Pregnancy complications in women with polycystic ovary syndrome

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Submitted on September 25, 2014; resubmitted on May 31, 2015; accepted on June 4, 2015

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BACKGROUND: The great majority of studies performed so far concerning women diagnosed with polycystic ovary syndrome (PCOS) have focused on diagnosis, menstrual cycle abnormalities, hirsutism and infertility. Although progress has been made in developing methods for achieving a pregnancy and reducing multiple gestations in women with PCOS, little attention has been paid to pregnancy complications and subsequent child outcomes. This review aims to summarize current knowledge regarding the clinical and pathophysiological features of pregnancy and children in women with PCOS.

METHODS: A literature search up to April 2015 was performed in PubMed, Medline, the Cochrane Library and Web of Science without language restriction. All articles were initially screened for title and abstract and full texts of eligible articles were subsequently selected. Systematic reviews with meta-analysis were initially included for each specific subject. Recent randomised controlled trials (RCTs), which were not included in the systematic reviews, were also included. In addition to evidence from meta-analyses or RCTs, we used non-randomized prospective, uncontrolled prospective, retrospective and experimental studies. When specific data for patients with PCOS was lacking, results from general population studies were reported.

RESULTS: Women with PCOS exhibit a clinically significant increased risk of pregnancy complications compared with controls. Data which were not adjusted for BMI or other confounders demonstrated in PCOS a 3–4-fold increased risk of pregnancy-induced hypertension and pre-eclampsia, a 3-fold increased risk of gestational diabetes and 2-fold higher chance for premature delivery. Features characteristic of PCOS, such as hyperandrogenerism, obesity, insulin resistance and metabolic abnormalities, may contribute to the increased risk of obstetric and neonatal complications.
Limited available data suggest that offspring of women with PCOS have an increased risk for future metabolic and reproductive dysfunction. Underlying pathophysiological mechanisms of pregnancy complications along with its association with health of offspring remain uncertain. To date, the strategies for prevention and management of pregnancy complications in women with PCOS, and whether long-term health of these women is influenced, and to what extent, by pregnancy and/or pregnancy complications, remain to be elucidated.

**Conclusions:** Women with PCOS show an increased risk of pregnancy complications. Heterogeneous aetiological factors involved in PCOS and associated co-morbidities may all be involved in compromised pregnancy and child outcomes. In women with PCOS, a possible relationship with genetic, environmental, clinical and biochemical factors involved in this complex condition, as well as with pregnancy complications and long-term health for both mother and child, remains to be established.

**Key words:** complications / obstetrics / PCOS / polycystic ovary syndrome / pregnancy

**Introduction**

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by hyperandrogenism, ovarian dysfunction and polycystic ovarian morphology (PCOM). PCOS is more than just a reproductive disorder, and is currently considered a syndrome with metabolic consequences that could affect women’s health during different stages of reproductive and post-reproductive life (Dunaif and Fauser, 2013; Orio and Palomba, 2014).

The economic impact of PCOS is enormous. For example, the costs for the USA healthcare system to identify and manage PCOS are ∼4 billion dollars yearly, excluding the treatment of the serious conditions associated with PCOS, such as infertility, type 2 diabetes mellitus and cardiovascular disease (National Institute of Health, 2012). Over the years, the interest in reproductive health, cosmetics and the psychological and long-term health consequences of PCOS has increased.

Several data were published concerning maternal, neonatal and obstetric complications in women with PCOS. Three meta-analyses demonstrated an increased risk of pregnancy complication in women with PCOS (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013). Moreover, these results were not adjusted for BMI or other confounders, and were obtained after data synthesis from studies, largely retrospective or prospective, with relatively small sample sizes. Currently, more attention is paid to long-term implications of PCOS on maternal health in later life and the health of the offspring (Legro et al., 2014a; Silver, 2014). Notwithstanding this amount of published data, only a single consensus document discussed the effect of PCOS on pregnancy concluding that women with PCOS may be at increased risk for adverse pregnancy and neonatal outcomes (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). It was highlighted that the obstetric risk may be exacerbated by obesity and/or insulin resistance (IR) and a closer follow-up should be provided during pregnancy (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012).

An important issue in studying pregnancy complications in women with PCOS is the definition of the specific diagnostic features of PCOS, since the distinct variability in hormonal and metabolic abnormalities among various PCOS phenotypes could significantly influence the obstetric and neonatal outcomes observed (Palomba et al., 2010a; Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). The effect of obesity and/or IR and/or metabolic/hormonal abnormalities, which appear to vary across PCOS phenotypes, could play a crucial role (Moran et al., 2015). Although maternal factors can play an independent role in infertile patients not selected for PCOS (Romundstad et al., 2008), the time-to-pregnancy (Messerlian et al., 2013), the wide use of fertility drugs and treatments (Pinborg et al., 2013a, b; Malchau et al., 2014) and the potential higher rate of multiple pregnancies (Johnston et al., 2014) in infertile patients are all related to an increased relative risk of pregnancy complications. Although these data were obtained on infertile populations not selected for PCOS, the findings can be translated into infertile women with PCOS increasing the absolute risk of pregnancy complications up to clinically significant threshold.

In line with these considerations, the current comprehensive review was aimed at summarizing the current knowledge regarding pregnancy complications in women with PCOS and its potential pathophysiology.

**Methods**

For this review, an extensive literature search was performed in PubMed, Medline, the Cochrane Library and Web of Science. Literature available up to April 2015 was included.

The following keywords were used for the search, alone or in combination: polycystic ovary syndrome, polycystic ovary disease, polycystic ovaries, polycystic ovarian morphology, PCOS, PCOD, PCO, PCOM, oligoovulation, anovulation, oligomenorrhea, amenorrhea, hyperandrogenism, hirsutism, phenotypes, obesity, insulin resistance, weight gain, infertility, sterility, diabetes mellitus, gestational diabetes, pre-eclampsia, pregnancy-induced hypertension, offspring, maternal health, neonatal health, perinatal health, child health, pregnancy, delivery, labour, placenta, trophoblast, Caesarean section, pregnancy complications, obstetric complications, neonatal complications, perinatal complications, mortality, morbidity, systematic review, meta-analysis, randomized controlled trials, RCT. Additional journal articles were identified from the bibliography of the studies included.

All articles were initially screened for title and abstract without language restriction. Full texts of eligible articles were subsequently selected. Systematic reviews with meta-analysis were initially included for each specific subject. Recent published RCTs, which were not included in the systematic reviews, were also included. Besides evidence from meta-analyses or RCTs, we also used non-randomized prospective, uncontrolled prospective, retrospective and experimental studies. When specific data for PCOS patients were lacking, results from general population studies were reported.

**Pregnancy complications in women with PCOS**

Many studies have been performed comparing pregnancy outcomes in women with PCOS versus controls. Almost all retrospective and...
prospective studies concerning maternal, neonatal and birth complications have been summarized in three systematic reviews with meta-analyses (Boomsma et al., 2006; Kjerulf et al., 2011; Qin et al., 2013). The first meta-analysis, published in 2006, analysed 15 studies with a total of 720 women with PCOS and 4505 controls (Boomsma et al., 2006). An additional meta-analysis, published in 2011, included the same studies and added eight more recently published studies with a total of 2544 women with PCOS and 89 848 controls (Kjerulf et al., 2011). The most recent meta-analysis, published in 2013, added another four studies for a total of 27 studies involving 4982 women with PCOS and 119 692 controls (Qin et al., 2013). Table I shows the odds ratios (ORs) with 95% confidence intervals (CIs) of the three available meta-analyses for the most important pregnancy complications (Boomsma et al., 2006; Kjerulf et al., 2011; Qin et al., 2013).

