Metabolic parameters in cord blood of neonate of mothers with obese and non-obese PCOS and controls: retrospective cohort study

Sanaz Alizadeh, Shahideh Jahanian Sadatmahalleh, Fatemeh Razavinia, Mahnaz Bahri Khomami, Malihe Nasiri, Ashraf Moini and Saeideh Ziaei*

Abstract

Background: Polycystic ovary syndrome (PCOS) is characterized by reproductive disorder and increased risk of metabolic syndrome. This study aimed to assess the metabolic parameters in the cord blood of neonates of mothers with obese PCOS and comparison with non-obese PCOS and controls.

Methods: This retrospective cohort study was conducted in Arash and Kamali Hospital in 2017–2018. The biochemical test was conducted on 78 neonates from obese PCOS mothers, 78 neonates from non-obese PCOS mothers, and 78 neonates from healthy mothers. Finally, cord blood lipid profile and insulin and blood sugar were determined by specific kits. Correlations between variables were compared with chi-square, Mann-Whitney's U, Kruskal-Wallis H tests and regression model by SPSS 23 and P < 0.05 was considered significant.

Results: Triglycerides (TG) and high-density lipoprotein cholesterol (HDL) were higher in cord blood of newborn of obese PCOS women than non-obese PCOS and controls (P = 0.02, P < 0.001, respectively). Also, the mean insulin was higher in cord blood of neonate of non-obese PCOS women than in obese PCOS and controls (12.26 ± 12.79 vs. 11.11 ± 16.51 vs. 6.21 ± 10.66, P = 0.01). But in the study, there was no significant difference between the mean of umbilical cord low-density lipoprotein cholesterol (LDL), total cholesterol and blood sugar in three groups. The logistic regression model showed that metabolic parameters were related to PCOS.

Conclusions: In the present study, there was a significant difference between the mean of umbilical cord HDL, cholesterol, and the insulin level in the three groups. But, there was no significant association between the mean of blood sugar, LDL, and TG in the groups. The metabolic disorder in PCOS might affect cord blood lipid and insulin and adulthood health.

Keywords: Polycystic ovary syndrome, Metabolic parameters, Neonate, Pregnancy

* Correspondence: Ziaei_sa@modares.ac.ir

© The Author(s). 2021 Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Background
Polycystic ovary syndrome (PCOS), affecting 6–10% reproductive-aged women, is one of the most common endocrine disorders [1]. It is a multifactorial condition related to gen and environmental risk factors [2]. PCOS is associated with hormonal dysregulation such as hyperandrogenemia and disturbed gonadotropin secretion [2]. These result in chronic anovulation, and menstrual disorder obesity and insulin resistance, type II diabetes mellitus, dyslipidemia, hyperlipidemia, and cardiovascular disease [3]. Metabolic syndrome is reported in 7–43% of women with PCOS [4–6]. Metabolic syndrome is associated with insulin resistance, hypertension, obesity, lower HDL, higher LDL, and increased fasting blood sugar (FBS) [5]. Metabolic syndrome and PCOS are both associated with increased rate of adverse neonatal and maternal pregnancy outcomes including gestational diabetes mellitus (GDM), hyperlipidemia, hypertension in mother, and maternal obesity and diabetes have been associated with macrosomia, risk for obesity, glucose intolerance and androgen level disorder of the infant and the offspring [7].

Recent data report that there is an association between intrauterine environment (such as hyperglycemia, hyperandrogenism and hyperlipidemia) and health status in adulthood [8–10]. Therefore, maternal hormonal imbalance and dyslipidemia may have adverse short and long term impact on infant’s health. Recent studies have shown that maternal PCOS increases testosterone in the infant [11]. Increased testosterone levels in infant cause vascular endothelial damage [11], hypertension and cardiovascular disease in adulthood [12, 13]. Also, Maternal obesity and PCOS lead to increased blood glucose and lipids [14], type 2 diabetes [15], neonatal and adolescent obesity [16], and increased risk of developing PCOS and metabolic syndrome in offspring [17]. increase disease (diabetes, obesity, cardiovascular disease) and economic and psychological burden in the person, in the family and in the society [18].

