Birth weight in offspring of mothers with polycystic ovarian syndrome

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BACKGROUND: A relationship between reduced fetal growth and the polycystic ovary syndrome (PCOS) has been proposed in girls with PCOS. However, the birth weight in the offspring of PCOS mothers has not been systematically investigated. The aim of this study was to establish the birth weight of newborns of mothers with PCOS and to compare it with a control group of newborns of normal women matched by age and weight at the beginning of pregnancy. METHODS: The birth weight of 47 infants born from singleton pregnancies in women with well-documented PCOS was compared with 180 infants born from singleton pregnancies in healthy controls. RESULTS: The prevalence of small for gestational age (SGA) infants was significantly higher in the PCOS group compared to the control group (12.8% versus 2.8%, respectively, $P < 0.02$). Moreover, SGA infants born to PCOS mothers were smaller than those born to control mothers ($P < 0.05$). The prevalence of large for gestational age infants (LGA) was similar in both groups, but birth length of LGA newborns was greater in PCOS women than controls ($P < 0.05$). CONCLUSIONS: PCOS mothers showed a significantly higher prevalence of SGA newborns which cannot be completely attributed to pregnancy complications, and seems to be more related to the PCOS condition of the mother.

Key words: birth weight/macrosomia/metformin/polycystic ovary syndrome/small for gestational age

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age, characterized by irregular menses, chronic anovulation, infertility and hyperandrogenism (Adams *et al.*, 1986; Hull, 1987; Zawadzki and Dunaif, 1992; Ehrmann *et al.*, 1995; Franks, 1995; Knochenhauer *et al.*, 1998). Obesity is a common feature of PCOS; however, the disease may also occur in lean women. In addition, women with PCOS may also exhibit peripheral insulin resistance and reduced β-cell function, with increased risk of developing glucose intolerance or frank diabetes (Holte 1996; Dunaif 1987, 1989, 1997). Thus, women with PCOS may be at high risk for pregnancy complications such as gestational diabetes and hypertension (Urman *et al.*, 1997). A relationship between reduced fetal size and the PCOS condition has been proposed in girls (Ibáñez *et al.*, 1998). According to the data obtained retrospectively in reproductive-age PCOS women, we have recently established that the prevalence of low birth weight ($< 2.500\,\mathrm{kg}$) in these women was significantly higher (18.4%) compared to normally cycling women (7.5%) (Benitez *et al.*, 2001). However, the birth weight in newborns of PCOS mothers has not been systematically investigated.

The aim of the present study was to establish the birth weight in newborns of PCOS mothers compared with a control group of newborns of normal women matched by age and weight at the beginning of pregnancy.

Material and methods

Subjects

Forty-seven pregnant women with PCOS with singleton pregnancies were sequentially recruited for the study from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile, who had desired fertility and were placed on a 6 month diet and exercise treatment program as previously described (Sir-Petermann *et al.*, 2001). Diagnosis of PCOS was made according to the diagnostic criteria for PCOS of the NIH consensus (Zawadzki and Dunaif, 1992) and the Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group (2004). Preconceptional inclusion criteria were: chronic oligomenorrhoea or amenorrhoea, hirsutism, serum testosterone concentration $> 0.6\,\mathrm{ng/ml}$ and/or free androgen index (FAI) > 5.0, androstenedione concentration $> 3.0\,\mathrm{ng/ml}$ and a characteristic ovarian morphology on ultrasound

based on the criteria described by Adams *et al.* (1986). Normogly-caemic patients with and without clinical signs of hyperinsulinaemia (waist–:hip ratio >0.85), and with different grades of hyperinsuli-naemia evaluated by an oral glucose tolerance test, were included.

All women had been anovulatory as indicated by progesterone measurements and ultrasound examinations. Hyperprolactinaemia, androgen-secreting neoplasm, Cushing's syndrome and attenuated 21-hydroxylase deficiency, as well as thyroid disease, were excluded by appropriate tests.