Multiple pregnancy

Multiple pregnancies are the most important cause of the increased perinatal morbidity observed following fertility treatments, with special regard to women with PCOS affected by anovulatory infertility (Johnston et al., 2014). Most of the risk of pregnancy complications is due to the preterm delivery rates of multiple births. However, multiple pregnancies are also related to many other obstetric and neonatal complications (Johnston et al., 2014).

The higher incidence of multiple pregnancy in PCOS might underlie the poorer outcomes observed. Twin pregnancies have a 10-fold increased risk of small for gestational age (SGA) newborns and a 6-fold increased risk of premature delivery (Rao et al., 2004; Society of Obstetricians and Gynaecologists of Canada, 2014). The rates of perinatal mortality and admission to a neonatal intensive care unit (NICU) are about six and three times higher in twin pregnancies, respectively, compared with singletons (Rao et al., 2004). However, one meta-analysis showed no difference in multiple pregnancy rates between women with PCOS and controls, but comparison of outcomes from multiple pregnancies in women PCOS with controls was not possible because of the lack of stratification in the studies included (Boomsma et al., 2006).

Recently, a population-based cohort study (Løvvik et al., 2015) on 20 965 twin pregnancies showed that women with a previous diagnosis of PCOS had a higher risk of infants delivered preterm [risk ratio (RR) 1.96, 95% CI 1.05–1.36], very preterm (RR 1.82, 95% CI 1.30–2.53) and with low birthweight (RR 1.39, 95% CI 1.10–1.76). However, after adjusting for BMI and gestational age, the differences were no longer statistically significant (Løvvik et al., 2015).

Miscarriage

It is still debated whether women with PCOS have an increased risk of miscarriage compared with women without a fertility disorder. According to the PCOS consensus of 2012, miscarriage rates are suggested to be comparable, although available data show conflicting results (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). A meta-analysis of studies concerning women with and without PCOS undergoing IVF demonstrated no difference in miscarriage rates (OR 0.9, 95% CI 0.5–1.8; Heijnen et al., 2006). None of the nine studies included in this meta-analysis showed any difference in miscarriage rate. Recently, a large Australian study demonstrated that the miscarriage rate was more frequent in women with PCOS than in controls (20 versus 15%, respectively, \( P = 0.003 \)), although PCOS was not an independent risk factor for pregnancy loss but the miscarriage rate was strongly influenced by BMI (Joham et al., 2014a).

Pregnancy-induced hypertension and pre-eclampsia

All three meta-analyses (Boomsma et al., 2006; Kjerulf et al., 2011; Qin et al., 2013) reported a three to four times increased risk of pregnancy-induced hypertension (PIH) in women with PCOS (Table I). The majority of the studies included had a retrospective design, but no significant effect between outcome and study type (retrospective versus prospective) could be detected by meta-regression (Qin et al., 2013).

Women with PCOS also present a 3–4-fold increased risk of developing pre-eclampsia (PE) during pregnancy (Boomsma et al., 2006; Kjerulf et al., 2011; Qin et al., 2013). Similarly to PIH, many studies were retrospective, but no significant influence of study design on the results was found (Qin et al., 2013). In addition, all studies reporting on the incidence of PE described confounders, such as differences in parity, BMI and multiple pregnancies. Therefore, no sub-analysis for high-quality studies was performed (Boomsma et al., 2006). However, one Swedish population-based cohort study compared 3787 women with PCOS to 1 191 336

<table>
<thead>
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<th>Table I. Main data synthesis from three published meta-analyses on pregnancy complications in women with PCOS.</th>
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<td><strong>Outcome</strong></td>
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<td>Preterm delivery</td>
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<td>Neonatal</td>
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<td>SGA</td>
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<td>LGA</td>
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<td>Macrosomia</td>
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Data are ORs (95% CIs).

GMD, gestational diabetes mellitus; LGA, large for gestational age; PE, pre-eclampsia; PIH, pregnancy-induced hypertension; SGA, small for gestational age.
women without PCOS, and a significantly increased incidence of PE (OR 1.45, 95% CI 1.24–1.69) was found after adjusting for BMI and use of assisted reproductive technologies (ART; Roos et al., 2011).

More recently, two further studies on PIH and PE among women with PCOS were published (Naver et al., 2014; Palomba et al., 2014a). In the first study, a significantly increased risk of PE (OR 3.18, 95% CI 2.18–4.62) was observed in women with PCOS, however, this effect faded (OR 1.69, 95% CI 1.09–2.88) when adjusted for BMI and parity (Naver et al., 2014). However, when data were analysed for hyperandrogenic women with PCOS only, a significantly (OR 2.41, 95% CI 1.26–4.58) increased risk of PE was found (Naver et al., 2014). The second study was a case–control study showing a significantly increased risk of PIH and PE in a heterogeneous population of women with and without PCOS (12.7 and 8% versus 5.3 and 2%, respectively; Palomba et al., 2014a, b).

**Gestational diabetes mellitus**

Gestational diabetes mellitus (GDM) is the most commonly described pregnancy complication in women with PCOS. Its early diagnosis is crucial and its careful treatment significantly reduces the incidence of related maternal and neonatal complications (Ngai et al., 2014; Poolsup et al., 2014). The risk of GDM is about three times higher in women with PCOS (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013). A multicentre RCT, aimed at assessing the efficacy of metformin in reducing pregnancy complications in 274 pregnancies of women with PCOS, showed an incidence of GDM of 17.6 and 16.9% in the metformin and placebo group, respectively (Vanky et al., 2010). In the large Swedish study (Roos et al., 2011), GDM was more than 2-fold higher in pregnant women with PCOS (OR 2.32, 95% CI 1.88–2.88), also after adjusting data for confounders. More recently, in a large community-based cohort of reproductive-aged women, PCOS was independently associated with an increased risk of GDM (OR 2.1, 95% CI 1.1–3.9) after adjusting for age, BMI, hypertension, smoking and demographic factors (Joham et al., 2014b). A recent prospective study showed an incidence of GDM about three times higher in PCOS patients than in controls (14.7 versus 5.3%, respectively; Palomba et al., 2014a, b). Finally, a large prospective cohort study (de Wilde et al., 2014) demonstrated an even higher incidence of GDM (two or more plasma glucose levels exceeding the following cut-off points after a 100-g glucose load: fasting glucose ≥5.3 mmol/l, 1 h glucose ≥10.0 mmol/l, 2 h glucose ≥8.6 mmol/l and 3 h glucose ≥7.8 mmol/l (American Diabetes Association, 2003) of up to 22% in 189 women with PCOS. However, the data were not compared with a control group of women without PCOS.

**Other maternal complications**

Data on the risk of delivery by cesarean section in women with PCOS are controversial. One meta-analysis (Boomsma et al., 2006) reported a significantly higher Caesarean delivery risk (OR 1.56, 95% CI 1.20–2.02), whereas the other two meta-analyses (Kjerulff et al., 2011; Qin et al., 2013) demonstrated no significant influence of PCOS on the risk of a Caesarean section. The risk of assisted vaginal delivery was not higher in women with PCOS (Boomsma et al., 2006; Kjerulff et al., 2011).

**Fetal/neonatal outcomes**

Data regarding the increased incidence of adverse fetal outcomes in women with PCOS are inconclusive. Two meta-analyses (Boomsma et al., 2006; Kjerulff et al., 2011) demonstrated that women with PCOS have a 2-fold increased risk of preterm delivery in contrast to the most recent meta-analysis (Qin et al., 2013) which demonstrated no effect (Table I). No distinction has been made between induced or spontaneous preterm delivery. Therefore, it is not known whether preterm delivery was, for example, due to induction of labour because of placental insufficiency or for other reasons.

