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MATERNO-FETAL MEDICINE

Polycystic ovarian syndrome and pregnancy outcome

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Abstract
Introduction Polycystic ovarian syndrome (PCOS) is a common disease of the endocrine system among the women of reproductive age with an incidence ranging from 5 to 10%.
Method This study is a mini-review of pregnancy and perinatal outcome in women with PCOS.
Results The syndrome is associated with increased risk of pregnancy complications such as gestational diabetes, gestational hypertension, preeclampsia, and preterm labor, while no strong association was found with congenital anomalies or spontaneous miscarriages. Furthermore, women with PCOS seem to experience increased risk of cesarean delivery while their newborns face increased perinatal morbidity and mortality. Metformin use seems to reduce the risk of obstetrical complications; however, prospective studies are necessary on the field.
Conclusion Further studies should be organised in order to evaluate the role of PCOS in pregnancy.

Keywords Polycystic ovaries · Preeclampsia · Hypertension · Gestational diabetes mellitus · Preterm delivery · Metformin · Hyperandrogenism · Oligoanovulation

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common diseases of the endocrine system in women of reproductive age. The incidence ranges from 5 to 10% in different studies [1–3]. About 70% of women who have anovulation and normal serum gonadotropin levels suffer from the syndrome [2], while 50% of those with PCOS have increased body weight or are obese [4]. The clinical and laboratory picture of PCOS is characterized by a combination of symptoms such as oligo/amenorrhea, clinical or laboratory evidence of elevated androgens and ultrasound imaging of polycystic ovaries [3]. According to ESHRE/ASRM [3], women with PCOS were separated in the following groups: (a) women with hyperandrogenism, oligoanovulation, and PCO (full-blown syndrome); (b) women with hyperandrogenism and oligoanovulation, but without the ultrasound appearance of PCO; (c) women with hyperandrogenism and PCO (ovulatory PCOS); and (d) women with oligoanovulation and PCO (non-hyperandrogenic PCOS).

The metabolic findings of PCOS imply increased insulin resistance, hirsutism, increased androgens levels, dyslipidaemia, and hypertension, factors which increase the incidence of delayed cardiovascular problems [4]. Thus, about 40% of middle-aged women with PCOS present diabetes mellitus type II or glucose intolerance [4].

The PCOS is often accompanied by infertility requiring ovulation induction by using clomiphene citrate and/or gonadotropins [4]. Pregnancy is a predisposing factor of increased insulin resistance [4]. It is estimated that 25–70% of women with PCOS show an increase in insulin resistance and have an increased risk of developing complications during pregnancy, especially gestational diabetes [5]. Indeed, according to the Barker hypothesis, there is an in utero fetal programing of fetal nutrition and of the endocrine and metabolic environment in which the fetus develops, a fact that explains why PCOS complications might affect the fetus [6]. Many women with PCOS

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undergo assisted reproduction techniques in an effort to achieve pregnancy, fact which increases the incidence of multiple pregnancies with all the consequences caused by them compared to the singleton pregnancies [7]. Although, literature review about PCOS and pregnancy outcomes was previously conducted [8–17], it is still uncertain, however, to what extent PCOS itself affects pregnancy outcome in general and perinatal outcome.

This mini-review contains the relevant literature search for publications in PubMed and relevant references from the initially identified articles between the years 1960 and 2010. The used keywords included the terms "PCOS", "complication", "pregnancy", "metformin", "diabetes mellitus", "spontaneous abortion", "miscarriage", "congenital anomalies", "preeclampsia", and hypertension". The purpose of the review is to present the complications, the perinatal morbidity and mortality of women with PCOS, and the possible therapeutic role of metformin in those cases. All data that did not use the English language were excluded. From the relevant articles on the field, the potential role of PCOS in such conditions is presented.

Complications of pregnant women with PCOS

Complications of the first trimester of pregnancy which were studied in women with PCOS were the miscarriages and fetal congenital abnormalities. It has been suggested that PCOS is associated with an intrauterine inflammatory response characterized by elevated white blood count and CRP which impedes implantation [18–21]. The obesity that characterizes the syndrome also appears to play an important role in the pathophysiological pathway [5, 22, 23].

Some studies, and particularly that of Sir-Petermann et al. [24–27], have indicated no relationship of PCOS to the presence of congenital anomalies. However, a meta-analysis in 2006 revealed a 1.6–1.7 relative risk [26]. Sir-Petermann et al. [27] reported that the incidence of birth defects among pregnant women with PCOS and normal pregnancies was not found to be statistically different (OR 0.70; 95% CI 0.11–4.39).