We selected 180 normal pregnant women of similar age, socio-economic level and BMI with singleton pregnancies as a control group. The control women had a history of regular 28- to 32- day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and were not receiving any drug therapy. These women were recruited from the prenatal care unit of our hospital from the 12th week of gestation during the same time period.

Only non-smoking and non-alcohol or drug abusing PCOS and control pregnant women were included in the study. All subjects had given their written consent to their participation in the study, which was approved by the local ethics committee.

Study protocol

Both groups of pregnant women were followed in the same prenatal care unit. Duration of gestation, initial BMI, BMI in the third trimester, weight gain during pregnancy and blood pressure were recorded.

During gestational week 22–28 the women were admitted to the Clinical Research Center in the morning (08:30–09:00) after an overnight fast of between 8 and 12 h and a 2 h, 75 g oral glucose tolerance test was performed in accordance with published criteria (World Health Organization, 1999). Pregnancy-induced hyperten-sion was defined as gestational hypertension (blood pressure ≥140/90 mm Hg without proteinuria at a gestational age >20 weeks on two or more occasions) or pre-eclampsia (blood pressure ≥140/90 mm Hg with proteinuria >0.3 g/24 h after 20 weeks ges-tation).

Immediately after delivery, a physical examination of the new-born was performed. Anthropometric measurements at birth were recorded, including weight, length and head circumference. Weight and length were transformed into standard deviation score (SDS) using local normative data for newborns (Juez *et al.*, 1989; Soto *et al.*, 2003), adjusting for differences in gestational age and gender. SDS were calculated using the formula SDS = (x − mean)/SD. Infants were defined as small for gestational age (SGA) infants (birth weight <5th percentile), appropriate for gestational age (AGA) infants (birth weight >5th and <90th percentile) and large for gestational age (LGA) infants (birth weight >90th percentile) (de Rooy and Hawdon, 2002; Das and Sysyn, 2004). Infants show-ing evidence of malformations or genetic disorders were excluded from the study.

Statistical evaluation

Data are expressed as means and SD when normally distributed, and as medians and interquartile ranges when not normally distributed. Prevalence of SGA or LGA in PCOS and control groups was assessed by chi-square (χ^2). Differences in the pregnancy character-istics of control and PCOS mothers and in the respective newborns were assessed by Student's *t*-test and differences between SGA and LGA infants born to PCOS and control mothers were assessed by the Mann–Whitney test. The potential confounding effects of con-tinuous variables related to birth weight such as maternal height, were assessed by analysis of co-variance (ANCOVA). Logistic regression techniques were used to assess the association between

the PCOS status and SGA and for adjusting by the possible con-founding effects of covariates such as maternal height, parity and gestational diabetes. Statistical analysis was performed using the statistical package for Social Science Software (SPSS 10.0). A *P* value of less than 0.05 was considered to be statistically significant.

Results

Table I shows the clinical characteristics of the two groups of pregnant women. By design, age and initial BMI were not different between both groups. Maternal height was compar-able in both groups (Control: 1.57 ± 0.1 m versus PCOS: 1.60 ± 0.1 m; $P = 0.07$). There were significant differences in weight gain during pregnancy and BMI during the third trimester of pregnancy between women with PCOS and nor-mal women ($P < 0.01$). Systolic and diastolic blood press-ures were also significantly higher in PCOS women, and two pregnant women with PCOS (4.25%) were diagnosed with pre-eclampsia. In addition, the incidence of gestational dia-betes according to the World Health Organization criteria was significantly higher ($P = 0.02$) in the PCOS group (12.2%) compared to the control group [0.5% (data not shown)]. On the other hand, 61.2% of the PCOS patients were primiparous and 42.8% of the controls were primi-parous [$P = 0.038$ (data not shown)].