As a result, due to the importance of the issue, we aimed to assess the metabolic parameters (LDL and HDL, triglycerides, cholesterol, blood sugar, and insulin) in the cord blood of neonate of mothers with obese PCOS and comparison with non-obese PCOS and controls.

Methods
This retrospective cohort study was conducted among pregnant women in Arash Hospital in Tehran and Kamali Hospital in Karaj from 2017 to 2018. The study protocol was approved by the ethics committee of Tarbiat Modares University (IR.TMU.REC.1395.367). Informed consent was obtained from all participants.

Using the equality of means in three groups formula, sample size is calculated by taking 99% confidence coefficient and power 90% and effect size 0.3 [17]. In this study, 234 women- neonate were enrolled in the study according to the inclusion criteria and available method and divided into three groups (78 neonates from obese PCOS mothers, 78 neonates from non-obese PCOS, and 78 neonates from healthy mothers). Also, informed consent was obtained from all participating mothers.

In this study, we recruited 18–40 years women with a spontaneous singleton pregnancy, Iranian nationality and ability to read and write (n = 250). We excluded those with chronic metabolic (such as phenylketonuria, thyroid, diabetes and etc) and non-metabolic diseases (such as cardiovascular disease, chronic kidney disease and etc), a history of chemotherapy or radiotherapy, hyperprolactinemia or androgen-secreting neoplasms, late-onset 21-hydroxylase deficiency, adult-onset congenital adrenal hyperplasia, the Cushing’s syndrome, and thyroid disease and also smokers (n = 16).

PCOS is diagnosed in those with having at least two of the following three symptoms before pregnancy: oligomenorrhea or amenorrhea (O), clinical and/or biochemical hyperandrogenism (H), and polycystic ovaries on ultrasound (P) [19].

The controls were healthy women with regular menstrual cycles. They had no history of any long-term medication intake (due to its effects on PCOS symptoms and diseases, lipids and blood glucose, or drug side effects (obesity, liver dysfunction, etc.)), hyperandrogenemia, hirsutism, gestational diabetes, thyroid dysfunction, galactorrhea, and hypertension.

Infants with genetic disorders, abnormalities, or preterm birth were excluded from the study.

In each PCOS group, 31 male and 29 female neonates were examined. As a control group, we examined 34 male and 26 female infants born to healthy mothers. Newborns in both groups (control and PSCO) had normal birth weight.

The three groups (control, obese and non-obese PCOS) were group matched for age, education, employment, social-economic status, parity, and gestational age at labor, as well as the neonate’s sex. Neonates with genetic disorders, malformation or preterm delivery were excluded from the study.

We finally included 234 pregnant women in the analyses. Women with PCOS were then categorized to those with (pre-pregnancy BMI > 30) and without obesity (pre-pregnancy BMI < 30). Pre-pregnancy weight and BMI was reported from the subject’s final doctor’s visit or on admission to the hospital.

Laboratory measurements
The umbilical cord blood samples (5 ml) were collected immediately post-delivery by researcher. The samples were centrifuged and the serum was separated and
frozen at −70 °C until processed for the metabolic index in the laboratory. Serum levels of triglycerides (TG) and cholesterol were determined by standard colorimetric assays (Pars Azmoon, Iran), LDL and HDL were measured by immunoturbidimetric. Also, serum levels of insulin were determined by chemiluminescent immunoassay (CLIA) (DiaSorin, Saluggia, Italy), blood sugar concentration was measured by photometric.

Statistical analysis
Statistical analysis was performed by using Statistical Package for Social Science (SPSS, version 23, SPSS Inc., Chicago, IL, USA).

The normality assumption of variables was tested by using the Kolmogorov-Smirnov test and data are presented as mean ± SD, number (percentage) and median (IQR1-IQR3). Also, correlations between variables were compared with chi-square, tukey test, One Way ANOVA and Kruskal-Wallis H tests. In addition, to detect the association between metabolic parameters in cord blood of neonate and PCOS with Logistic regression model with Logit link function (to estimate the odds ratio of metabolic parameters with 95% confidence intervals) was run. In this study, $P < 0.05$ was considered significant.