In a large cohort study (Roos et al., 2011), infants born to mothers with PCOS were more frequently delivered prematurely (OR 2.21, 95% CI 1.69–2.90) and had an increased risk of meconium aspiration (OR 2.02, 95% CI 1.13–3.61). Another recent cohort study confirmed an increased risk of preterm delivery (OR 2.28, 95% CI 1.51–3.45) (Naver et al., 2014). This increased risk was confined to hyperandrogenic women with PCOS (OR 2.78, 95% CI 1.62–4.77) since normoandrogenic women did not show an increased risk (OR 1.35, 95% CI 0.54–3.39).

The meta-analysis published in 2006 found no difference in risk for SGA neonates (Boomsma et al., 2006), whereas a later meta-analysis found an almost 2-fold increased risk of SGA (Kjerulff et al., 2011). These results were supported by a recent case–control study, which found a 2-fold increased risk for SGA infants in non-obese infertile women with PCOS who underwent ART compared with neonates of control patients with a tubal infertility factor (20.2 versus 11.5%, respectively; Han et al., 2011). In contrast, another recent study showed no difference between women with PCOS and controls regarding the risk of SGA (Naver et al., 2014). Only one meta-analysis reported incidences of large for gestational age (LGA) neonates and found no difference for this particular outcome between women with and without PCOS (Kjerulff et al., 2011). However, one population-based study demonstrated that neonates of patients with PCOS (compared with neonates of control patients with tubal factor) were more frequently LGA (OR 1.39, 95% CI 1.19–1.62; Roos et al., 2011). Obesity was a confounding factor. In fact, obese cases had a significantly increased incidence of LGA compared with obese controls (21.1 versus 0%, respectively), whereas the incidence of LGA in non-obese cases was not significantly different from non-obese controls (2.2 versus 4%, respectively; Han et al., 2011). Instead of LGA, one meta-analysis reported incidences of macrosomia, which turned out to be similar in women with and without PCOS (Boomsma et al., 2006). These findings are unexpected since, after correction for confounders, there was a significantly increased risk of GDM among women with PCOS, which is evidently related to the delivery of a LGA or macrosomic neonate (Ahlsson et al., 2010).

Recently, differences in fetal outcomes between women with and without PCOS have been observed only regarding fetal growth (Palomba et al., 2014a). Specifically, the rate of normal for gestational age neonates was significantly lower in PCOS compared with non-PCOS women (68.3 versus 87.3%, respectively, P = 0.001), whereas the incidence of SGA (15.9 versus 6.3%, respectively, P = 0.021) and LGA (12.7 versus 4.9%, respectively, P = 0.041) was significantly higher (Palomba et al., 2014a).

Neonates born to women with PCOS had a 2-fold increased risk for admission to the NICU (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013). An Apgar score lower than seven at 5 min was more frequent in neonates born to women with PCOS (OR 1.41, 95% CI 1.09–1.83; Roos et al., 2011). Moreover, perinatal mortality was evidently higher in women with PCOS (OR 3.07, 95% CI 1.03–9.21; Boomsma et al., 2006).
Offspring health

An overview of all studies concerning the offspring of women with PCOS is shown in Table II.

In general, children born to mothers with PCOS are considered to be at increased risk of developing endocrine and cardiovascular dysfunction (Kent et al., 2008; Battaglia et al., 2009). Increased cardiometabolic risk in offspring of women with PCOS is thought to be due to both genetic and environmental factors, starting within the intrauterine environment (Xu et al., 2014). According to the Barker-hypothesis, lifetime health can be strongly related to the intrauterine environment; i.e. being born to a mother who has suffered pregnancy complications may increase the risk of metabolic abnormalities, such as obesity and early IR, in PCOS offspring (Barker 1991; Battaglia et al., 2002; Kent et al., 2008; Sir-Petermann et al., 2009).

Women with PCOS are considered to have a reduced breastfeeding rate (Vanky et al., 2008) that resulted significantly related to midpregnancy androgen levels (Carlson et al., 2010). This could be a further risk factor for their offspring, since two systematic reviews demonstrated that children in a non-PCOS population who were not breastfed had a higher blood pressure and dyslipidemia in adult life compared with children who were breastfed (Owen et al., 2002; Martin et al., 2005). In addition, maternal obesity, as observed in women with PCOS, is causally related to a long-term increase in offspring adiposity (Lawlor et al., 2012). Moreover, offspring of women with PCOS may be at increased risk of cardiovascular diseases later in life because, in response to genetic and environmental risk factors, endothelial dysfunction can develop as early as the first decade of life (Boutzios et al., 2013). A higher systolic blood pressure has been demonstrated in offspring of mothers who developed GDM (Acetti et al., 2012). During adolescence of non-PCOS offspring, GDM seems to increase the systolic blood pressure, the cardiac output and the stroke volume, while it decreases the risk in total peripheral resistance compared with controls during stress (Krishnaveni et al., 2015). Thus, it is reasonable to suppose that the increased incidence of GDM observed in women with PCOS could influence negatively the cardiovascular risk factors of their offspring.

Research interest gradually shifted towards the follow-up of children (especially girls) born to women with PCOS. Studies performed so far usually started with children, sometimes comparing outcomes with retrospective data regarding pregnancy and mother. Daughters of women with PCOS show some features of PCOS before and during puberty (Battaglia et al., 2002; Sir-Petermann et al., 2009). Dehydroepiandrosteredione sulphate concentrations are increased in daughters of women with PCOS during the onset of puberty and around 30% have an exacerbated adenarche (Maliqueo et al., 2009). Girls with amplified adenarche associated with precocious pubarche were found to be at higher risk for ovarian hyperandrogenism in adolescence (Ibáñez et al., 1993; de Zegher and Ibáñez, 2006). This association was linked to prepubertal, pubertal and post-pubertal hyperinsulinaemia (Ibáñez et al., 1997). Early metformin treatment was reported to prevent or delay the development of hirsutism, androgen excess, oligomenorrhea and PCOS more effectively than late metformin (Ibáñez et al., 2011).

Little is known about the androgenic status of daughters of women with PCOS. One study observed increased testosterone levels during puberty in daughters of women with PCOS (Sir-Petermann et al., 2007). In PCOS daughters, hyperinsulinaemia and an increased ovarian volume are present before the onset of puberty and this persists during puberty (Maliqueo et al., 2009). A significant association was found between reduced fetal growth, infantile catch-up in weight, precocious pubarche and hyperinsulinaemic hyperandrogenism in adolescence in daughters of women who were not selected for PCOS (Ibáñez et al., 1998). In particular, reduced fetal growth with infantile catch-up growth is suggested to be a pathway to PCOS (de Zegher and Ibáñez, 2006). A modest advance in bone age has been observed as well in pubertal daughters of women with PCOS, possibly secondary to the hyperinsulinaemia or adrenal hyperandrogenism (Maliqueo et al., 2009).

Moreover, in a highly selected PCOS population, daughters of women with PCOS seem to have an increased risk of autism spectrum disorders, which is probably due to an unbalanced prenatal exposure to high testosterone levels (Palomba et al., 2012a). Considering the early onset and the nature of the alterations, daughters of women with PCOS are a high-risk group for metabolic and reproductive disorders (Sir-Petermann et al., 2009; Maliqueo et al., 2012).

Pre-pregnancy overweight in women with PCOS influences negatively the prevalence of preterm birth and the birthweight of the singleton newborn, as demonstrated by a recent retrospective analysis comparing overweight and normal-weight pregnant women with PCOS (De Fréne et al., 2014). On the other hand, as previously reported, the body weight of women with PCOS increases significantly more during pregnancy compared with healthy controls (Palomba et al., 2012b, c, 2014a). Thus, considering the prevalence of overweight and obesity in PCOS, many women with PCOS can either become obese or their obesity may worsen severely during and after pregnancy.

