Human Reproduction Update, Vol.21, No.5 pp. 575–592, 2015
Advanced Access publication on June 27, 2015 doi:10.1093/humupd/dmv029

human reproduction update

Pregnancy complications in women with polycystic ovary syndrome

Stefano Palomba[1,*], Marlieke A. de Wilde[2], Angela Falbo[1], Maria P.H. Koster[2], Giovanni Battista La Sala[1,3], and Bart C.J.M. Fauser[2]

[1]Unit of Gynecology & Obstetrics, IRCCS - Arcispedale Santa Maria Nuova, Viale Risorgimento 80, Reggio Emilia 42123, Italy [2]Department of Reproductive Medicine & Gynecology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584 CX, The Netherlands [3]University of Modena and Reggio Emilia, Via Università 4, Modena 41100, Italy

*Correspondence address. E-mail: stefanopalomba@tin.it

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

TABLE OF CONTENTS

- Introduction
- Methods
- Pregnancy complications in women with PCOS
  - Multiple pregnancy
  - Miscarriage
  - Pregnancy-induced hypertension and pre-eclampsia
  - Gestational diabetes mellitus
  - Other maternal complications
  - Fetal/neonatal outcomes
  - Offspring health
- Pathophysiologic considerations regarding PCOS pregnancy complications
  - Relevance of the heterogeneous PCOS features
  - PCOS-related infertility interventions
  - PCOS-related comorbidities
  - Placenta
- Prevention and management of pregnancy complications in women with PCOS
- Conclusion and future perspectives

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 were 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 hyperandrogenism, 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; Kjerulff *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 (Kjerulff *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; Kjerulff *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; Kjerulff *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; Kjerulff *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 I. Main data synthesis from three published meta-analyses on pregnancy complications in women with PCOS.

Outcome	Boomsma *et al.* (2006)	Kjerulff *et al.* (2011)	Qin *et al.* (2013)
Maternal			
PIH	3.67 (1.98–6.81)	4.07 (2.75–6.02)	3.07 (1.82–5.18)
PE	3.47 (1.95–6.17)	4.23 (2.77–6.46)	3.28 (2.06–5.22)
GDM	2.94 (1.70–5.08)	2.82 (1.94–4.11)	2.81 (1.99–3.98)
Preterm delivery	1.75 (1.16–2.62)	2.20 (1.59–3.04)	1.34 (0.56–3.23)
Neonatal			
SGA	1.16 (0.31–5.12)	2.62 (1.35–5.10)	—
LGA	—	1.56 (0.92–2.64)	—
Macrosomia	1.13 (0.73–1.75)	—	—

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 0.99–2.88) 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 $\geq$5.3 mmol/l, 1 h glucose $\geq$10.0 mmol/l, 2 h glucose $\geq$8.6 mmol/l and 3 h glucose $\geq$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 (Carlsen *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 dyslipidaemia 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 (Aceti *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 rise 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). Dehydroepiandrostenedione sulphate concentrations are increased in daughters of women with PCOS during the onset of puberty and around 30% have an exacerbated adrenarche (Maliqueo *et al.*, 2009). Girls with amplified adrenarche 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, oligomenorrhoea 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 Frène *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; Carlsen *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.