Table 1: Homogeneity of three groups of obese and non-obese PCOS mothers and controls in terms of demographic characteristics

| Variables          | Obese mothers with PCOS ($n = 78$) | Non-obese mothers with PCOS ($n = 78$) | Control ($n = 78$) | $P$-value |
|--------------------|------------------------------------|----------------------------------------|-------------------|-----------|
| Age (years)$^a$    | 28.4 ± 5.16                        | 27.7 ± 4.54                            | 26.4 ± 5.18       | 0.089     |
| BMI (kg/m²)$^a$    | 31.10 ± 3.11                       | 26.06 ± 4.18                           | 25.18 ± 2.93      | 0.01      |
| Education$^b$      |                                    |                                        |                   |           |
| Diploma (< 12 years) | 64 (82.1)                          | 66 (84.6)                              | 73 (93.6)        | 0.07      |
| College education ($\geq$ 12 years) | 14 (17.9)                         | 12 (15.4)                              | 5 (6.4)          |           |
| Income (Rial)$^b$  |                                    |                                        |                   |           |
| (2,000,000)        | 23 (29.5)                          | 20 (25.6)                              | 28 (35.9)        | 0.46      |
| (2,000,000–3,000,000) | 33 (42.3)                          | 37 (47.4)                              | 36 (46.2)        |           |
| (> 3,000,000)      | 22 (28.2)                          | 21 (27)                                | 14 (17.9)        |           |
| Gravid$^b$         |                                    |                                        |                   |           |
| 1                  | 30 (38.5)                          | 39 (49.9)                              | 30 (38.5)        | 0.29      |
| 2                  | 27 (34.6)                          | 25 (32.1)                              | 31 (39.7)        |           |
| 3                  | 14 (17.9)                          | 9 (11.5)                               | 12 (15.4)        |           |
| 4                  | 7 (9)                              | 5 (6.5)                                | 5 (6.4)          |           |
| Parity$^b$         |                                    |                                        |                   |           |
| 1                  | 50 (65)                            | 58 (69.85)                             | 50 (65)          | 0.625     |
| 2                  | 20 (25)                            | 15 (18.75)                             | 18 (22.5)        |           |
| 3                  | 8 (10)                             | 9 (11.4)                               | 10 (12.5)        |           |
| Infants Gender$^c$ |                                    |                                        |                   |           |
| Male               |                                    |                                        |                   |           |
| Female             |                                    |                                        |                   |           |

PCOS Polycystic Ovary Syndrome, $^a$Values are given as mean ± SD using One Way ANOVA, $^b$Values are given as a number (%) using Kruskal Wallis test, $^c$
The mean rank serum level of HDL in obese PCOS and non-obese PCOS and the control group was statistically significant \((P < 0.001)\). And the umbilical cord HDL in control was significantly lower compared with two groups \((P < 0.001)\).

In the present study, there was no significant difference between the mean rank of umbilical cord LDL \((P = 0.71)\), cholesterol \((P = 0.22)\) and sugar \((P = 0.41)\) level in the three groups.

Logistic regression model showed metabolic parameters insulin \((\text{OR} = 1.048, 95\% \text{ CI: } 1.008–1.090, P = 0.01)\), TG \((\text{OR} = 1.024, 95\% \text{ CI: } 1.009–1.039, P = 0.002)\) in obese PCOS women and insulin \((\text{OR} = 1.053, 95\% \text{ CI: } 1.012–1.095, P = 0.01)\), HDL \((\text{OR} = 0.967, 95\% \text{ CI: } 0.948–0.987, P = 0.001)\) and TG \((\text{OR} = 1.026, 95\% \text{ CI: } 1.011–1.041, P = 0.001)\) in non-obese PCOS women were related to PCOS. And one unit increase in insulin level increases 4.8% odds of obese PCOS and 5% non-obese PCOS compared to controls. Also, One unit increase in TG level, the chance of obese PCOS at 2.4% and the chance of non-obese PCOS at 2.6% was higher than control. But, one unit increase in HDL level, decreases 3.3% chance of non-obese PCOS compared to controls (Table 3).