In this regard, excessive gestational weight gain has been associated with increased odds of childhood overweight/obesity, independent of several potential confounders (including PCOS) and mediators. Its impact seemed greater among normal-weight women, suggesting that the effect may be independent of genetic predictors of obesity (Sridhar et al., 2014). The timing of excessive gestational weight gain should also be taken into account as an important factor influencing offspring health (Davenport et al., 2013). Maternal obesity was closely related to an excess of all-cause mortality and to an increased hospital admission for cardiovascular events in their adult offspring (Reynolds et al., 2013). The findings above (Davenport et al., 2013; Reynolds et al., 2013; Sridhar et al., 2014) were obtained in populations that were not selected for PCOS.

Initial data on metformin administration in pregnant women with PCOS demonstrated a lesser weight gain during pregnancy when compared with controls who received placebo (Vanky et al., 2010; Carlsson et al., 2012), suggesting a potential role of the PCOS-related IR on gestational weight gain and of the metformin treatment on long-term complications in children.

In conclusion, available data suggest that women with PCOS have a 3–4-fold increased risk of PIH/PE and a 3-fold increased risk of GDM. After adjusting for confounders, the risk of PIH/PE and GDM is 1.5 and 2 times higher, respectively, in women with PCOS compared with women without PCOS. Data on miscarriages, preterm delivery and neonatal health are too few, contrasting and/or heterogeneous to be considered conclusive. At the moment, the impact of being born to a mother with PCOS on long-term child health is still unclear. However, risk factors for adverse child health, including excess preconception maternal weight, excess gestational weight gain and GDM suggest child health may be adversely affected in PCOS.
### Table II. Summary of studies performed in children of women with PCOS.

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<th>Study</th>
<th>Cases (n) Daughters</th>
<th>Controls (n) Daughters</th>
<th>Age (years) Cases versus controls</th>
<th>Outcomes</th>
<th>Conclusion</th>
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<td>Battaglia et al. (2002)</td>
<td>15</td>
<td>10</td>
<td>7.6 ± 0.6 versus 6.9 ± 0.6*</td>
<td>PCOM, endocrine profile, bone age</td>
<td>PCOS daughters have an increased risk of PCOM, which could be a sign of genetic predisposition</td>
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<tr>
<td>Crisosto et al. (2007)</td>
<td>28</td>
<td>33</td>
<td>11.4 ± 2.5 versus 11.5 ± 2.2*</td>
<td>AMH</td>
<td>Peripubertal PCOS daughters have an increased AMH</td>
</tr>
<tr>
<td>Sir-Petermann et al. (2007)</td>
<td>75</td>
<td>49</td>
<td>6.0 [4.0–9.0] versus 6.0 [4.0–9.0]*</td>
<td>Metabolic and endocrine profile</td>
<td>Prepubertal PCOS daughters have lower levels of adiponectin, higher levels of insulin after stimulation. Pubertal PCOS daughters have higher levels of testosterone, triglycerides, insulin after stimulation and lower levels of SHBG</td>
</tr>
<tr>
<td>Battaglia et al. (2009)</td>
<td>17</td>
<td>20</td>
<td>24.2 ± 3.7 versus 26.3 ± 4.3*</td>
<td>Hormonal and biochemical profile, ovarian blood flow, arterial stiffness, IR</td>
<td>Daughters of women with PCOS have an increased risk of cardiovascular diseases, due to a significantly increased blood pressure, arterial stiffness, and glucose and insulin levels</td>
</tr>
<tr>
<td>Sir-Petermann et al. (2009)</td>
<td>99</td>
<td>84</td>
<td>Average age 7–15 years</td>
<td>Ovarian volume, IR, metabolic and endocrine profile</td>
<td>PCOS daughters have IR and increased ovarian volume in prepuberty and puberty, and biochemical abnormalities in late puberty</td>
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<td>Maliqueo et al. (2009)</td>
<td>98</td>
<td>51</td>
<td>5.7 [3.9–7.6] versus 5.9 [3.7–6.4]*</td>
<td>Adrenal function, bone age</td>
<td>Increased serum DHEAS, exacerbated adrenarche, advance in bone age in PCOS daughters</td>
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<td>Kent et al. (2008)</td>
<td>17 and 15</td>
<td>21 and 17</td>
<td>Female 9.1 ± 3.4 versus 9.5 ± 3.0*</td>
<td>Reproductive and metabolic profile</td>
<td>Lower LH levels in PCOS daughters, midpubertal higher urinary testosterone in PCOS sons</td>
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<td>Palomba et al. (2012a)</td>
<td>13 and 17</td>
<td>24 and 21</td>
<td>Female 6.5 ± 1.9 versus 6.7 ± 1.8*</td>
<td>PDD</td>
<td>Daughters of hyperandrogenic PCOS women have a higher risk of PDD</td>
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<td>Anderson et al. (2010)</td>
<td>25 and 14</td>
<td>18 and 13</td>
<td>Neonates</td>
<td>Birthweight, endocrine profile in cord blood</td>
<td>No significant difference in birthweight. Estrogens and androstenedione were lower in offspring of PCOS women</td>
</tr>
<tr>
<td>Boutzios et al. (2013)</td>
<td>19 and 22</td>
<td>52 and 58b</td>
<td>Neonates</td>
<td>Anthropometric, metabolic, and endocrine profile, oxidative stress</td>
<td>PCOS neonates have a similar metabolic, hormonal and oxidative stress status as neonates of mother with GDM. Mothers and neonates have the same level of hyperandrogenism, hyperinsulinism and oxidative stress</td>
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<td>Barry et al. (2010)</td>
<td>10</td>
<td>20 and 10</td>
<td>Neonates</td>
<td>Fetal (intrauterine) environment</td>
<td>PCOS daughters are exposed to intrauterine hyperandrogenism</td>
</tr>
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</table>

AMH, anti-Müllerian hormone; DHEAS, dehydroepiandrostenedione sulphate; IR, insulin resistance; PCOM, polycystic ovary morphology; PDD, pervasive developmental disorders; SHBG, sex hormone binding globulin.

*Eumenorrheic, normal weight, non-hirsute daughters of women with PCOS.

*The control group consisted of 54 women who developed GDM during pregnancy and 56 healthy normo-ovulatory women.

*Mean ± SE.

*Mean ± SD.

*Median and range.
Pathophysiologic considerations regarding PCOS pregnancy complications

The increased incidence of pregnancy complications in women with PCOS can be the result of several coinciding factors. As detailed below, the features of PCOS, as well as other clinical and biochemical characteristics frequently associated with the syndrome, have also been related to obstetric/neonatal complications. These factors can, independently or in concert, play a role in the pathophysiology of adverse pregnancy outcomes in women with PCOS (Fig. 1).

Relevance of the heterogeneous PCOS features

Clinical and/or biochemical hyperandrogenism, ovarian dysfunction with related oligo-amenorrhea and PCOM are the three main criteria for the diagnosis of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004; Legro et al., 2013).