Study	Cases (*n*) Daughters	Controls (*n*) Daughters	Age (years) Cases versus controls	Outcomes	Conclusion
Battaglia *et al.* (2002)	15	10	7.6 ± 0.6 versus 6.9 ± 0.6[c]	PCOM, endocrine profile, bone age	PCOS daughters have an increased risk of PCOM, which could be a sign of genetic predisposition
Crisosto *et al.* (2007)	28	33	11.4 ± 2.5 versus 11.5 ± 2.2[d]	AMH	Peripubertal PCOS daughters have an increased AMH
Sir-Petermann *et al.* (2007)	75	49	6.0 [4.0–9.0] versus 6.0 [4.0–9.0][e] 12.5 [10.0–16.0] versus 12.4 [10.0–17.0][e]	Metabolic and endocrine profile	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
Sir-Petermann *et al.* (2009)	99	84	Average age 7–15 years	Ovarian volume, IR, metabolic and endocrine profile	PCOS daughters have IR and increased ovarian volume in prepuberty and puberty, and biochemical abnormalities in late puberty
Battaglia *et al.* (2009)	17[a]	20	24.2 ± 3.7 versus 26.3 ± 4.3[d]	Hormonal and biochemical profile, ovarian blood flow, arterial stiffness, IR	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
Maliqueo *et al.* (2009)	98	51	5.7 [3.9–7.6] versus 5.9 [4.0–7.6][e] 10.6 [8.2–13.0] versus 10.6 [8.7–12.9][e]	Adrenal function, bone age	Increased serum DHEAS, exacerbated adrenarche, advance in bone age in PCOS daughters
Maliqueo *et al.* (2012)	92	76	8.7 ± 0.3 versus 12.8 ± 0.3[c]	Endocrine and metabolic profile	PCOS daughters have a higher level of adiponectin during the prepubertal period, which may be associated with metabolic and reproductive abnormalities
	Daughters and sons	**Daughters and sons**	**Cases versus controls**		
Kent *et al.* (2008)	17 and 15	21 and 17	Female 9.1 ± 3.4 versus 9.5 ± 3.0[d] Male 9.7 ± 3.4 versus 8.8 ± 3.0[d]	Reproductive and metabolic profile	Lower LH levels in PCOS daughters, midpubertal higher urinary testosterone in PCOS sons
Palomba *et al.* (2012a)	13 and 17	24 and 21	Female 6.5 ± 1.9 versus 6.7 ± 1.8[d] Male 7.2 ± 1.8 versus 6.8 ± 1.7[d]	PDD	Daughters of hyperandrogenic PCOS women have a higher risk of PDD
Anderson *et al.* (2010)	25 and 14	18 and 13	Neonates	Birthweight, endocrine profile in cord blood	No significant difference in birthweight. Estrogens and androstenedione were lower in offspring of PCOS women
Boutzios *et al.* (2013)	19 and 22	52 and 58[b]	Neonates	Anthropometric, metabolic, and endocrine profile, oxidative stress	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
	Daughters	**Daughters and sons**	**Cases versus controls**		
Barry *et al.* (2010)	10	20 and 10	Neonates	Fetal (intrauterine) environment	PCOS daughters are exposed to intrauterine hyperandrogenism

AMH, anti-Mullerian hormone; DHEAS, dehydroepiandrostenedione sulphate; IR, insulin resistance; PCOM, polycystic ovary morphology; PDD, pervasive developmental disorders; SHBG, sex hormone binding globulin.
[a]Eumenorrheic, normal weight, non-hirsute daughters of women with PCOS.
[b]The control group consisted of 54 women who developed GDM during pregnancy and 56 healthy normo-ovulatory women.
[c]Mean ± SE.
[d]Mean ± SD.
[e]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-amenorrhoea 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).