**Discussion**

The current study aimed at assessing the umbilical cord blood’s HDL, LDL, TG, cholesterol, insulin, and sugar level in the newborns of PCOS mothers compared to the controls.

In the present study, there was a significant difference between the mean of umbilical cord TG and HDL levels in the women PCOS (obese PCOS and non-obese) and controls. However, there was no association between total cholesterol and LDL levels in the groups. In several studies including Mehrabian et al. [20], observed a significant relationship between serum TG and LDL levels in neonates of PCOS women compared to controls, but, there was no difference between serum cholesterol and HDL levels. Also, Maliqueo et al. [21], reported not the association between serum levels of cholesterol, TG, HDL and LDL in the cord blood of neonates with PCOS.

**Table 2** Metabolic Parameters in cord blood of obese and non-obese PCOS mothers and controls

| Variables             | Obese mothers with PCOS \((n = 78)\) | Non-obese mothers with PCOS \((n = 78)\) | Control \((n = 78)\) | \(P\)-value |
|-----------------------|-------------------------------------|----------------------------------------|---------------------|-------------|
| Insulin \((\mu\text{IU/ml})^a\) | 5.40 (1.70–14.40) | 9.50 (3.55–18.55) | 2.45 (1.60–6.05) | 0.01 |
| Blood Sugar \((\text{mg/dl})^a\) | 74.50 (54.25–91.50) | 73.50 (53.00–92.50) | 77.00 (53.25–100.00) | 0.41 |
| Total Cholesterol \((\text{mg/dl})^a\) | 73.00 (56.25–83.50) | 70.50 (58.00–85.75) | 65.00 (55.25–79.00) | 0.22 |
| HDL Cholesterol \((\text{mg/dl})^a\) | 30.50 (16.25–45.00) | 21.00 (18.00–31.75) | 30.50 (16.25–45.00) | < 0.001 |
| LDL Cholesterol \((\text{mg/dl})^a\) | 21.00 (16.00–28.75) | 23.00 (15.00–28.00) | 21.00 (18.00–29.00) | 0.71 |
| Triglycerides \((\text{mg/dl})^a\) | 45.50 (34.25–65.50) | 45.00 (32.25–59.00) | 31.00 (19.00–48.50) | 0.02 |

**Table 3** Predictors of metabolic syndrome in obese PCOS, non-obese PCOS, and controls women using logistic regression model

| Variables             | \(\beta\) | Odds Ratio | 95\% CI | \(P\)-value |
|-----------------------|-----------|-----------|--------|-------------|
| **Obese mothers with PCOS** |           |           |        |             |
| Insulin \((\mu\text{IU/ml})\) | 0.048 | 1.048 | 1.008–1.090 | 0.018 |
| Blood Sugar \((\text{mg/dl})\) | 0.003 | 1.003 | 0.997–1.009 | 0.325 |
| Total Cholesterol \((\text{mg/dl})\) | 0.016 | 1.016 | 0.997–1.036 | 0.102 |
| HDL Cholesterol \((\text{mg/dl})\) | −0.001 | 0.999 | 0.991–1.007 | 0.822 |
| LDL Cholesterol \((\text{mg/dl})\) | −0.027 | 0.973 | 0.936–1.011 | 0.156 |
| Triglycerides \((\text{mg/dl})\) | 0.024 | 1.024 | 1.009–1.039 | 0.002 |

| Variables             | \(\beta\) | Odds Ratio | 95\% CI | \(P\)-value |
|-----------------------|-----------|-----------|--------|-------------|
| **Non-obese mothers with PCOS** |           |           |        |             |
| Insulin \((\mu\text{IU/ml})\) | 0.053 | 1.053 | 1.012–1.095 | 0.010 |
| Blood Sugar \((\text{mg/dl})\) | −0.001 | 0.999 | 0.991–1.007 | 0.816 |
| Total Cholesterol \((\text{mg/dl})\) | 0.013 | 1.013 | 0.933–1.035 | 0.206 |
| HDL Cholesterol \((\text{mg/dl})\) | −0.033 | 0.967 | 0.948–0.987 | 0.001 |
| LDL Cholesterol \((\text{mg/dl})\) | −0.018 | 0.982 | 0.945–1.021 | 0.357 |
| Triglycerides \((\text{mg/dl})\) | 0.026 | 1.026 | 1.011–1.041 | 0.001 |