Hyperandrogenism might influence the risk of pregnancy complications, as shown from clinical data on the most frequent causes of the hyperandrogenic state during pregnancy (i.e. pregnancy luteoma and hyperreactio luteinalis; Kaňová and Bičíková, 2011; Makieva et al., 2014). In pregnant women with PCOS, androgen levels are significantly higher compared with non-PCOS controls (Sir-Peterman et al., 2002; Falbo et al., 2010) and increase significantly throughout pregnancy (Falbo et al., 2010). Although specific data on androgen synthesis, pharmacodynamics and pharmacokinetics during pregnancy in women with PCOS are scarce (Makieva et al., 2014), an abnormal steroidogenic function (Escobar et al., 2011) of the placenta in women with PCOS (Maliqueo et al., 2013) was demonstrated. Hyperandrogenic women with PCOS have a 4-fold increased risk of adverse pregnancy outcomes compared with healthy controls (Palomba et al., 2010a). In PCOS, hyperandrogenism is closely related to the incidence and extension of microscopic alterations in early trophoblast invasion and placentation (Palomba et al., 2012d, 2013a, 2014c). Serum testosterone and sex hormone-binding globulin (SHBG) concentrations in women with hypertensive complications of pregnancy are significantly increased and decreased, respectively (Urman et al., 1997; Acromite et al., 1999; Serin et al., 2001) suggesting that free testosterone might mediate hemodynamic changes underlying the development of PE by inducing a state of sympathetic and vascular hyperactivity (Shobel et al., 1996). High androgen levels could also affect neonatal weight, impairing the maternal energy homeostasis changes and the nutrient transport through the placenta and/or with a direct effect on fetal growth (Berger et al., 1984; Sir-Petermann et al., 2005; Falbo et al., 2010).

The alterations in endovascular trophoblast invasion and placentation may be the result of a suboptimal implantation process due to the direct effect of androgens on the endometrium and/or to a specific tissue susceptibility (Cakmak and Taylor, 2011; Kajihara et al., 2013). However, androgens can exert an action after the first phases of pregnancy as well. In animal models, the excess of maternal androgens decreases placental size, affects the ability of the placenta to deliver nutrients to the fetus, alters placental steroidogenesis and leads to dysregulation of lipid metabolism in the adult female offspring (Sun et al., 2012). Finally, androgens can increase the incidence of adverse pregnancy outcomes by acting on cervical remodelling and myometrial function (Makieva et al., 2014).

Figure 1  Potential causes of the increased risk in pregnancy complications in women with PCOS. All factors shown in the figure can increase the risk of obstetric/neonatal complications directly and/or through an altered trophoblast invasion and placentation. PCOM, polycystic ovarian morphology.
Women with oligo- or anovulation have a 5-fold increased risk of adverse pregnancy outcomes (Palomba et al., 2010a). Infertile women with ovulatory disorders have an increased risk (RR 1.52, 95% CI 1.23–1.87) of GDM, as demonstrated by large cohort study on 40,773 pregnancies (Tobias et al., 2013). In addition, the risk of having a significantly lower Apgar score at 5 min after delivery is two times higher among newborns of women with ovulatory dysfunction compared with newborns of non-PCOS controls (Grigorescu et al., 2014). Moreover, women who conceive without treatment after a long time-to-pregnancy period have an increased risk of preterm birth (OR 1.31, 95% CI 1.21–1.42; Messerlian et al., 2013). These findings remained significant after adjusting for relevant confounders using regression models (Messerlian et al., 2013). A recent document of the Society of Obstetricians and Gynaecologists of Canada underlines the increasing evidence that infertility/subfertility is an independent risk factor for obstetrical complications and adverse perinatal outcomes, even without the addition of ART (Society of Obstetricians and Gynaecologists of Canada, 2014). The effect of PCOM, as a single feature, on adverse pregnancy outcome was not significant in pregnant women with PCOS (Palomba et al., 2010a).

### PCOS-related infertility interventions

Although a proportion of women with PCOS may achieve pregnancy without intervention (Hudecova et al., 2009), the great majority shows anovulatory infertility. The contribution of infertility per se (Messerlian et al., 2013) and of the factors leading to infertility (Romundstad et al., 2008) to the increased risk of pregnancy complications is well defined. In fact, pregnancies achieved after a time-to-pregnancy of more than 12 months have more probability of ending prematurely and the children often present lower weight at birth than those born after a shorter time-to-pregnancy (Messerlian et al., 2013). In overweight or obese women with PCOS, a non-pharmacological intervention consisting of a combination of hypocaloric diet, increased physical activity and individualized behavioural modification plan can be effective in losing weight and maintaining the weight loss. It could improve natural and/or artificial reproductive outcomes (Norman et al., 2004; Maheshwari et al., 2007; Moran et al., 2009) reducing pregnancy complications related to excess body weight (see below). A clinical RCT aimed at assessing the impact of lifestyle intervention in reducing the rate of infertile overweight and obese women who need fertility treatment and in improving the reproductive outcomes is in progress (Mutsaerts et al., 2010). Ovulation induction is the first choice treatment in patients without obesity or in patients in whom a non-pharmacological approach has failed. Live birth is achieved in ~80% in women with PCOS undergoing treatment within 2 years (Veltman-Verhulst et al., 2012). Although there is a lack of evidence-based data in this area, infertility treatments are considered to be potential confounders in the evaluation of pregnancy complications in PCOS, both because of its possible direct effects on treatment-related multiple pregnancies (Fauser et al., 2005) and pregnancy (Pinborg et al., 2013a,b). Of note, women who delivered singletons after ovulation induction had a risk of preterm delivery which was significantly higher compared with women who conceived without ovulation induction within 1 year (OR 1.45, 95% CI 1.21–1.74; Pinborg et al., 2013a,b).

The traditional first choice ovulation induction treatment in women with PCOS and anovulatory infertility is the anti-estrogen clomiphene citrate (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008; Balen, 2013). This view, however, is challenged by a recent well-designed RCT suggesting higher live birth rates using the aromatase inhibitor letrozole (Legro et al., 2014b). A low but significantly higher incidence of multiple pregnancies was observed in patients with PCOS treated with clomiphene citrate compared with patients who received metformin (Legro et al., 2007) or letrozole treatment (Legro et al., 2014b). Recently, a 60% increased risk for SGA has been detected in women who conceived after clomiphene citrate ovulation induction followed by intrauterine insemination (IUI) compared with women who conceived after IUI in natural cycles (OR 1.6, 95% CI 1.2–2.4; Malchau et al., 2014). Both clomiphene citrate and letrozole are considered teratogenic by the US Food and Drug Administration (FDA) and their use as ovulation inductors has been suggested to be associated with birth defects (Palomba, 2015). Moreover, recent data demonstrated a very low incidence of congenital malformations (Legro et al., 2014b) and no different from those observed in women who conceived naturally (Sharma et al., 2014). More studies are needed to substantiate these findings (Palomba, 2015).

Since intrinsic IR is a typical characteristic of women with PCOS (Diamanti-Kandarakis and Dunaf, 2012) with a prevalence ranging from 75 to 95% according to BMI (Sepoto et al., 2013), a large amount of studies have been performed to investigate the effect of insulin sensitizers on ovulation induction, particularly the biguanide metformin (Palomba et al., 2009b). Currently, the use of metformin is not recommended as an infertility drug (Tarlatzis et al., 2008; Legro et al., 2013) due to negative results of the largest RCT comparing metformin to clomiphene citrate (Legro et al., 2007). However, its use is still common in clinical practice (Conway et al., 2014). A meta-analysis including PCOS patients with a BMI < 32 kg/m² demonstrated that clomiphene citrate did not result in better outcomes compared with metformin treatment (Misso et al., 2013). The miscarriage rate of women with PCOS who received metformin was statistically similar to that observed after clomiphene citrate administration (Tang et al., 2012). Metformin addition to common fertility drugs did not improve the miscarriage rate (Palomba et al., 2009c; Tang et al., 2012) and no clinically significant benefit on reproductive outcomes was demonstrated in PCOS patients when metformin was co-administered with gonadotrophin in IVF and non-IVF cycles or during pregnancy (Lautatzis et al., 2013; Palomba et al., 2013b, 2014d). Although a well-designed multicentre, randomized, double-blind, placebo-controlled trial (Morin-Papunen et al., 2012) confirmed no specific effect of metformin pretreatment and co-treatment in infertile women with PCOS who received standard treatment on miscarriage rate (15.2 versus 17.9%, for metformin and placebo arm, respectively; P = 0.080), metformin significantly improved the pregnancy (53.6 versus 40.4%, for metformin and placebo arm, respectively; P = 0.006) and live birth (41.9 versus 28.8%, for metformin and placebo arm, respectively; P = 0.014) rates. Finally, a recent meta-analysis (Cassina et al., 2014) demonstrated no effect on major malformations (OR 0.86, 95% CI 0.18–4.08) or any effect on fetal growth and perinatal outcome in women with PCOS who discontinued the treatment at the moment of diagnosing a pregnancy compared with women who were treated with metformin during the first trimester of pregnancy. In conclusion, metformin should be considered as safe but scientific data are still scarce to recommend its use to improve reproductive/pregnancy outcomes in women with PCOS in clinical practice (Teede et al., 2011).