Table II shows the clinical data of the newborn babies of PCOS mothers and of controls. A significantly shorter length of gestation was observed in the PCOS group compared to the control group (38.2 versus 39.2 weeks, $P < 0.05$). How-

Table I. Clinical characteristics of normal pregnant women (control) and pregnant women with polycystic ovarian syndrome (PCOS)

	Control ($n = 180$)	PCOS ($n = 47$)
Age (years)	26.2 ± 5.2	24.6 ± 5.9
Height (m)	1.57 ± 0.1	1.60 ± 0.1
Initial body mass index (kg/m^2)	26.3 ± 3.5	27.5 ± 4.2
Body mass index in third trimester (kg/m^2)	30.9 ± 3.9	$34.0 \pm 4.8*$
Weight gain during pregnancy (kg)	11.3 ± 4.6	$16.8 \pm 9.8*$
Systolic blood pressure in third trimester (mm Hg)	117.7 ± 8.0	$127.7 \pm 17.2*$
Diastolic blood pressure in third trimester (mm Hg)	73.5 ± 7.3	$80.3 \pm 11.0*$

Values are means ± SD.
*$P < 0.01$ between normal pregnant and PCOS pregnant women.

Table II. Clinical characteristics of newborns of normal pregnant and pregnant PCOS women

	Control ($n = 180$)	PCOS ($n = 47$)
Gestational age (weeks)	39.2 ± 0.8	$38.2 \pm 3.0*$
Birth weight (g)	3469.4 ± 414.6	3303.5 ± 775.6
Birth weight SDS	0.1 ± 1.0	0.2 ± 1.7
Length (cm)	50.1 ± 1.9	49.9 ± 3.9
Birth length SDS	0.1 ± 1.0	0.4 ± 1.6
Head circumference (cm)	34.9 ± 1.4	34.5 ± 2.3

Values are means ± DS.
SDS: standard deviation score adjusted for gestational age and gender.
*$P < 0.05$ between control and PCOS.

ever, excluding the four preterm infants corresponding to the PCOS group, gestational age was not different between both groups [Control: 39.2 (37.0–40.0) versus PCOS: 39.0 (36.0–42.0) weeks, $P = 0.366$]. Considering that all the women in this study had singleton pregnancies, the shorter gestation in the PCOS group cannot be attributed to the influence of multiple pregnancies. No differences were observed in birth weight and SDS birth weight when maternal height was considered in the ANCOVA analysis.

The proportion of SGA newborns of PCOS mothers was significantly higher than that observed in newborns of control mothers (12.8% versus 2.8%, $P = 0.014$) (Figure 1). Only two SGA babies were born to PCOS mothers with pre-eclampsia who underwent preterm induction of labour. In the PCOS group, SGA infants were not associated with parity, maternal height and gestational diabetes when the logistic regression analysis was used. Moreover, as shown in Table III, birth weights in SGA newborns of PCOS mothers were lower than in those of control mothers ($P < 0.05$). According to the ANCOVA analysis, this difference was near significant ($F = 0.00329$, $P = 0.06$) when maternal height was considered. However, maternal height was comparable between both groups of mothers with SGA infants [Control: 1.59 (1.54–1.60) versus PCOS: 1.57 (1.55–1.62)].

On the other hand, parity was comparable in both groups of mothers with SGA newborns. Only one mother of each group was multiparous (Control: 20.0% and PCOS: 16.6%).

