

# Comparison of the metabolic parameters and androgen level of umbilical cord blood in newborns of mothers with polycystic ovary syndrome and controls

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**Background:** This study aimed to assess the metabolic parameters and androgen concentration in the cord blood of newborns of mothers with polycystic ovary syndrome (PCOS) in comparison with controls. **Materials and Methods:** This cross-sectional study was conducted in 2010-2011 in Isfahan, Iran. Biochemical tests were conducted on 40 infants, born from singleton pregnancies in women with PCOS and an equal number of controls. **Results:** The mean weight gain during pregnancy was higher in women with PCOS than in controls ( $16.02 \pm 4.39$  vs.  $9.10 \pm 2.20$  kg, respectively,  $P < 0.0001$ ). The mean birth weight was lower in newborns of mothers with PCOS than in controls ( $2905.25 \pm 415.59$  vs.  $3223.25 \pm 425.02$  grams, respectively,  $P = 0.001$ ). The mean testosterone was higher in cord blood of newborns of PCOS women than in controls ( $5.58 \pm 3.20$  vs.  $2.28 \pm 0.62$  pg/ml,  $P < 0.0001$ ). Triglycerides and LDL-C were lower in cord blood of newborns, born from PCOS women than in controls ( $P = 0.001$ ). The birth weight of the newborns of PCOS mothers was negatively correlated to free testosterone of cord blood ( $R = -0.26$ ,  $P = 0.04$ ). **Conclusion:** The metabolic aberration in PCOS might influence fetal birth weight and cord blood lipid profile. These disorders may be caused by an exposure to elevated testosterone level during fetal life. The offspring of PCOS women may be at higher risk for chronic diseases in later life. The clinical impact of our findings should be confirmed in future longitudinal studies.

**Key words:** Androgen, metabolism, neonate, polycystic ovary syndrome, pregnancy

## INTRODUCTION

Maternal hormones support fetal growth and development. There is a growing body of evidence that the endocrine, nutritional and metabolic milieu during the fetal period may have lifelong programming effects.<sup>[1-4]</sup> Therefore, it is possible to propose that newborns of the women with polycystic ovary syndrome (PCOS) are exposed to an abnormal metabolic milieu during fetal life, and consequently to chronic diseases in later life.

PCOS is one of the most common endocrine disorders among women. Based on national Institute of Health (NIH) criteria,<sup>[5]</sup> its prevalence is 7% among women of reproductive age in our community in Iran.<sup>[6]</sup>

It is suggested that an insulin resistance and compensatory hyperinsulinemia are key pathologic factors in PCOS.<sup>[7-10]</sup> This disorder appears to be associated with an increased risk of metabolic alterations

including an insulin resistance, type II diabetes mellitus, and dyslipidemia. Thus, women with PCOS may be at risk for pregnancy complications such as gestational diabetes and hypertension.<sup>[11]</sup> An insulin may act directly and / or indirectly through the pituitary, to stimulate an ovarian androgen production. Serum levels of the androgens may be elevated. The free testosterone level is thought to be the best measure, with elevated levels found in most of PCOS patients.<sup>[12-14]</sup>

This study aimed to assess the metabolic parameters and androgen concentration in the cord blood of newborns, of mothers with PCOS in comparison with controls.

## MATERIALS AND METHODS

### Participants

This cross-sectional study was conducted in 2010-2011 in Isfahan, Iran. The study was approved by Research and

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Ethics Committee, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran (Project number:289181). Written informed consent was obtained from mothers.

The study comprised 80 mother-neonate pairs including 40 newborns from the mothers with PCOS, and an equal number of newborns from healthy mothers, referred to the same hospital.

Diagnosis of PCOS was made according to the criteria of National Institutes of Health (NIH), i.e. chronic oligomenorrhea or amenorrhea and hirsutism or serum testosterone concentration of  $> 0.6$  ng/ml and/or free androgen index (FAI)  $> 5.0$ , androstenedione concentration  $> 3.0$  ng/ml.<sup>[5]</sup> Those patients with hyperprolactinemia, androgen – secreting neoplasms, Cushing's syndrome and late-onset 21- hydroxylase deficiency and thyroid disease were not recruited.

For control group, we selected 40 healthy women with singleton pregnancy and history of regular menstrual cycles; without hirsutism, any other manifestations of hyperandrogenism, galactorrhea, thyroid dysfunction, gestational diabetes, hypertension, and history of any chronic medication use. They were matched with the PCO group in terms of age, socio-economic levels and body mass index (BMI).

Fetal serum sex steroid and glucocorticoid levels increases under stress during labor. It is suggested that the serum lipid levels differ in during vaginal delivery from those during elective cesarean section, and it may be a consequence of elevated glucocorticoid activity.<sup>[15]</sup> Thus, we recruited mothers who underwent elective cesarean section.