Ovulation induction with gonadotrophins is indicated when clomiphene citrate resistance or failure has occurred (Thessaloniki ESHRE/
ASRM-Sponsored PCOS Consensus Workshop Group, 2008). No difference in any outcome among different gonadotrophins has been demonstrated (Nugent et al., 2000). Miscarriage rates of 12.5% have been reported and the multiple pregnancy rates varied between 4 and 18% (Hamilton-Fairley et al., 1991; Balen et al., 1994; Christin-Maire et al., 2003). Safety data of gonadotrophin administration on maternal and neonatal wellbeing were not specific for PCOS populations and considered all old premarketing studies (Palomba et al., 2009a). Laparoscopic ovarian drilling is the third treatment choice, after clomiphene citrate and gonadotrophins, for women with anovulatory PCOS; the miscarriage rate was low (~4–9%), like the number of women who had a multiple pregnancy (<10%; Farquhar et al., 2012). IVF or ICSI are the last procedures suggested for treating infertility in patients with PCOS (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). The reproductive outcomes of IVF in PCOS patients were not different from controls without PCOS (Heijnjen et al., 2006). However, the risk of GDM was increased in patients who received ART compared with those who did not receive ART (OR 1.28, 95% CI 1.20–1.37); that risk remained the same for mothers who had singletons (OR 1.26, 95% CI 1.18–1.36) but not for women who had twins (OR 1.18, 95% CI 0.94–1.48; Wang et al., 2013). No significant increased risk of birth defects was associated with IVF after adjustment for parental factors (Davies et al., 2012). Furthermore, an increased risk of birth defects associated with ICSI was observed, likely due to the assisted reproduction procedure itself or to the increased incidence of male factor (Davies et al., 2012; Pandey et al., 2012). In conclusion, because anovulatory infertility is associated with PCOS, the use of ovulation inducers and ART could increase the absolute risk of pregnancy complications in PCOS populations. Furthermore, specific data about the effect of interventions for infertile patients with PCOS on obstetric and neonatal risk are limited.

PCOS-related comorbidities

Obesity is the comorbidity most closely related to PCOS (Lim et al., 2012; Sirmans and Pate, 2013), which is more prevalent in the more severe PCOS phenotypes and aggravates the reproductive phenotype (Morgan et al., 2015). Thus, it is intuitive that a high proportion of women with PCOS, independently of PCOS itself, experience the deleterious effects of overweight/obesity on maternal and fetal wellbeing (Cedergren, 2004; Lawlor et al., 2012; Stuebe et al., 2012; Cnattingius et al., 2013; Johansson et al., 2014). Obesity increases the general risk of miscarriage (Metwally et al., 2008). Obese women with or without PCOS have an increased risk of maternal complications, such as thromboembolism (Larsen et al., 2007; Guelinckx et al., 2008) and PIH/PE (Sattar et al., 2001; Abdollahi et al., 2003; O’Brien et al., 2003). Visceral obesity, a typical feature of women with PCOS (Lim et al., 2012), is associated with a 2- and 3-fold increased risk of PIH and PE, respectively (Sattar et al., 2001; Abdollahi et al., 2003). Recent data suggest that the risk of PE in obese patients is correlated positively with body fat (Sween et al., 2015). When obesity and PCOS features are simultaneously present, their effects on pregnancy may amplify the absolute risk. A meta-analysis demonstrated that all studies in which PE was used as primary end-point reported a higher BMI in women with PCOS versus controls (Boomsma et al., 2006).

Obese women have an increased risk of assisted vaginal delivery and Caesarean delivery, especially when combined with excessive gestational weight gain (Dietz et al., 2005; Yu et al., 2006). A linear trend was observed between maternal BMI before conception and the risk for both elective and unplanned Caesarean section (Barau et al., 2006; Guelinckx et al., 2008).

Obesity is an independent risk factor for the development of GDM (Yogev and Catalano, 2009) and this risk is positively associated with BMI before conception (Torloni et al., 2009). Among GDM patients, the risk of other maternal and fetal complications was higher in women with PCOS compared with women without PCOS (Palomba et al., 2012b, c). Clinical observations demonstrated higher gestational weight gain in women with PCOS than in BMI-matched non-PCOS controls suggesting that the extension of weight gain can be an important co-factor for the increased adverse short and long-term effects of pregnancy on PCOS and vice versa (Palomba et al., 2014a, b, c). Of note, women with PCOS, especially when obese, have an increased incidence of symptoms of sleep-disordered breathing (Legro et al., 2013; Shreeve et al., 2013) that are independent risk factors for pregnancy complications (Bisson et al., 2014; Pamidi et al., 2014).

Finally, fetuses of obese mothers have an increased risk of developing abnormalities such as neural tube defects (Rasmussen et al., 2008), congenital heart defects (Cai et al., 2014) and omphalocele (Srimri and Dimitrios, 2010). Associations between maternal obesity and an increased risk of macrosomia or LGA (Guelinckx et al., 2008), preterm delivery (McDonald et al., 2010; Cnattingius et al., 2013), stillbirth (Chu et al., 2007), admission to the NICU (Stothard et al., 2009) and infant mortality (Salihu et al., 2007; Johansson et al., 2014) have been demonstrated as well.

IR with compensatory hyperinsulinaemia is probably one of the cornerstones in the pathogenesis of PCOS and in the development of short- and long-term complications related to PCOS (Diamanti-Kandarakis and Dunaif, 2012). A disturbed insulin action is present already early in pregnancy in women with PCOS who develop GDM (de Wilde et al., 2015). However, IR is associated with and modulated by total body fat and central fat mass (Morgan et al., 2015). A normal pregnancy induces a state of hyperinsulinaemic IR in order to ensure constant metabolic supplies to the growing fetus (Hodson et al., 2013). However, women with PIH/PE had distinctly elevated insulin levels compared with women with an uncomplicated pregnancy (Lorentzen et al., 1998), suggesting a crucial role of the abnormal hyperinsulinaemic IR in the development of hypertensive disorders in pregnancy (Mikola et al., 2001; Haakova et al., 2003; Seely and Solomon, 2003). The risk of spontaneous abortion was more than 8-fold higher in insulin resistant versus non-insulin resistant women, whereas no difference was found in women with PCOS versus women without PCOS, suggesting that IR is an independent risk factor for miscarriage (Tian et al., 2007). Serum levels of insulin-like growth factor binding protein-1 and glycodeolin, biochemical markers of IR, were lower and related to the extent of endovascular trophoblast invasion in pregnant women with PCOS (Palomba et al., 2012d). IR may influence the risk of miscarriage through several direct and indirect mechanisms of action (Irwin et al., 2001; Seppälä et al., 2002; Cakmak and Taylor, 2011; Lam et al., 2011; Chakraborty et al., 2013a, b). Increasing observations link metabolic abnormalities to an increased risk of pregnancy complications. An association between type 2 diabetes or GDM with pregnancy complications was demonstrated (Horvath et al., 2010). However, the risk of PIH (OR 4.43, 95% CI 1.17–16.72), preterm deliveries (OR 1.92, 95% CI 1.12–3.42) and hyperbilirubinaemia (OR 3.18, 95% CI 1.14–8.82) was significantly higher in patients with both PCOS and GDM compared with women.