No clear evidence is found whether there is an increased risk of spontaneous abortion rates in women with PCOS. Some authors have reported that women with PCOS have a 33% chance of spontaneous abortion [28, 29]. Both insulin resistance and increased body weight are associated with PCOS. In a recent study, an increased incidence of miscarriage rates is found in women with increased insulin resistance [30]. Furthermore, an increased incidence of miscarriages in pregnant women with increased body weight has been shown [31]. It has also been demonstrated that miscarriage rates are increased in women with elevated serum levels of LH. More specifically, high serum levels of LH, abnormal production of progesterone, high serum levels of androgens, hyperomokysteinaimia, and increased levels of glucodelins and IGFBP-2 appear to be involved in the pathogenesis of the syndrome [24, 28, 32–36]. Nevertheless, when gonadotropins are used in assisted reproduction techniques in women with the syndrome, no increased spontaneous abortions rates have been mentioned [32, 37]. On the contrary, other studies did not find increased rates of spontaneous abortions in women with PCOS. In those studies, however, women without PCOS were compared to women with either unique ultrasound findings of polycystic ovaries [29, 38, 39] or obese women with or without PCOS [40, 41] or women with high levels of luteal phase LH and testosterone [42].

Complications associated with PCOS in the second to third trimester of pregnancy are the impaired glucose tolerance, gestational diabetes, arterial hypertension, and preeclampsia [43–54].

Holte et al. [43] showed in 1998 that the prevalence of gestational diabetes was significantly higher among PCOS versus non-PCOS women. In the same metaanalysis, it has been shown that women with history of PCOS and no statistical significant difference in BMI and/or age had increased incidence of gestational diabetes [43]. Mikola et al. [44] also indicated an increased risk for gestational diabetes primarily because of obesity than the PCOS itself. Obesity is associated with elevated insulin levels and glucose intolerance. For this reason, in the same study one-third of the patients with PCOS were overweight. Alshammari et al. [13] in another study showed that women with both PCOS and gestational diabetes mellitus have an increased risk of obstetric complications such as pregnancy-induced hypertension/preeclampsia, preterm labor, and need for phototherapy treatment of newborns for hyperbilirubinemia. In a recent metaanalysis, women with PCOS had an increased risk of gestational diabetes [45]. However, the metaanalysis did not count confounding factors such as age, gravida, and multiple pregnancies, which are correlated with gestational diabetes.

Studies have reported increased risk of preeclampsia [46], hypertension [47, 48], and gestational diabetes [49–52] in women with anoovulating cycles. Regarding arterial hypertension during pregnancy in women with PCOS, it has been shown that there is a statistically significant difference in systolic, diastolic, and mean arterial pressure in these women compared to normal women. This finding has also been shown by Hu et al. [53] after measuring carotid stiffness in pregnant women with PCOS. All previous studies and a recent metaanalysis have shown the correlation of arterial hypertension during pregnancy in women with PCOS [47, 54]. In the same metaanalysis, a 3.5 times higher risk for preeclampsia and 1.75 times for preterm

birth have been shown in pregnant women with PCOS [54]. It should be mentioned that the rates of iatrogenic preterm labor are increased in women with PCOS [44, 55]. However, Legro et al. [12] showed that birthweight in families with PCOS has no substantive association either with reproductive or with metabolic abnormalities in women with PCOS or their relatives.

Regarding the manner in handling childbirth, older studies showed high rates of cesarean sections [44, 55]. A meta-analysis by Boomsa et al. [54] in 2008 showed that women with PCOS had a 1.5 times higher risk of cesarean section. But when the control group was matched for age and BMI, no statistically significant difference was found regarding normal delivery, forceps use or cesarean section [54].

Newborns of women with PCOS had a 2.31 times higher risk of admission to intensive care unit for neonates and three times higher perinatal mortality than neonates of women without PCOS [54]. Perinatal morbidity of these neonates could be explained by prematurity and intrauterine growth retardation, and the IVF attempts these women with the syndrome undergo. It is also noteworthy that despite the fact that mothers with PCOS have an increased risk of gestational diabetes, fetal macrosomia was not mentioned [54].