Newborns with preterm delivery, malformation or genetic disorders were not included into the study.

## Measures

### Physical examination

All pregnant women were visited by the same gynecologist. Weight gain during pregnancy was recorded for all studied women. After delivery, physical examination of newborns was performed by a pediatrician; weight, length and head circumference were measured by calibrated instruments and under standard protocols.

### Laboratory measurements

We collected umbilical mixed arterial-venous cord blood immediately after delivery, and were centrifuged, serum was kept frozen at  $-70^{\circ}\text{C}$  until analysis. Serum insulin, triglycerides (TG), cholesterol, high density lipoprotein (HDL) cholesterol and low density lipoprotein cholesterol (LDL-C), total testosterone, free testosterone and dehydroepiandrosterone sulfate were measured.

Cord blood lipid profile was determined by standard colorimetric assays (Pars Azmoon, Iran), serum insulin and testosterone were determined by *chemiluminescent immunoassay* (DiaSorin, Saluggia, Italy).

### Statistical analysis

Data were analyzed by SPSS software version 15.0 (SPSS Inc., Chicago, IL., USA). To compare the quantitative variables, the Student's t or Mann-Whitney U-tests were used, when applicable. The  $\chi^2$  test was used to compare the categorical variables. An association between continuous variable was assessed by the Spearman correlation test. The significance level was set at  $P < 0.05$ .

## RESULTS

The clinical characteristics of the PCOS and control groups are presented in Table 1. According to the study design, the age and the initial BMI of the mothers were not significantly different between groups. The mean weight gain during pregnancy was higher in women with PCOS than in controls ( $16.02 \pm 4.39$  vs.  $9.10 \pm 2.20$  kg, respectively,  $P < 0.0001$ ).

Table 2 presents the clinical characteristics of newborns of both the groups studied. The mean birth weight of newborns of mothers with PCOS was lower compared with controls ( $2905.25 \pm 415.59$  vs.  $3223.25 \pm 425.02$  grams, respectively,  $P = 0.001$ ). As presented in Table 3, mean TG and LDL-C levels were lower in cord blood of newborns born from PCOS women than in controls ( $P = 0.001$ ), whereas testosterone was higher in cord blood of newborns of PCOS women than in controls ( $P = 0.0001$ ).

The birth weight of newborns of PCOS women had a weak negative correlation with mother's BMI ( $R = -0.29$ ,  $P = 0.03$ ), but the corresponding figure was positive in controls ( $R = 0.33$ ,  $P = 0.01$ ). Moreover, the birth weight in newborns of

**Table 1: Characteristics of pregnant women with PCOS and controls**

|   | PCOS (N = 40)     | Controls (N = 40) | P        |
|---|-------------------|-------------------|----------|
| Age (year)  | 27.03 $\pm$ 3.45  | 28.24 $\pm$ 1.28  | 0.82     |
| Weight before pregnancy (kg)                          | 65.47 $\pm$ 11.32 | 67.33 $\pm$ 14.91 | 0.53     |
| Height (cm)   | 159.20 $\pm$ 2.43 | 159.55 $\pm$ 3.40 | 0.59     |
| Body mass index before pregnancy (kg/m <sup>2</sup> ) | 25.84 $\pm$ 4.45  | 26.39 $\pm$ 4.45  | 0.61     |
| Weight gain during pregnancy (kg)                     | 16.02 $\pm$ 4.39  | 9.10 $\pm$ 2.20   | < 0.0001 |

PCOS: Polycystic ovary syndrome; Values are mean and standard deviation (SD)

**Table 2: Clinical characteristics of newborns of PCOS mothers and controls**

|                         | PCOS (N = 40)    | Controls (N = 40) | P     |
|-------------------------|------------------|-------------------|-------|
| Gestational age (weeks) | 39 ± 0.65        | 39 ± 0.65         | 0.85  |
| Birth weight (kg)       | 2905.25 ± 415.59 | 3223.25 ± 425.02  | 0.001 |
| Birth length (cm)       | 48.78 ± 1.83     | 49.10 ± 2.01      | 0.45  |
| Head circumference (cm) | 34.75 ± 1.46     | 35.45 ± 1.69      | 0.05  |

PCOS: Polycystic ovary syndrome; Values are mean and standard deviation (SD)

