other words, they could only "rule in" but could not "rule out" insulin resistance as evaluated by the clamp test, which was considered the gold standard [6].

Interestingly, it has also previously been pointed out that not PCOS itself, but associated factors including higher age and BMI put the patient at risk of developing of GDM [7]. A study in more than 1800 pregnant women revealed that by using a modified two-step screening strategy which included clinical risk factors, the number of oral glucose tests needed would be decreased substantially [8].

We acknowledge that the retrospective design and the fact that all the women undergoing LOD had been pre-treated with several CC stimulations constitute limitations of the present study, although the latter aspect seems of minor relevance, given that a mean of 57.7 ± 27.2 days elapsed between the last CC application and LOD.

In conclusion, in PCOS women, neither CC stimulation nor LOD for CC resistance carries higher risks for pregnancy-associated complications, at least in singleton pregnancies. Thus, treatment-depending pregnancy risks should not influence physicians when choosing the type of infertility treatment. Moreover, obstetricians need not fear increased risks for their patients in the event of LOD/CC resistance

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