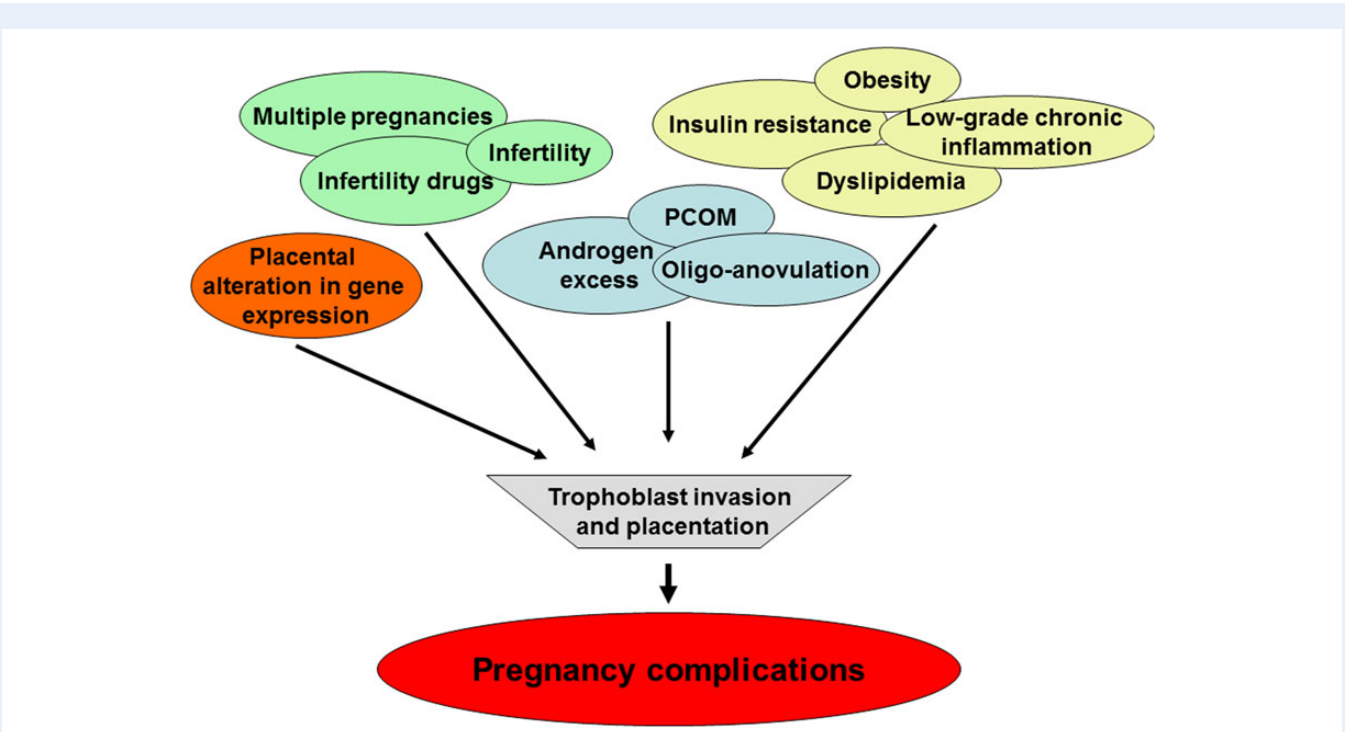

Figure 1 Potential causes of the increased risk in pregnancy complications in women with PCOS. All factors shown in the figure can increase the risk of obstetric/neonatal complications directly and/or through an altered trophoblast invasion and placentation. PCOM, polycystic ovarian morphology.

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 Dunaif, 2012) with a prevalence ranging from 75 to 95% according to BMI (Stepto *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/m^2 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-Maitre *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 miscarriages 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 (Heijnen *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 (Moran *et al.*, 2015). Thus, it is intuitive that a high proportion of women with PCOS will, 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 cofactor 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 (Sirimi and Dimistrios, 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 (Moran *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 glycodelin, 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

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 Henriksen, 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 the two 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/intervillositis 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 placentation (Murray, 2012). 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 placentation (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

0.39, 95% CI 0.22–0.70; Thangaratinam *et al.*, 2012). A trend towards reduction of the risk of GDM (RR 0.78, 95% CI 0.57–1.08), preterm delivery (RR 0.78, 95% CI 0.60–1.02), intrauterine death (RR 0.15, 95% CI 0.02–1.20) and birth trauma (RR 0.36, 95% CI 0.11–1.2) should also be highlighted to pregnant obese women (Thangaratinam *et al.*, 2012). At the moment, limited data are available about the effect of weight loss during pregnancy in obese women (Furber *et al.*, 2013) and several study protocols are in progress on this topic (Briley *et al.*, 2014; Seneviratne *et al.*, 2014). However, a dietary and/or physical activity intervention in women with PCOS could avoid the excess in weight gain observed during pregnancy.

In consideration of available data suggesting that 2.9% of women of reproductive age in the USA are affected by pregestational diabetes (Hayes *et al.*, 2011), it should be crucial to screen all women who are planning a pregnancy, with special regard to women with PCOS (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012; Peterson *et al.*, 2015). In this regard, the American Diabetes Association has included the PCOS among the criteria for testing type 2 diabetes in asymptomatic adult individuals at the first prenatal visit (American Diabetes Association, 2011), even if universal, instead of selective, screening was recommended by the International Association of Diabetes and Pregnancy Study Groups (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010). However, the risk of developing GDM can be also predicted in women with PCOS with high precision before conception based on the following features: first-degree relatives with type 2 diabetes, fasting glucose, insulin, androstenedione and SHBG concentrations (de Wilde *et al.*, 2014). This approach, followed by preconception care aimed at ensuring an adequate glycaemic control, could reduce the cost and health burden associated with GDM especially in women with non-PCOS-related risk factors, such as obesity, advanced age and a particular ethnicity (Torloni *et al.*, 2009; Peterson *et al.*, 2015).