**Table 3: Metabolic parameters and androgen concentration in cord blood of PCOS mothers and controls**

|                           | PCOS (N = 40) | Controls (N = 40) | P        |
|---------------------------|---------------|-------------------|----------|
| Insulin (µIU/ml)          | 7.76 ± 2.49   | 7.69 ± 1.75       | 0.88     |
| Cholesterol (mg/dl)       | 69.93 ± 14.19 | 75.85 ± 21.2      | 0.16     |
| HDL cholesterol (mg/dl)   | 25.83 ± 7.28  | 29.03 ± 6.66      | 0.04     |
| LDL cholesterol (mg/dl)   | 26.25 ± 6.45  | 36.17 ± 7.68      | < 0.0001 |
| Triglycerides (mg/dl)     | 60.48 ± 23.28 | 85.10 ± 33.80     | < 0.0001 |
| Free testosterone (pg/ml) | 5.58 ± 3.20   | 2.28 ± 0.62       | < 0.0001 |

PCOS: Polycystic ovary syndrome; Values are mean and standard deviation (SD)

PCOS mothers was negatively correlated to free testosterone of the cord blood ( $R = -0.26$ ,  $P = 0.04$ ).

## DISCUSSION

We found that the cord blood LDL-C and TG mean levels were significantly lower in PCOS than in control group; whereas the corresponding figure was not significantly different for the mean insulin, total-cholesterol and HDL-C.

It is well-documented that an intrauterine environment and fetal programming can have long-term impact on chronic diseases in later life.<sup>[1-4,16]</sup> In cord blood, total cholesterol level is lower than in adults, with a relatively higher proportion of HDL-C. In addition to genetic factors, ethnic differences, gestational age, fetal size, and mode of delivery influencing the composition of cord blood lipoproteins in normal pregnancies.<sup>[17-20]</sup> Fetal metabolism changes during pregnancy pathologies, for instance, while fat deposit is exaggerated in gestational diabetes, it is limited in fetal growth restriction.<sup>[21,22]</sup>

Limited experience exists about the metabolic changes in cord blood of neonates of PCOS women. The findings of our study on an alteration in the fetal lipid profile may be due to the changes in transplacental transport, which may be an appropriate physiological response to an adverse in utero environment in PCOS mothers. However, a study in Chile did not confirm the changes in the cord blood lipid profile of PCOS women.<sup>[23]</sup> The difference in the findings of these two studies might be because of the ethnic differences in cord blood lipid profile, and in part because of the mode of delivery, because we had recruited only those mothers who underwent elective cesarean section. In view of increasing evidence about fetal programming of chronic non-communicable diseases, the factors influencing cord blood lipids of PCOS mothers are suggested as an important area for further research.

In our study, androgen concentration was significantly higher in the cord blood of PCOS women than in controls. Women with PCOS have a significant increased androgen concentration, which would provide a placenta source of androgen to the fetus, and might have a long-term impact. A recent experimental study showed that elevated plasma maternal testosterone levels may cause low birth weight and then a rapid catch-up growth and hypertension in female offspring. The high testosterone level may be associated with decreased activity and expression of eNOS, which may alter endothelium-dependent vascular responses.<sup>[24]</sup> In our study, the elevated testosterone levels in cord blood of newborns of PCOS mothers may be a predictor of endothelial dysfunction and high blood pressure in the future of these infants; this hypothesis should be verified in long-term longitudinal studies.

In the present study, although weight gain during pregnancy was higher in women with PCOS than in controls, the birth weight of their offspring was significantly lower than in controls. This may be because of the fetal exposure to elevated testosterone levels, as documented by some experimental studies.<sup>[25-27]</sup>

A growing body of evidence supports the fetal programming of adult diseases and the crucial role of intrauterine growth retardation in this regard.<sup>[28-32]</sup> Therefore, the lower birth weight of PCOS women's offspring may increase the risk of chronic non-communicable diseases in later life.

The beneficial effects of metformin use during pregnancy on reducing maternal complications are documented in some studies;<sup>[33,34]</sup> however, the possible adverse effects has limited its use during pregnancy.<sup>[35]</sup> Findings of recent studies are promising for continuing metformin during pregnancy.<sup>[36,37]</sup> It can be suggested that metformin use by PCOS pregnant women may also have long-term beneficial

effects for their offspring; its safety should be confirmed in longitudinal studies.

In addition to favorable effects for women, controlling PCOS may have long-term effects for their offspring in terms of primordial prevention of chronic non-communicable diseases.

### Study limitations & strength

The main limitation of this study is its cross-section nature; therefore, the cause-effect cannot be assessed. The strength is the study novelty and adding information to the limited experience in this field.

## CONCLUSION

The metabolic aberration and hyperandrogenemia in PCOS might influence fetal serum lipid and birth weight. These disorders may be caused by an exposure to elevated testosterone level during fetal life. The offspring of PCOS women may be at higher risk for chronic diseases in later life. The clinical impact of our findings should be confirmed in future longitudinal studies.

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