PCOS Polycystic Ovary Syndrome, \(\text{OR}\) odds ratios, \(\text{CI}\) confidence intervals
and controls. The difference in the findings of these three studies might be because of the ethnic differences in cord blood lipid profile, and anthropometric differences in the neonate, type of delivery, gestational age, race, lifestyle, diet and etc.

At least half of the patients with PCOS are obese. In addition, over 50% of PCOS women have android obesity. Android obesity increases cardiovascular disease risk and decreases HDL. On the other hand, in obese women, sex hormone-binding globulin (SHBG) decreases and testosterone increases. Increasing testosterone decreases lipoprotein lipase activity in abdominal adipose cells and disrupts the anti-lipolytic effect of insulin [22, 23]. And obesity causes insulin resistance and hyperinsulinemia. Insulin resistance and hyperinsulinemia play an important role in dislipidemia (the degree and type of dyslipidemia vary in women with PCOS). Hyperinsulinemia inhibits lipolysis and increases non-esterified fatty acid. Increasing non-esterified fatty acid increases TG and decreases HDL [2, 23]. Also, increased LDL is of heterogeneous origin in these persons [24].

In this study, serum insulin levels in neonates of non-obese PCOS mothers were higher than obese PCOS and controls. Nevertheless, there was no significant difference between the cord blood sugar levels in the three groups. But, Mehrabian et al. [20], reported no association between umbilical cord insulin levels in the PCOS and controls. Maliqueo et al. [21], observed not the correlation between umbilical cord insulin and glucose levels in the groups. Also, Sergio et al. [25], showed that Serum glucose and insulin levels and insulin resistance were not different in male neonates (2–3 months) with PCOS and non-PCOS women.

The difference in the findings of studies might be because of differences in sample size, genetic variation, nutritional status, cultural differences and lifestyle in the study population. Half of the PCOS people are not obese [12]. But, there is insulin resistance and hyperinsulinemia in all women with PCOS that is not known etiology so far [26–28]. A sedentary lifestyle [29] and a high-calorie diet [30] may play a role in increasing insulin resistance and blood insulin level (independent of obesity) in PCOS women.

Our study limitations, infant anthropometric was not measured and was not investigated the association with metabolic parameters. Also, the relationship between maternal and neonatal metabolic parameters was not evaluated. In addition, the control group was not divided into obese and non-obese groups. Also, the sample size is small.

Conclusions
In conclusion, our results indicate a significant association between insulin, HDL, TG in cord blood of neonate of obese PCOS women than in non-obese PCOS and controls. But, there was no significant difference between the mean of umbilical cord LDL, total cholesterol and blood sugar in three groups. The metabolic disorder in PCOS might affect cord blood lipid and insulin. These disorders may be an increased risk for chronic diseases (cardiovascular disease, Diabet, etc) in adulthood. As a result, screening in PCOS women prevents neonatal and adult complications.

Abbreviations
FBS: Fasting blood sugar; GDM: Gestational diabetes mellitus; HDL: High-density lipoprotein cholesterol; LDL: Low-density lipoprotein cholesterol; PCOS: Polycystic ovary syndrome; SHBG: Sex hormone-binding globulin; TG: Triglycerides

Acknowledgments
This study was carried out with the kind collaboration of the participants. The authors would also like to appreciate the staff of Arash Hospital and Kamali Hospital for their valuable contributions.

Informed consent
Informed consent was obtained from all individual participants included in the study.