Certainly, in infertile women with PCOS maximum effort should be made to reduce the time to pregnancy (Messerlian *et al.*, 2013) and to avoid multiple pregnancies (Løvvik *et al.*, 2015) using strategies and/or drugs that induce mono-ovulation and always using the elective single embryo transfer in ART cycles.

At present, no indication for a specific management of pregnant women with PCOS women is available. A Norway registry study on 3506 women (unselected for the PCOS) with 4990 singleton births demonstrated that measuress of blood pressure, TG, cholesterol, high-density lipoprotein-cholesterol (HDL) and glucose assessed before pregnancy were associated with increased risk of preterm birth and shorter gestational length (Magnussen *et al.*, 2011). Throughout gestation, special attention should be paid to early changes in acute-phase proteins, to dyslipidaemia and to abnormally low haemoglobin and haematocrit levels because these biochemical markers are all related to a higher risk for pregnancy complications in women with PCOS (Palomba *et al.*, 2014a, b). Very few data on instrumental pregnancy monitoring have been published on PCOS populations. Women with PCOS commonly showed more abnormal uterine artery Doppler indices during the early phases of pregnancy suggesting a potential role of ultrasonography in selecting PCOS patients at high risk of adverse pregnancy and perinatal outcomes (Palomba *et al.*, 2010b). However, the real and pragmatic usefulness of the routine Doppler examination of the uterine arteries in clinical practice, like that of the previously mentioned biochemical markers, is still unknown in this specific high-risk population.

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 acetilsalicylic 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 co-morbidities 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 (Braakhekke *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.).

References

Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb Haemost* 2003;**89**:493–498.

Aceti A, Santhakumaran S, Logan KM, Philipps LH, Prior E, Gale C, Hyde MJ, Modi N. The diabetic pregnancy and offspring blood pressure in childhood: a systematic review and meta-analysis. *Diabetologia* 2012;**55**:3114–3127.

Acromite MT, Mantzoros CS, Leach RE, Hurwitz J, Dorey LG. Androgens in preeclampsia. *Am J Obstet Gynecol* 1999;**180**:60–63.

Agha M, Agha RA, Sandell J. Interventions to reduce and prevent obesity in pre-conceptual and pregnant women: a systematic review and meta-analysis. *PLoS One* 2014;**9**:e95132.

Ahlsson F, Lundgren M, Tuvemo T, Gustafsson J, Haglund B. Gestational diabetes and offspring body disproportion. *Acta Paediatr* 2010;**99**:89–93.

Alshammari A, Hanley A, Ni A, Tomlinson G, Feig DS. Does the presence of polycystic ovary syndrome increase the risk of obstetrical complications in women with gestational diabetes? *J Matern Fetal Neonatal Med* 2010;**23**:545–549.

American College of Obstetricians and Gynecologists. Committee opinion no. 549: obesity in pregnancy. *Obstet Gynecol* 2013;**121**:213–217.

American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2003; **26**:S103–S105.

American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011;**34**:S11–S61.

Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). *Hum Reprod* 2012;**27**:14–24.

Anderson H, Fogel N, Grebe SK, Singh RJ, Taylor RL, Dunaif A. Infants of women with polycystic ovary syndrome have lower cord blood androstenedione and estradiol levels. *J Clin Endocrinol Metab* 2010;**95**:2180–2106.

Baker AM, Klein RL, Moss KL, Haeri S, Boggess K. Maternal serum dyslipidemia occurs early in pregnancy in women with mild but not severe preeclampsia. *Am J Obstet Gynecol* 2009;**201**:293.e1–293.e4.

Balen AH. Ovulation induction in the management of anovulatory polycystic ovary syndrome. *Mol Cell Endocrinol* 2013;**373**:77–82.