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who only developed GDM, even after adjusting for confounders (Alshammari et al., 2010).

Several studies correlated serum lipid concentrations with obstetric or neonatal outcomes, especially with PIH and PE (Lorentzen and Henrik-sen, 1998; Enquobahrie et al., 2004; Ray et al., 2006; Catov et al., 2007; Baker et al., 2009; Magnussen et al., 2011; Jan et al., 2012; Vrijkotte et al., 2012). A lot of metabolic changes are physiological in normal pregnancy. Visceral fat accumulation and hyperlipidaemia, which are metabolic adaptations to support fetal growth, are two of the most important changes in lipid metabolism associated with gestation (Herrera and Ortega-Senovilla, 2010). Women with PCOS have higher serum low-density lipoprotein (LDL) and triglyceride (TG) concentrations before and during pregnancy compared with healthy controls (Palomba et al., 2014b). After adjusting for confounders, serum LDL and TG levels during pregnancy were directly and independently related to pregnancy complications (Palomba et al., 2014b). Although the role of LDL and TG in the pathogenesis of obstetric complications in women with PCOS is not entirely clear, it can be hypothesized that elevated plasma lipid concentrations may induce endothelial dysfunction due to oxidative stress from free radicals, lipid peroxides and vascular damage (Kaaja et al., 1995; Hubel, 1998; Sattar et al., 1998).

Increased free radicals are part of the inflammatory changes observed in pregnancy, along with activation of peripheral blood leucocytes, increased white blood cells (WBC), ferritin, and C-reactive protein (CRP) levels, and production of pro-inflammatory cytokines (Sacks et al., 1998; Kühnert and Schmidt, 2000; Valsamakis et al., 2010; Cao and O’Brien, 2013). Moreover, an abnormal low-grade inflammatory state during pregnancy had an effect on the pathogenesis of adverse pregnancy and neonatal outcomes (Wolf et al., 2003; Sacks et al., 2004; Vanky et al., 2008; Du et al., 2013) with particular regard for the development of PIH/PE, glucose intolerance and GDM (Wolf et al., 2003; Sacks et al., 2004; Du et al., 2013; Parchim et al., 2015). Specifically, first-trimester CRP levels were significantly related to the risk of developing GDM (RR 3.6, 95% CI 1.2–11.4 comparing highest CRP tertile versus lowest tertile) in a cohort of pregnant women unselected for PCOS (Wolf et al., 2003). This inflammatory response was generalized and it seemed to mediate the vascular damage seen in PE and intrauterine growth restriction (Sir-Petermann et al., 2002; Parchim et al., 2015). Even if PCOS is not universally considered an inflammatory process, a state of low-grade chronic inflammation is known to be associated with this condition and with PCOS-related IR (Carmina et al., 2006; Duleba and Dokras, 2012; González, 2012). A recent clinical study demonstrated that, during pregnancy, the absolute values and the increase of low-grade chronic inflammation markers were higher in women with PCOS than in healthy controls (Palomba et al., 2014a). This suggests that pregnancy could enhance the chronic low-grade inflammation, which is typical for PCOS. Moreover, a significant and direct association between low-grade chronic inflammation markers, such as WBC, CRP and ferritin levels, and the risk of adverse obstetric/neonatal outcomes was demonstrated in women with PCOS (Palomba et al., 2014a).

**Placenta**

Hormone-independent alterations in important pathways in the regulation of placenta nutrient transport for fetal growth in women with PCOS have been recently detected, suggesting that the placenta in PCOS could be altered (Maliqueo et al., 2015). However, the placenta may be also a common target of all aberrations observed during pregnancy in women with PCOS. Trophoblast and placental tissue of women with PCOS are hyperandrogenic and/or insulin resistant micro-environment targets of epigenetic factors, including infertility treatments (Palomba et al., 2014c).

The placenta of women with PCOS, also in uncomplicated pregnancies, shows histological changes (i.e. chronic villitis/intervillitisosis and increased thickness of stem villi arterial walls) compatible with local micro-vascular and inflammatory damage (Palomba et al., 2013a). These findings vary according to the PCOS phenotype (Palomba et al., 2014c) and reflect subclinical alterations which have already been described in non-pregnant women with PCOS, i.e. low-grade chronic inflammation (Orio et al., 2005) and/or endothelial impairment (Orio et al., 2004). Thus, an abnormal pattern of low-grade chronic inflammation in combination with a subclinical impairment of vascular structure and function could result in a hypoxic state with abnormalities of physiological changes and remodelling of spiral vessels, with subsequent reduced depth of endovascular trophoblast and abnormal placentalization (Murray, 2011). These abnormalities of the utero-placental circulation have been confirmed by Doppler velocimetry in pregnant women with PCOS (Palomba et al., 2010b, 2012d).

Potential compensatory morphometric adaptations of the placenta were also observed in women with PCOS (Palomba et al., 2013a) suggesting that placental plasticity (Coan et al., 2010) may improve the materno-fetal oxygen and nutrient transfer during normal pregnancy. In PCOS, a reduced placental plasticity, due to impaired trophoblast invasion and/or the impossibility of further compensatory adaptations to external noxae, may be the keystones for the development of subsequent complications (Palomba et al., 2012d, 2013a).

In conclusion, PCOS and its diagnostic features, play a crucial role in the increased risk of the pregnancy complications observed. Several features (such as IR, metabolic alterations and chronic low-grade inflammation and/or clinical comorbidities (such as obesity or type 2 diabetes) closely related to the syndrome could increase that risk to a clinically significant threshold. All potential risk factors could influence the risk of obstetric/neonatal complications directly and/or through altered trophoblast invasion and placentalization (Fig. 1). However, pregnancy complications in women with PCOS could also be the result of a primary subclinical dysfunction of the placenta.

**Prevention and management of pregnancy complications in women with PCOS**

Evidence-based data on the efficacy of preconception weight loss as intervention for preventing pregnancy complications are limited (Agha et al., 2014). Since almost all observational findings showed a lower risk of obstetric and neonatal adverse outcomes in normal-weight women (versus overweight/obese), losing weight before conception up to an optimal body weight is suggested (American College of Obstetricians and Gynecologists, 2013).

Pregnant obese women, irrespective of PCOS, should be informed about the beneficial effects of dietary and/or physical activity during pregnancy on the gestational weight gain (Agha et al., 2014) and the risks of PE (RR 0.74, 95% CI 0.60–0.92) and shoulder dystocia (RR
Different pharmacological measures have been proposed in women with PCOS during pregnancy in order to reduce the obstetric and neonatal risks even if the drugs tested in that population are few. Indeed, most of the data available concerns metformin. Metformin is effective and safe for the treatment of GDM (Balsells et al., 2015), particularly for overweight and obese women. Potential advantages for the use of metformin over insulin in GDM were suggested regarding maternal weight gain during pregnancy, neonatal outcomes (including less visceral fat) and patient compliance (Rowan et al., 2008; Lautatzis et al., 2013; Sivalingam et al., 2014). Moreover, patients with PCOS and multiple risk factors for IR may not meet their treatment goals with metformin alone (Romualdi et al., 2013), and may require supplementary insulin (Lautatzis et al., 2013). However, the beneficial effects of metformin on GMD are more significant in non-RCTs (Zhuo et al., 2014). In fact, the only RCT on metformin administration through pregnancy in women with PCOS did not show any effect on the prevalence of GDM, despite the finding of reduced maternal weight gain observed during pregnancy (Vanky et al., 2010). Thus, it is still unknown whether prophylactic metformin administration can really reduce the incidence of GDM and the weight gain during pregnancy in women with PCOS providing long-term benefits for mother and baby (Sivalingam et al., 2014).