Authors’ contributions
Study concept and design: SZ. Acquisition of data: SA,FR. Analysis and interpretation of data: MN, SZ, FR, ShJS, AM. Drafting of the manuscript: SZ, FR, SA, ShJS, MBK, AM. Critical revision of the manuscript for important intellectual content: SZ, ShJS, MBK, FR. Statistical analysis: MN, SZ, FR, ShJS, SA. Administrative, technical, and material support: MN, SZ, FR, ShJS, SA, AM, MBK. The author(s) read and approved the final manuscript.

Funding
The authors declare that they have no Funding.

Availability of data and materials
All data generated and analyzed in this study are included in this published manuscript.

Declarations
Ethics approval and consent to participate
All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. On May 23th, 2016, the study was approved by the ethics committee of the Tarbiat Modares University (IR.TMU.REC.1395.367).

Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interests.

Author details
1Department of Reproductive Health and Midwifery, Faculty of Medical Sciences, Tarbiat Modares University, P.O. Box: 1415-111, Dr. Saeideh Ziae, Tehran, Iran. 2Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton, Vic, Australia. 3Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran. 4Breast Disease Research Center (BDRC), School of Medicine, Tehran University of Medical Science, Tehran, Iran. 5Department of Obstetrics and Gynecology, Tehran University of Medical Sciences, Tehran, Iran. 6Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran.