Balen AH, Braat DD, West C, Patel A, Jacobs HS. Cumulative conception and live birth rates after the treatment of anovulatory infertility: safety and efficacy of ovulation induction in 200 patients. *Hum Reprod* 1994;**9**:1563–1570.

Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ* 2015;**21**;350:h102.

Barau G, Robillard PY, Hulsey TC, Dedecker F, Laffite A, Gérardin P, Kauffmann E. Linear association between maternal pre-pregnancy body mass index and risk of Caesarean section in term deliveries. *BJOG* 2006;**113**:1173–1177.

Barker DJ. The intrauterine environment and adult cardiovascular disease. *Ciba Found Symp* 1991;**156**:3–10.

Barrett ES, Parlett LE, Windham GC, Swan SH. Differences in ovarian hormones in relation to parity and time since last birth. *Fertil Steril* 2014;**101**:1773–1780.

Barry JA, Kay AR, Navaratnarajah R, Iqbal S, Bamfo JE, David AL, Hines M, Hardiman PJ. Umbilical vein testosterone in female infants born to mothers with polycystic ovary syndrome is elevated to male levels. *J Obstet Gynaecol* 2010;**30**:444–446.

Battaglia C, Regnani G, Mancini F, Iughetti L, Flamigni C, Venturoli S. Polycystic ovaries in childhood: a common finding in daughters of PCOS patients. A pilot study. *Hum Reprod* 2002;**17**:771–776.

Battaglia C, Mancini F, Cianciosi A, Busacchi P, Persico N, Paradisi R, Facchinetti F, de Aloysio D. Cardiovascular risk in normal weight, eumenorrheic, non-hirsute daughters of patients with polycystic ovary syndrome: a pilot study. *Fertil Steril* 2009;**92**:240–249.

Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *Br Med J* 2007; **335**:974.

Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009;**373**:1773–1779.

Berger NG, Repke JT, Woodruff JD. Markedly elevated serum testosterone in pregnancy without foetal virilization. *Obstet Gynecol* 1984;**63**:260–262.

Bisson M, Sériès F, Giguère Y, Pamidi S, Kimoff J, Weisnagel SJ, Marc I. Gestational diabetes mellitus and sleep-disordered breathing. *Obstet Gynecol* 2014; **123**:634–641.

Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;**12**:673–683.

Boutzios G, Livadas S, Piperi C, Vitoratos N, Adamopoulos C, Hassiakos D, Iavazzo C, Diamanti-Kandarakis E. Polycystic ovary syndrome offspring display increased oxidative stress markers comparable to gestational diabetes offspring. *Fertil Steril* 2013;**99**:943–950.

Braakhekke M, Kamphuis EI, van Rumste MM, Mol F, van der Veen F, Mol BW. How are neonatal and maternal outcomes reported in randomised controlled trials (RCTs) in reproductive medicine? *Hum Reprod* 2014;**29**:1211–1217.

Briley AL, Barr S, Badger S, Bell R, Croker H, Godfrey KM, Holmes B, Kinnunen TI, Nelson SM, Oteng-Ntim E *et al.* A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Pregnancy Childbirth* 2014;**14**:74.

Cai GJ, Sun XX, Zhang L, Hong Q. Association between maternal body mass index and congenital heart defects in offspirng: a systematic review. *Am J Obst Gynecol* 2014; **211**:91–117.

Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. *Hum Reprod Update* 2011;**17**:242–253.

Cao C, O'Brien KO. Pregnancy and iron homeostasis: an update. *Nutr Rev* 2013; **71**:35–51.

Carlsen SM, Jacobsen G, Vanky E. Mid-pregnancy androgen levels are negatively associated with breastfeeding. *Acta Obstet Gynecol Scand* 2010;**89**:87–94.

Carlsen SM, Martinussen MP, Vanky E. Metformin's effect on first-year weight gain: a follow-up study. *Pediatrics* 2012;**130**:1222–1226.

Carmina E, Orio F, Palomba S, Longo RA, Cascella T, Colao A, Lombardi G, Rini GB, Lobo RA. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. *Am J Med* 2006;**119**:356.e1–356.e6.

Cassina M, Donà M, Di Gianantonio E, Litta P, Clementi M. First-trimester exposure to metformin and risk of birth defects: a systematic review and meta-analysis. *Hum Reprod Update* 2014;**20**:656–669.