The clinical characteristics of the LGA newborns are given in Table IV. Birth length SDS was greater, but head circumference was smaller in LGA newborns of PCOS mothers compared to those of controls ($P < 0.05$). However, the prevalence of LGA infants was similar in both groups (Control: 11.1% versus PCOS: 17.0%, $P = 0.396$) (Figure 1 LGA/control bar seems higher than 11.1%). Nevertheless, weight gain during pregnancy in PCOS mothers with LGA infants was significantly higher compared to control mothers [(17.64 (12.0–25.0) versus 13.08 (5.60–20.20) kg;
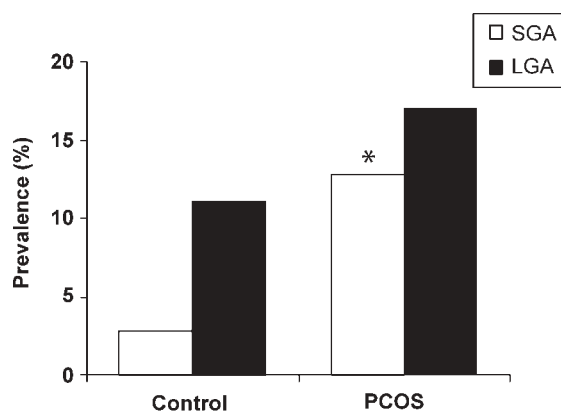
Table III. Clinical characteristics of small for gestational age newborns of normal and PCOS women

	Control ($n = 5$)	PCOS ($n = 6$)
Gestational age (weeks)	40.0 (40.0–40.0)	37.5 (34.8–39.5)
Birth weight (g)	2770 (2760.0–2820.0)	2075.0 (1440–2500.0)*
Birth weight SDS	−1.79 (−1.9 to −1.7)	−2.7 (−3.7 to −2.0)
Length (cm)	48.0 (47.0–48.0)	42.0 (39.0–48.0)
Birth length SDS	−0.8 (−1.0 to −0.6)	−2.4 (−3.8 to −1.4)
Head circumference (cm)	32.0 (32.0–33.0)	34.0 (31.5–34.0)
Ponderal index	2.5 (2.5–2.7)	2.2 (2.1–2.5)

Values are medians and interquartile ranges.
SDS: standard deviation score adjusted for gestational age and gender.
*$P < 0.05$ between control and PCOS.

Table IV. Clinical characteristics of large for gestational age newborns of normal and PCOS women

	Control ($n = 20$)	PCOS ($n = 8$)
Gestational age (weeks)	39.5 (39.0–40.0)	38.5 (38.0–39.3)
Birth weight (g)	4130.0 (3980.0–4412.5)	4075.0 (3787.5–4438.8)
Birth weight SDS	1.8 (1.5–2.2)	2.1 (1.4–2.7)
Length (cm)	52.0 (50.0–53.0)	53.5 (51.8–55.0)
Birth length SDS	1.2 (0.5–1.6)	2.5 (2.1–2.8)*
Head circumference (cm)	37.0 (36.0–37.0)	35.0 (34.0–36.0)*
Ponderal index	3.0 (2.8–3.2)	2.7 (2.5–2.8)

Values are medians and interquartile ranges.
SDS: standard deviation score adjusted for gestational age and gender.
*$P < 0.05$ between control and PCOS.

$P = 0.036$)]. The incidence of gestational diabetes in the mothers was also similar, with one mother in each group.

No significant differences were found in the sex distribution of the newborns between the groups (Control: 53.9% females and 46.1% males; PCOS: 46.8% females and 53.2% males). No pregnant patients in this study developed signs or symptoms of virilization and the female newborns of these patients were not virilized.

Discussion

In the present study, we established that women with PCOS showed a significantly higher prevalence of SGA newborns compared to control mothers. The numbers of AGA and LGA infants, however, were non-significantly different in both groups of women.

Individual variability in growth rates during infancy is dependent on both genetic and environmental factors. Genetically determined insulin resistance results in impaired insulin-mediated growth (Hattersley and Tooke, 1999). For example, fetuses with monogenic disorders affecting insulin secretion or insulin sensitivity exhibit intrauterine growth retardation, which strongly supports the fetal insulin hypothesis (Temple *et al.*, 1995, 1996; Thomas *et al.*, 1995; Hattersley *et al.*, 1998).

In addition, it has been proposed that the endocrine, nutritional and metabolic milieu of the fetus may have a 'programming' effect, which may persist into adult life (Barker,

Figure 1. Prevalence of small for gestational age (SGA) and large for gestational age (LGA) infants born to control mothers and mothers with polycystic ovarian syndrome (PCOS).