Page 5 of 6
1. Mehrabadi S, Jahanian Sadatmahalleh S, Kazemnejad A. Association of
depression and anxiety with cognitive function in patients with polycystic
ovary syndrome. J Mazandaran Univ Med Sci. 2017;27(147):159–70.
2. Akbarzadeh M, Naderi T, Dabbaghmanesh MH. The glucose metabolism
dyslipidemia among girls with different phenotype polycystic
ovary syndrome. J Res Med Sci. 2019;24:72.
3. Cunningham F, Leveno K, Bloom S, Dashe J, Hoffman B, Casey B, Spong CF.
Williams Obstetrics 24/E. McGraw Hill Professional. New York: McGraw-Hill
Education/Medical; 2018.
4. Apridonidze EPA, Iurono MJ, Nelse JE. Prevalence and characteristics of the
metabolic syndrome in women with polycystic ovary syndrome. Clin
Endocrinol Metab. 2005;90(4):1929–35.
5. Gambineri A, Pelusi C, Vicennati V, Pagotto U. Obesity and the polycystic
ovary syndrome. Obes Rev. 2003;42688–96.
6. Johnson WD, Kroon JJ, Greenway FL, Bouchard C, Ryan D, Katzmarzyk PT.
Prevalence of risk factors for metabolic syndrome in adolescents: national
health and nutrition examination survey (NHANES), 2001–2006. Arch Pediatr
Adolesc Med. 2009;163:371–7.
7. Anderson H, Fogel N, Grebe SK, Singh RJ, Taylor RL, Dunaif A. Infants of
women with polycystic ovary syndrome have lower cord blood
androstenedione and estradiol levels. J Clin Endocrinol Metab. 2010;
95(5):2180–6.
8. Rinaudo P, Wang E. Fetal programming and metabolic syndrome. Annu Rev
Physiol. 2012;74:107–30.
9. Hodyl NA, Stark MJ, Osei-Kunah A, Clifton VL. Prenatal programming of the
innate immune response following in utero exposure to inflammation: a
sexually dimorphic process? Expert Rev Clin Immunol. 2011;7:579–92.
10. Briaia DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult
disease: the role of adipocytokines. Eur J Endocrinol. 2009;160:337–47.
11. Huang A, Brennan K, Azziz R. Prevalence of hyperandrogenemia in the
polycystic ovary syndrome diagnosed by the National Institutes of health
1990 criteria. Fertil Steril. 2010;93:1938–41.
12. Berek JS, Berek & Novak's Gynecology. 15th ed. Tehran: Golban Nashr
Education/Medical; 2018.
13. Cunningham F, Leveno K, Bloom S, Dashe J, Hoffman B, Casey B, Spong CY.
Williams Obstetrics 24/E. McGraw Hill Professional. New York: McGraw-Hill
Education/Medical; 2018.
14. Akbarzadeh M, Naderi T, Dabbaghmanesh MH. The glucose metabolism
and dyslipidemia among girls with different phenotype polycystic
ovary syndrome. J Res Med Sci. 2019;24:72.
15. Briana DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult
disease: the role of adipocytokines. Eur J Endocrinol. 2009;160:337–47.
16. Johnson WD, Kroon JJ, Greenway FL, Bouchard C, Ryan D, Katzmarzyk PT.
Prevalence of risk factors for metabolic syndrome in adolescents: national
health and nutrition examination survey (NHANES), 2001–2006. Arch Pediatr
Adolesc Med. 2009;163:371–7.
17. Anderson H, Fogel N, Grebe SK, Singh RJ, Taylor RL, Dunaif A. Infants of
women with polycystic ovary syndrome have lower cord blood
androstenedione and estradiol levels. J Clin Endocrinol Metab. 2010;
95(5):2180–6.
18. Rinaudo P, Wang E. Fetal programming and metabolic syndrome. Annu Rev
Physiol. 2012;74:107–30.
19. Hodyl NA, Stark MJ, Osei-Kunah A, Clifton VL. Prenatal programming of the
innate immune response following in utero exposure to inflammation: a
sexually dimorphic process? Expert Rev Clin Immunol. 2011;7:579–92.
20. Briaia DD, Malamitsi-Puchner A. Intrauterine growth restriction and adult
disease: the role of adipocytokines. Eur J Endocrinol. 2009;160:337–47.
21. Huang A, Brennan K, Azziz R. Prevalence of hyperandrogenemia in the
polycystic ovary syndrome diagnosed by the National Institutes of health
1990 criteria. Fertil Steril. 2010;93:1938–41.
22. Berek JS, Berek & Novak's Gynecology. 15th ed. Tehran: Golban Nashr
Education/Medical; 2018.
23. Ng NYH, Jiang G, Cheung LP, Zhang Y, Tam CHT, Luk AOY, et al.
Progression of glucose intolerance and cardiometabolic risk factors over a
decade in Chinese women with polycystic ovary syndrome: a case-control
study. PLoS Med. 2019;16(10):e1002953. https://doi.org/10.1371/journal.
pmed.1002953.
24. Legro RS, Azizi R, Ehrmann D, Freeman AG, O’Keefe M, Ghazzi MN. Minimal
response of circulating lipids in women with polycystic ovary syndrome to
improvement in insulin sensitivity with Troglitazone. Clin Endocrin Metab.
2003;88:5137–44.
25. Sergio E, Recabarren SR, Ros R, Maliqueo M, Echiburú B. Metabolic profile
in sons of women with polycystic ovary syndrome. J Clin Endocrin Metab.
2008;93(5):1820–6.
26. Brouns G, Bachelot A, Monnere L, Vaillant J, Joquet G, Velvaydorn FL.
Triglycerides as a metabolic target in afrocaribbean infertile women with
polycystic ovary syndrome. Metab Syndr Relat Disord. 2019;17(10):500–4.
https://doi.org/10.1089/met.2019.0041.
27. Martínez-García MA, Moncayo S, Insensier M, Álvarez-Blasco F, Luque-
Ramírez M, Escobar-Moreale HF. Metabolic cytokines at fasting and during
macronutrient challenges: influence of obesity, female androgen excess and
sex. Nutrients. 2019;11(11):2566. https://doi.org/10.3390/nu11112566.
PUBLISHED 2019 Oct 24.
28. Elia LD, Sterazul P. Excess body weight, insulin resistance and isolated
syntic hypertenion: potential pathophisiological links. High Blood Press
Cardiovasc Prev. 2018;25(1):17-23.
29. Hambury NM, McKick CJ, Huang AL, Shenouda SM, Willsdamsy ME, Schulz
E. Physical inactivity rapidly induces insulin resistance and microvascular
dysfunction in healthy volunteers. Arterioscler Thromb Vasc Biol. 2007;
27(12):2650–6.
30. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF.
Carbohydrate nutrition, insulin resistance, and the prevalence of the
metabolic syndrome in the Framingham offspring cohort. Diabetes Care.
2004;27(10):538–46.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in
published maps and institutional affiliations.