Catov JM, Bodnar LM, Kip KE, Hubel C, Ness RB, Harger G, Roberts JM. Early pregnancy lipid concentrations and spontaneous preterm birth. *Am J Obstet Gynecol* 2007;**197**:610.e1–617.e1.

Cedergren MI. Maternal morbid obesity and the risk of adverse pregnancy outcome. *Obstet Gynecol* 2004;**103**:219–224.

Chakraborty P, Banerjee S, Saha P, Nandi SS, Sharma S, Goswami SK, Chakravarty B, Kabir SN. Aspirin and low-molecular weight heparin combination therapy effectively prevents recurrent miscarriage in hyperhomocysteinemic women. *PLoS One* 2013a; **8**:e74155.

Chakraborty P, Goswami SK, Rajani S, Sharma S, Kabir SN, Chakravarty B, Jana K. Recurrent pregnancy loss in polycystic ovary syndrome: role of hyperhomocysteinemia and insulin resistance. *PLoS One* 2013b;**8**:e64446.

Christin-Maitre S, Hugues JN, Recombinant FSH Study Group. A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome. *Hum Reprod* 2003;**18**:1626–1631.

Chu SY, Kim SY, Lau J, Schmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a meta-analysis. *Am J Obstet Gynecol* 2007;**197**: 223–228.

Cnattingius S, Villamor E, Johansson S, Edstedt Bonamy AK, Persson M, Wikström AK, Granath F. Maternal obesity and risk of preterm delivery. *J Am Med Assoc* 2013; **309**:2362–2370.

Coan PM, Vaughan OR, Sekita Y, Finn SL, Burton GJ, Constancia M, Fowden AL. Adaptations in placental phenotype support fetal growth during undernutrition of pregnant mice. *J Physiol* 2010;**588**:527–538.

Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, Kelestimur F, Macut D, Micic D, Pasquali R *et al.* European survey of diagnosis and management of the polycystic ovary syndrome: results of the ESE PCOS Special Interest Group's Questionnaire. *Eur J Endocrinol* 2014;**171**:489–498.

Crisosto N, Codner E, Maliquero M, Echiburù B, Sanchez F, Cassorla F, Sir-Peterman T. Anti-Mullerian hormone levels in peripubertal daughters of women with polycyatic ovary syndrome. *J Clin Endocrinol Metab* 2007;**92**:2739–2743.

Cusimano MC, Pudwell J, Roddy M, Cho CK, Smith GN. The maternal health clinic: an initiative for cardiovascular risk identification in women with pregnancy-related complications. *Am J Obstet Gynecol* 2014;**210**:438.e1–438.e9.

Daan NMP, Louwers YV, Koster MPH, Eijkemans MJC, de Rijke YB, Lentjes EWG, Fauser BCJM, Laven JSE. Cardiovascular and metabolic profiles amongst different PCOS phenotypes: who is really at risk? *Fertil Steril* 2014;**102**:1444–1451.

Davenport MH, Ruchat SM, Giroux I, Sopper MM, Mottola MF. Timing of excessive pregnancy-related weight gain and offspring adiposity at birth. *Obstet Gynecol* 2013;**122**:255–261.

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, Chan A. Reproductive technologies and the risk of birth defects. *N Engl J Med* 2012; **366**:1803–1813.

De Frène V, Vansteelandt S, T'Sjoen G, Gerris J, Somers S, Vercruysse L, De Sutter P. A retrospective study of the pregnancy, delivery and neonatal outcome in overweight versus normal weight women with polycystic ovary syndrome. *Hum Reprod* 2014; **29**:2333–2338.

de Wilde MA, Veltman-Verhulst SM, Goverde AJ, Lambalk CB, Laven JS, Franx A, Koster MP, Eijkemans MJ, Fauser BC. Preconception predictors of gestational diabetes: a multicentre prospective cohort study on the predominant complication of pregnancy in polycystic ovary syndrome. *Hum Reprod* 2014;**29**:1227–1236.

de Wilde MA, Goverde AJ, Veltman-Verhulst SM, Eijkemans MJ, Franx A, Fauser BC, Koster MP. Insulin action in women with polycystic ovary syndrome and its relation to gestational diabetes. *Hum Reprod* 2015;**30**:1447–1453.

de Zegher F, Ibáñez L. Prenatal growth restraint followed by catch-up of weight: a hyperinsulinemic pathway to polycystic ovary syndrome. *Fertil Steril* 2006; **86**:S4–S5.

Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. *Endocr Rev* 2012; **33**:981–1030.

Dietz PM, Callaghan WM, Morrow B, Cogswell ME. Population-based assessment of the risk of primary Cesarean delivery due to excess prepregnancy weight among nulliparous women delivering term infants. *Matern Child Health J* 2005; **9**:237–244.

Du M, Basu A, Fu D, Wu M, Centola M, Jenkins AJ, Hanssen KF, Garg SK, Hammad SM, Scardo JA *et al*. Serum inflammatory markers and preeclampsia in type 1 diabetes: a prospective study. *Diabetes Care* 2013;**36**:2054–2061.

Duleba AJ, Dokras A. Is PCOS an inflammatory process? *Fertil Steril* 2012;**97**:7–12.

Dunaif A, Fauser BC. Renaming PCOS-a two-state solution. *J Clin Endocrinol Metab* 2013;**98**:4325–4328.

Enquobahrie DA, Williams MA, Butler CL, Frederick IO, Miller RS, Luthy DA. Maternal plasma lipid concentrations in early pregnancy and risk of preeclampsia. *Am J Hypertens* 2004;**17**:574–581.

Escobar JC, Patel SS, Beshay VE, Suzuki T, Carr BR. The human placenta expresses CYP17 and generates androgens de novo. *J Clin Endocrinol Metab* 2011;**96**: 1385–1392.

Falbo A, Rocca M, Russo T, D'Ettore A, Tolino A, Zullo F, Orio F, Palomba S. Changes in androgens and insulin sensitivity indexes throughout pregnancy in women with polycystic ovary syndrome (PCOS): relationships with adverse outcomes. *J Ovarian Res* 2010;**3**:23.

Farquhar C, Brown J, Marjoribanks J. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database Syst Rev* 2012;**6**:CD001122.

Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. *Lancet* 2005;**365**:1807–1816.

Feghali M, Miodovnik M. Diabetes: hypertension during pregnancy and future diabetes mellitus. *Nat Rev Endocrinol* 2013;**9**:446–447.

Feig DS, Shah BR, Lipscombe LL, Wu CF, Ray JG, Lowe J, Hwee J, Booth GL. Preeclampsia as a risk factor for diabetes: a population-based cohort study. *PLoS Med* 2013;**10**:e1001425.

Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, Lawlor DA. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. *Circulation* 2012;**125**:1367–1380.

Furber CM, McGowan L, Bower P, Kontopantelis E, Quenby S, Lavender T. Antenatal interventions for reducing weight in obese women for improving pregnancy outcome. *Cochrane Database Syst Rev* 2013;**1**:CD009334.

González F. Inflammation in polycystic ovary syndrome: underpinning of insulin resistance and ovarian dysfunction. *Steroids* 2012;**77**:300–305.

Grigorescu V, Zhang Y, Kissin DM, Sauber-Schatz E, Sunderam M, Kirby RS, Diop H, McKane P, Jamieson DJ. Maternal characteristics and pregnancy outcomes after assisted reproductive technology by infertility diagnosis: ovulatory dysfunction versus tubal obstruction. *Fertil Steril* 2014;**101**:1019–1025.

Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. *Obes Rev* 2008;**9**:140–150.

Haakova L, Cibula D, Rezabek K, Hill M, Fanta M, Zivny J. Pregnancy outcome in women with PCOS and in controls matched by age and weight. *Hum Reprod* 2003; **18**:1438–1441.

Hamilton-Fairley D, Kiddy D, Watson H, Sagle M, Franks S. Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome. *Hum Reprod* 1991;**6**:1095–1099.

Han AR, Kim HO, Cha SW, Park CW, Kim JY, Yang KM, Song IO, Koong MK, Kang IS. Adverse pregnancy outcomes with assisted reproductive technology in non-obese women with polycystic ovary syndrome: a case–control study. *Clin Exp Reprod Med* 2011;**38**:103–108.