Sir-Petermann et al. [51] showed a dramatic increase in concentrations of androgens (testosterone, androstenedione, and DHEA-S) in women with PCOS during pregnancy. Androgens are of partially placental and ovarian origin. These androgen concentrations do not result in fetal masculinisation which could be explained by the coexistence of increased levels of estradiol, progesterone, SHBG, and also because of placental aromatase that converts androstenedione to oestrone and 16-hydroxytestosterone to estriol. Carlsen et al. [10] showed that although intrauterine metformin exposure seems to result in elevated SHBG levels in neonates, maternal and neonatal androgen and estrogen levels remain unaffected.

The study of pregnancy outcomes associated with the use of metformin among women diagnosed with PCOS is also important [28]. The use of metformin has been shown to reduce spontaneous abortion rates [28, 43, 56] through hyperinsulinemia control [57, 58] and/or reduction of serum androgens levels [46]. Jakudowicz et al. studied the correlation of miscarriage rates in patients with PCOS treated or not with metformin during their pregnancy. Metformin was used in 65 pregnant women with PCOS, while 31 of the control group did not use it. The abortion rate was 8.8 and 41.9%, respectively [46]. Nawaz et al. [9] showed that continuation of metformin during pregnancy significantly reduces from 49.9 to 12.5% early pregnancy loss in obese women with PCOS. In another study the incidence of spontaneous abortion was 17% in 72 women—of whom 62% had a spontaneous abortion experience and whose conception was completed with metformin use either throughout pregnancy or for the first 12 weeks of gestation [49]. Nevertheless, an increased risk of spontaneous abortion up to 35% in women with PCOS has been referred despite metformin use [59], and it has also been referred that metformin use is associated with an increased risk of preeclampsia in women with PCOS [49]. Palomba et al. [14] in a recent metaanalysis showed that preconceptional use of metformin has no effect on the abortion risk of women with PCOS. When the side effects of metformin in the infant have been studied, no teratogenesis, weight, and height problems or growth and psychosocial developmental defects in their first 18 months of life were mentioned [25, 49]. Bolton et al. [16] did not find any difference in major congenital malformation and/or need of neonatal intensive care between women with PCOS who continued or discontinued metformin use in the first trimester of pregnancy. Although metformin is excreted in breast milk, its concentration is minimal [60–62]. However, the puerperants are recommended to receive metformin for 2–3 h after breastfeeding [63, 64].

Although, Siasiakos et al. [17] commented that there is a plausible mechanism for PCOS to cause adverse pregnancy outcome relating to the action of insulin, the studies preceding their review had not been rigorous enough to prove it, some new studies since, notably by Palomba et al. [8, 11], add evidence of better quality to the possible but never proven direct (not due to obesity or iatrogenic) link between PCOS and outcomes. For example, Palomba et al. [8] concluded that uterine artery Doppler indices such pulsatility index (PI) and bilateral notch at first and mid-second trimester are commonly altered in pregnant women with PCOS than in controls showing predictive adverse perinatal outcomes. Moreover, Palomba et al. [11] showed that there is higher relative risk for adverse obstetric or neonatal outcomes in patients with the full-blown and non-PCO phenotypes than in those with the non-hyperandrogenic and ovulatory phenotypes.

It should be noted, however, that most of the above-mentioned studies are retrospective having different criteria for the women included. For example, Toulis et al. [15] mentioned the significant statistical heterogeneity among different studies which study the risk of gestational diabetes mellitus in women with PCOS. For this reason, they concluded that a correlation between gestational diabetes mellitus and PCOS is questionable [15]. Some use only ultrasound findings for the diagnosis of PCOS and others hormonal or clinical findings. Furthermore, BMI and the age of the women were conflicting parameters. A randomised controlled study including three groups of women (women with PCOS according to Rotterdam criteria treated with metformin, untreated women with PCOS and normal pregnant women) could offer useful results of the effectiveness

of metformin on perinatal outcome in pregnant women with PCOS.

Conclusion

The PCOS has an increased risk for maternal complications such as gestational diabetes, gestational hypertension, preeclampsia, and preterm labor. Especially, gestational diabetes is present independently of the obesity coexistence. The increased cesarean section rates of women with PCOS could be rather attributed to the obesity frequently seen in women with this syndrome. Perinatal morbidity and mortality are increased mainly due to the high incidence of maternal complications in women with PCOS. Metformin use seems to reduce the risk of miscarriage and diabetes mellitus. However, further studies are necessary in this field.

Conflict of interest statement None.