*$P < 0.01$ between Control and PCOS by χ^2 test

1994; Holemans *et al.*, 1998; Tchernitchin *et al.*, 1999; Rhind *et al.*, 2001). Intrauterine growth retardation is associated with several adult disorders such as cardiovascular disease, type 2 diabetes, obesity and hypertension (Barker *et al.*, 1993; Hoffman *et al.*, 1997; Bavdekar *et al.*, 1999; Jaquet *et al.*, 2000; Gray *et al.*, 2002; Ong and Dunger, 2002). In addition, low birth weight has been related with reproductive disorders (de Bruin *et al.*, 1998; Rhind *et al.*, 2001; Ibañez *et al.*, 2002a,b, 2003; Davies and Norman, 2002) including PCOS (Ibáñez *et al.*, 1998.

Recently, it has been proposed that fetal growth retardation may be related to prenatal exposure to sex steroids. In sheep, testosterone treatment during pregnancy may lead to growth-retarded male and female offspring (Manikkam *et al.*, 2004). We have recently demonstrated that pregnant women with PCOS exhibit a significant increase in androgen concentrations during pregnancy, which could provide a potential source of androgens to the fetus, and is perhaps another mechanism to explain the higher prevalence of low birth weight newborns in PCOS mothers (Sir-Petermann *et al.*, 2002). We should point out that, in the present study, the low birth weight of only two newborns could be attributed to pre-term induction of labour due to pre-eclampsia. Therefore, both the fetal programming hypothesis proposed by Barker and Osmond (1986) and the fetal insulin hypothesis proposed by Hattersley and Tooke (1999), and later supported by Hübinette *et al.* (2001), provide plausible mechanisms to help explain the higher prevalence of SGA newborns in PCOS mothers independently of pregnancy complications and maternal determinants of birth weight such as parity and maternal height (Hindmarsh *et al.*, 2002).

Thus, the offspring of PCOS mothers may represent a high-risk group with a great potential for early clinical intervention. In this regard, a treatment programme, including diet, exercise and insulin sensitising agents before pregnancy in those PCOS women who desire fertility, and diet and exercise in those who become pregnant, may constitute a timely therapeutic approach. Following this approach, the incidence of pregnancy complications such as gestational diabetes and pregnancy-induced hypertension observed in our PCOS patients was lower than that reported in the literature (Lesser and Garcia, 1997; Urman *et al.*, 1997). Moreover, as previously reported (Urman *et al.*, 1997), the incidence of pregnancy complications is higher in obese PCOS patients and obese control women than in lean women, indicating that obesity itself is a risk factor for the above complications. Nevertheless, the incidence of pregnancy complications in the same study was not greater among obese PCOS patients compared to lean PCOS patients, suggesting that PCOS itself may be the primary risk factor associated with an increased incidence of gestational diabetes and pregnancy-induced hypertension.

Another potential therapeutic intervention might be the use of metformin during pregnancy. According to the studies of Glueck *et al.* (2004), the benefits of continuing metformin through pregnancy could limit weight gain, improve insulin sensitivity and reduce androgen levels. These effects might prevent the development of pregnancy complications such as intrauterine growth retardation and exposure of the fetus to androgen excess. However, there is insufficient evidence to support the use of metformin during pregnancy at this time.

A relationship between PCOS and neonatal macrosomia was suggested many years ago (Wortsman *et al.*, 1991), but this potential relationship has been controversial (Urman *et al.*, 1997). In the present study, the prevalence of macrosomic infants in the PCOS group was 17% and in the control group 11%, this difference was not statistically significant. However, weight gain during pregnancy for PCOS mothers with LGA newborns was significantly greater compared to control mothers, therefore, the same therapeutic approach may be desirable for these patients.

In summary, PCOS mothers showed a significantly higher prevalence of SGA newborns which cannot be completely attributed to pregnancy complications or maternal determinants of birth weight and seems to be more related to the PCOS condition of the mother.

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