Data regarding the potential effect of metformin on the prevention of PIH and/or PE are scarce. Metformin administration during pregnancy reduced uterine artery impedance between 12 and 19 weeks of gestation (Salvesen et al., 2007). Thus, its administration in the early phases of pregnancy might influence the trophoblastic invasion of the maternal decidua allowing a successful placentation with consequent improvement of the pregnancy outcomes. Moreover, at present, clinical data seem to show a limited effect of metformin in preventing PIH and PE (Palomba et al., 2009b).

The studies that have evaluated other classes of drugs, such as low-molecular-weight heparin (LMWH) and acetylsalicylic acid (ASA) were few and on small sample sizes. ASA and LMWH, as monotherapy or a combined scheme, prevented spontaneous abortion and recurrent pregnancy loss in 336 PCOS patients with hyperhomocysteinaemia (Chakraborty et al., 2013a, b), and LMWH, alone or combined with metformin, reduced pregnancy loss in a little sample of 21 women with PCOS and coagulation disorders without any maternal–fetal side effects (Ramidi et al., 2009).

In conclusion, pregnant women with PCOS should be informed of the additional risks of their pregnancy in order to facilitate closer maternal/fetal surveillance and, thus, perform preventive and therapeutic interventions early, particularly for the more severe PCOS phenotypes. Although a close monitoring during pregnancy is suggested in women with PCOS, at the moment no specific guideline for preventing and managing pregnancy complication in PCOS patients is available, and clinical suggestions can be extrapolated only from populations with similar characteristics.

**Conclusion and future perspectives**

At the moment, there are more questions than answers concerning the association between pregnancy complications and PCOS.

Firstly, women with PCOS show an increased risk of pregnancy complications, but the specific mechanisms involved remain unclear. Available studies suggest that PCOS-related features, such as hyperandrogenism,
IR, obesity, dyslipidaemia and chronic low-grade inflammation, may play a crucial role in the first phases of pregnancy, i.e. during trophoblast invasion and placentation, and similarly to increase the long-term risk for mothers and children. In addition, pregnancy in PCOS patients can abnormally increase the usual physiological metabolic and inflammatory changes observed during pregnancy (Williams, 2003), worsening that risk.

Secondly, data on the effectiveness of intensive obstetric monitoring in pregnant women with PCOS are also lacking, as are potential monitoring strategies. Thus, the prevention of pregnancy complications in women with PCOS is a field of scientific interest, especially when they are affected by the more severe PCOS phenotype and/or when many other comorbidities and cofactors can increase the absolute risk to a clinically relevant threshold. Furthermore, few data are available in the literature on non-pharmacological and pharmacological interventions in pregnant women with PCOS. Recent data suggest specific clinical, biochemical and proteomic markers (de Wilde et al., 2014; Palomba et al., 2014a, b; Khan et al., 2015) as potential diagnostic tools to facilitate the identification of high-risk patients for obstetric and/or neonatal complications in pregnant populations with PCOS. Moreover, specific cut-offs need to be defined and/or their external validity confirmed.

Thirdly, possible effects of the reproductive history (including non-complicated and complicated pregnancies) of natural and assisted conceptions in women with PCOS on long-term maternal and offspring health are unknown. In fact, only 4.8 and 5.7% of studies of all clinical research in infertility reported on maternal and children outcomes, respectively (Brakhekke et al., 2014), and data on the short- and long-term health of mother and baby are scarce in the general infertility literature, let alone in relation to PCOS.

Serum testosterone levels in parous women are lower when compared with nulliparous women suggesting that (non-complicated) pregnancy could induce a long-term suppression of ovarian steroidogenesis and a better cardiometabolic profile (Barrett et al., 2014). Moreover, hyperandrogenic women with PCOS could be less likely to achieve a pregnancy either spontaneously or following infertility treatment (Imani et al., 1999, 2000) and have an increased risk for metabolic dysfunction and associated diseases later in life irrespective of parity or obstetric history. In this regard, the effect of hyperandrogenism on cardiovascular diseases after menopause is debated (Shaw et al., 2008; Moran et al., 2010; Wild et al., 2010; Polotsky et al., 2012, 2014; Daan et al., 2014). On the other hand, in women with PCOS, it is not known whether the complicated pregnancy increase the risk of long-term cardiovascular and metabolic disease of mothers with PCOS per se. Pregnancy complications could influence long-term maternal health independently of the presence of cardiovascular risk factors before pregnancy. In fact, more and more data suggest that pregnancy-related disorders, such as PIH, PE or GDM, are associated with an increased risk of development of type 2 diabetes (Feghali and Miodovnik, 2013; Feig et al., 2013), and of future maternal cardiovascular disease and mortality (Smith et al., 2001; Bellamy et al., 2007, 2009; Sabour et al., 2007; Veltman-Verhulst et al., 2010; Fraser et al., 2012). On the other hand, it is not possible to exclude that the underlying risk factors that lead to pregnancy complications may also lead to long-term health problems (Sattar et al., 2003). Independent epigenetic factors could affect the future history of the patient with PCOS. In particular, patients with the more metabolically disturbed PCOS phenotype could have an increased risk of obstetric/neonatal complications and these may, in turn, impair long-term outcome. On the other hand, patients with a milder PCOS phenotype and with fewer metabolic alterations may experience a complicated pregnancy and these events could significantly worsen the long-term cardiovascular risk for women with PCOS. In this view, the obstetric history could act as a sensitive screening tool to identify subgroups of young women with PCOS particularly at risk for cardiovascular diseases in order to suggest long-term follow-up by specialist referral and to influence the modifiable co-morbidities such as obesity (Spaan et al., 2012, Cusimano et al., 2014).

Finally, the long-term effects on offspring health of women with PCOS also remains to be explored, although an increasing body of data obtained in populations not selected for PCOS seems to suggest that both sons and daughters of women with PCOS can have an increased risk of future metabolic and reproductive dysfunction.

Future research is needed to clarify all previously mentioned experimental and clinical aspects. When the association between pregnancy complications and PCOS is clarified, wide interventional studies should be designed with the aim of reducing the risk of obstetric and neonatal complications in women with PCOS.

Authors’ roles

S.P. and B.C.J.M.F. gave substantial contributions to the conception or design of the work, the acquisition, analysis or interpretation of data; M.A.W., A.F., M.P.H.K. and G.B.L.S. gave substantial contributions to the acquisition and analysis of data. All authors (S.P., M.A.W., A.F., M.P.H.K., G.B.L.S. and B.C.J.M.F.) drafted and revised the manuscript, approved the final version and gave their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

The preparation of this manuscript was self-funded. No financial sponsor played any role in the design, execution, analysis and interpretation of data, or writing of the study.

Conflict of interest

B.C.J.M.F. received fees and grant support from the following companies (in alphabetic order); Actavis, Andromed, Ardana, COGI, Euroscreen, Finox Biotech, Ferring, GenOvum, Gedeon-Richter, Merck Serono, MSD, Organon, OvaScience, Pantharei Bioscience, PregLem, Roche, Schering, Schering Plough, Serono, Uteron, Watson laboratories and Wyeth. No commercial conflict of interest is declared by other authors (S.P., M.A.W., A.F., M.P.H.K. and G.B.L.S.).

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