References

1. Lane DE (2006) Polycystic ovary syndrome and its differential diagnosis. Obstet Gynecol Surv 61(2):125–135
2. Azziz R (2004) PCOS: a diagnostic challenge. Reprod Biomed Online 8(6):644–648
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19(1):41–47
4. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS (2006) A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 12(6):673–683
5. Godoy-Matos AF, Vaisman F, Pedrosa AP, Farias ML, Mendonηa LM et al (2009) Central-to-peripheral fat ratio, but not peripheral body fat, is related to insulin resistance and androgen markers in polycystic ovary syndrome. Gynecol Endocrinol 25(12):793–798
6. de Boo HA, Harding JE (2006) The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol 46(1):4–14
7. Clapauch R, Mattos TM (2008) Triplet pregnancy after metformin in a woman with polycystic ovary syndrome. Fertil Steril 89(5):1260.e1-2
8. Palomba S, Falbo A, Russo T, Battista L, Tolino A, Orio F, Zullo F (2010) Uterine blood flow in pregnant patients with polycystic ovary syndrome: relationships with clinical outcomes. BJOG 117(6):711–721
9. Nawaz FH, Rizvi J (2009) Continuation of metformin reduces early pregnancy loss in obese Pakistani women with polycystic ovarian syndrome. Gynecol Obstet Invest 69(3):184–189
10. Carlsen SM, Vanky E (2010) Metformin influence on hormone levels at birth, in PCOS mothers and their newborns. Hum Reprod 25(3):786–790
11. Palomba S, Falbo A, Russo T, Tolino A, Orio F, Zullo F (2009) Pregnancy in women with polycystic ovary syndrome: the effect of different phenotypes and features on obstetric and neonatal outcomes. Fertil Steril doi:10.1016/j.fertnstert.2009.10.043
12. Legro RS, Roller RL, Dodson WC, Stetter CM, Kunselman AR, Dunaif A (2010) Associations of birthweight and gestational age with reproductive and metabolic phenotypes in women with polycystic ovarian syndrome and their first-degree relatives. J Clin Endocrinol Metab 95(2):789–799
13. Alshammari A, Hanley A, Ni A, Tomlinson G, Feig DS (2010) Does the presence of polycystic ovary syndrome increase the risk of obstetrical complications in women with gestational diabetes? J Matern Fetal Neonatal Med 27:1–5
14. Palomba S, Falbo A, Orio F Jr, Zullo F (2009) Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 92(5):1646–1658
15. Toulis KA, Goulis DG, Kolibianakis EM, Venetis CA, Tarlatzis BC, Papadimas I (2009) Risk of gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and a meta-analysis. Fertil Steril 92(2):667–677
16. Bolton S, Cleary B, Walsh J, Dempsey E, Turner MJ (2009) Continuation of metformin in the first trimester of women with polycystic ovarian syndrome is not associated with increased perinatal morbidity. Eur J Pediatr 168(2):203–206
17. Siassakos D, Wardle P (2007) Polycystic ovary syndrome and pregnancy outcome: red herring or red flag? BJOG 114(8):922–932
18. Ibαpez L, Jaramillo AM, Ferrer A, de Zegher F (2005) High neutrophil count in girls and women with hyperinsulinaemic hyperandrogenism: normalization with metformin and flutamide overcomes the aggravation by oral contraception. Hum Reprod 20(9):2457–2462
19. Talbott EO, Zborowski JV, Boudreaux MY, McHugh-Pemu KP, Sutton-Tyrrell K, Guzick DS (2004) The relationship between C-reactive protein and carotid intima-media wall thickness in middle-aged women with polycystic ovary syndrome. J Clin Endocrinol Metab 89(12):6061–6067
20. Diamanti-Kandarakis E, Paterakis T, Alexandraki K, Piperi C, Aessopos A, Katsikis I et al (2006) Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin. Hum Reprod 21(6):1426–1431
21. Orio F Jr, Palomba S, Cascella T, Di Biase S, Manguso F, Tauchmanovŭ L et al (2005) The increase of leukocytes as a new putative marker of low-grade chronic inflammation and early cardiovascular risk in polycystic ovary syndrome. J Clin Endocrinol Metab 90(1):2–5
22. Mφhlig M, Spranger J, Osterhoff M, Ristow M, Pfeiffer AF, Schill T et al (2004) The polycystic ovary syndrome per se is not associated with increased chronic inflammation. Eur J Endocrinol 150(4):525–532
23. Puder JJ, Varga S, Kraenzlin M, De Geyter C, Keller U, Móller B (2005) Central fat excess in polycystic ovary syndrome: relation to low-grade inflammation and insulin resistance. J Clin Endocrinol Metab 90(11):6014–6021
24. Glueck CJ, Wang P, Fontaine RN, Sieve-Smith L, Tracy T, Moore SK (1999) Plasminogen activator inhibitor activity: an independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism 48(12):1589–1595
25. Glueck CJ, Goldenberg N, Pranikoff J, Loftspring M, Sieve L, Wang P (2004) Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. Hum Reprod 19(6):1323–1330
26. Gilbert C, Valois M, Koren G (2006) Pregnancy outcome after first-trimester exposure to metformin: a meta-analysis. Fertil Steril 86(3):658–663
27. Sir-Petermann T, Hitchsfeld C, Maliqueo M, Codner E, Echiburï B, Gazitïa R et al (2005) Birth weight in offspring of mothers with polycystic ovarian syndrome. Hum Reprod 20(8):2122–2126

28. Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE (2002) Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 87(2):524–529
29. Rai R, Backos M, Rushworth F, Regan L (2000) Polycystic ovaries and recurrent miscarriage—a reappraisal. Hum Reprod 15(3):612–615
30. Sugiura-Ogasawara M, Sato T, Suzumori N, Kitaori T, Kumagai K, Ozaki Y (2009) The polycystic ovary syndrome does not predict further miscarriage in Japanese couples experiencing recurrent miscarriages. Am J Reprod Immunol 61(1):62–67
31. Tian L, Shen H, Lu Q, Norman RJ, Wang J (2007) Insulin resistance increases the risk of spontaneous abortion after assisted reproduction technology treatment. J Clin Endocrinol Metab 92(4):1430–1433
32. Homburg R, Levy T, Berkovitz D, Farchi J, Feldberg D, Ashkenazi J, Ben-Rafael Z (1993) Gonadotropin-releasing hormone agonist reduces the miscarriage rate for pregnancies achieved in women with polycystic ovarian syndrome. Fertil Steril 59(3):527–531
33. Glueck CJ, Sieve L, Zhu B, Wang P (2006) Plasminogen activator inhibitor activity, 4G5G polymorphism of the plasminogen activator inhibitor 1 gene, and first-trimester miscarriage in women with polycystic ovary syndrome. Metabolism 55(3):345–352
34. Palomba S, Orio F Jr, Falbo A, Russo T, Tolino A, Zullo F (2005) Plasminogen activator inhibitor 1 and miscarriage after metformin treatment and laparoscopic ovarian drilling in patients with polycystic ovary syndrome. Fertil Steril 84(3):761–765
35. Bayraktar F, Dereli D, Ozgen AG, Yilmaz C (2004) Plasma homocysteine levels in polycystic ovary syndrome and congenital adrenal hyperplasia. Endocr J 51(6):601–608
36. Jakubowicz DJ, Essah PA, Seppδlδ M, Jakubowicz S, Baillargeon JP, Koistinen R, Nestler JE (2004) Reduced serum glycodelin and insulin-like growth factor-binding protein-1 in women with polycystic ovary syndrome during first trimester of pregnancy. J Clin Endocrinol Metab 89(2):833–839
37. Balen AH, Tan SL, MacDougall J, Jacobs HS (1993) Miscarriage rates following in vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum Reprod 8(6):959–964
38. Engmann L, Maconochie N, Sladkevicius P, Bekir J, Campbell S, Tan SL (1999) The outcome of in vitro fertilization treatment in women with sonographic evidence of polycystic ovarian morphology. Hum Reprod 14(1):167–171
39. Winter E, Wang J, Davies MJ, Norman R (2002) Early pregnancy loss following assisted reproductive technology treatment. Hum Reprod 17(12):3220–3223
40. Wang JX, Davies MJ, Norman RJ (2002) Obesity increases the risk of spontaneous abortion during infertility treatment. Obes Res 10(6):551–554
41. Bellver J, Rossal LP, Bosch E, Zïρiga A, Corona JT, Melındez F et al (2003) Obesity and the risk of spontaneous abortion after oocyte donation. Fertil Steril 79(5):1136–1140
42. Nardo LG, Rai R, Backos M, El-Gaddal S, Regan L (2002) High serum luteinizing hormone and testosterone concentrations do not predict pregnancy outcome in women with recurrent miscarriage. Fertil Steril 77(2):348–352
43. Holte J (1998) Polycystic ovary syndrome and insulin resistance: thrifty genes struggling with over-feeding and sedentary life style? J Endocrinol Invest 21(9):589–601
44. Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A (2001) Obstetric outcome in women with polycystic ovarian syndrome. Hum Reprod 16(2):226–229
45. Jensen RB, Chellakooty M, Vielwerth S, Vaag A, Larsen T, Greisen G et al (2003) Intrauterine growth retardation and consequences for endocrine and cardiovascular diseases in adult life: does insulin-like growth factor-I play a role? Horm Res 60(Suppl 3):136–148
46. Diamant YZ, Rimon E, Evron S (1982) High incidence of preeclamptic toxemia in patients with polycystic ovarian disease. Eur J Obstet Gynecol Reprod Biol 14(3):199–204
47. Fridstrφm M, Nisell H, Sjφblom P, Hillensjφ T (1999) Are women with polycystic ovary syndrome at an increased risk of pregnancy-induced hypertension and/or preeclampsia? Hypertens Pregnancy 18(1):73–80
48. Kashyap S, Claman P (2000) Polycystic ovary disease and the risk of pregnancy-induced hypertension. J Reprod Med 45(12):991–994
49. Glueck CJ, Wang P, Goldenberg N, Sieve-Smith L (2002) Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. Hum Reprod 17(11):2858–2864
50. Gjψnnaess H (1989) The course and outcome of pregnancy after ovarian electrocautery in women with polycystic ovarian syndrome: the influence of body-weight. Br J Obstet Gynaecol 96(6):714–719
51. Sir-Petermann T, Angel B, Maliqueo M, Carvajal F, Santos JL, Pιrez-Bravo F (2002) Prevalence of Type II diabetes mellitus and insulin resistance in parents of women with polycystic ovary syndrome. Diabetologia 45(7):959–964
52. Bjercke S, Dale PO, Tanbo T, Storeng R, Ertzeid G, Abyholm T (2002) Impact of insulin resistance on pregnancy complications and outcome in women with polycystic ovary syndrome. Gynecol Obstet Invest 54(2):94–98
53. Hu S, Leonard A, Seifalian A, Hardiman P (2007) Vascular dysfunction during pregnancy in women with polycystic ovary syndrome. Hum Reprod 22(6):1532–1539
54. Boomsma CM, Fauser BC, Macklon NS (2008) Pregnancy complications in women with polycystic ovary syndrome. Semin Reprod Med 26(1):72–84
55. Weerakiet S, Srisombut C, Rojanasakul A, Panburana P, Thakkinstian A, Herabutya Y (2004) Prevalence of gestational diabetes mellitus and pregnancy outcomes in Asian women with polycystic ovary syndrome. Gynecol Endocrinol 19(3):134–140
56. Glueck CJ, Bornovali S, Pranikoff J, Goldenberg N, Dharashivkar S, Wang P (2004) Metformin, pre-eclampsia, and pregnancy outcomes in women with polycystic ovary syndrome. Diabet Med 21(8):829–836
57. Schachter M, Raziel A, Friedler S, Strassburger D, Bern O, Ron-El R (2003) Insulin resistance in patients with polycystic ovary syndrome is associated with elevated plasma homocysteine. Hum Reprod 18(4):721–727
58. Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanainen JS (2003) Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88(10):4649–4654
59. Heard MJ, Pierce A, Carson SA, Buster JE (2002) Pregnancies following use of metformin for ovulation induction in patients with polycystic ovary syndrome. Fertil Steril 77(4):669–673
60. Hale TW, Kristensen JH, Hackett LP, Kohan R, Ilett KF (2002) Transfer of metformin into human milk. Diabetologia 45(11): 1509–1514
61. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S (2005) Excretion of metformin into breast milk and the effect on nursing infants. Obstet Gynecol 105(6):1437–1441
62. Gardiner SJ, Begg EJ, Kirkpatrick CM, Buckham RB (2004) Metformin therapy and diabetes in pregnancy. Med J Aust 181(3):174–175
63. Checa MA, Requena A, Salvador C, Tur R, Callejo J, Espinós JJ et al (2005) The Reproductive Endocrinology Interest Group of the Spanish Society of Fertility. Insulin-sensitizing agents: use in pregnancy and as therapy in polycystic ovary syndrome. Hum Reprod Update 11(4):375–390
64. Simmons D, Walters BN, Rowan JA, McIntyre HD (2004) Metformin therapy and diabetes in pregnancy. Med J Aust 180(9):462–464