Hayes DK, Fan AZ, Smith RA, Bombard JM. Trends in selected chronic conditions and behavioural risk factors among women of reproductive age. Behavioural Risk Factor Surveillance System, 2001–2009. *Prevent Chronic Dis* 2011;**8**:A120.

Heijnen EM, Eijkemans MJ, Hughes EG, Laven JS, Macklon NS, Fauser BC. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;**12**:13–21.

Herrera E, Ortega-Senovilla H. Maternal lipid metabolism during normal pregnancy and its implications to fetal development. *Clin Lipidol* 2010;**5**:899–911.

Hodson K, Man CD, Smith FE, Thelwall PE, Cobelli C, Robson SC, Taylor R. Mechanism of insulin resistance in normal pregnancy. *Horm Metab Res* 2013;**45**:567–571.

Horvath K, Koch K, Jeitler K, Matyas E, Bender R, Bastian H, Lange S, Siebenhofer A. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *Br Med J* 2010;**340**:c1395.

Hubel CA. Dyslipidemia, iron, and oxidative stress in preeclampsia: assessment of maternal and feto-placental interactions. *Semin Reprod Endocrinol* 1998;**16**: 75–92.

Hudecova M, Holte J, Olovsson M, Sundström Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve. *Hum Reprod* 2009;**24**:1176–1183.

Ibañez L, Potau N, Virdis R, Zampolli M, Terzi C, Gussinyé M, Carrascosa A, Vicens-Calvet E. Postpubertal outcome in girls diagnosed of premature pubarche during childhood: increased frequency of functional ovarian hyperandrogenism. *J Clin Endocrinol Metab* 1993;**76**:1599–1603.

Ibáñez L, Potau N, Zampolli M, Riqué S, Saenger P, Carrascosa A. Hyperinsulinemia and decreased insulin-like growth factor-binding protein-1 are common features in prepubertal and pubertal girls with a history of premature pubarche. *J Clin Endocrinol Metab* 1997;**82**:2283–2288.

Ibáñez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. *J Clin Endocrinol Metab* 1998;**83**:3558–3562.

Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Early metformin therapy (age 8–12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. *J Clin Endocrinol Metab* 2011;**96**: E1262–E1267.

Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab* 1999; **84**:1617–1622.

Imani B, Eijkemans MJ, de Jong FH, Payne NN, Bouchard P, Giudice LC, Fauser BC. Free androgen index and leptin are the most prominent endocrine predictors of ovarian response during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab* 2000;**85**:676–682.

International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva AD, Hod M, Kitzmiler JL *et al*. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010;**33**:676–682.

Irwin JC, Suen LF, Faessen GH, Popovici RM, Giudice LC. Insulin-like growth factor (IGF)-II inhibition of endometrial stromal cell tissue inhibitor of metalloproteinase-3 and IGF-binding protein-1 suggests paracrine interactions at the decidua: trophoblast interface during human implantation. *J Clin Endocrinol Metab* 2001; **86**:2060–2064.

Jan MR, Nazli R, Shah J, Akhtar T. A study of lipoproteins in normal and pregnancy-induced hypertensive women in tertiary care hospitals of the North West Frontier Province-Pakistan. *Hypertens Pregnancy* 2012;**31**:292–299.

Joham AE, Boyle JA, Ranasinha S, Zoungas S, Teede HJ. Contraception use and pregnancy outcomes in women with polycystic ovary syndrome: data from the Australian Longitudinal Study on Women's Health. *Hum Reprod* 2014a;**29**: 802–808.

Joham AE, Ranasinha S, Zoungas S, Moran L, Teede HJ. Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2014b;**99**:447–452.

Johansson S, Villamor E, Altman M, Bonamy AK, Granath F, Cnattingius S. Maternal overweight and obesity in early pregnancy and risk of infant mortality: a population based cohort study in Sweden. *Br Med J* 2014;**349**:g6572.

Johnston J, Gusmano MK, Patrizio P. Preterm births, multiples, and fertility treatment: recommendations for changes to policy and clinical practices. *Fertil Steril* 2014; **102**:36–39.

Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O. Serum lipoproteins, insulin, and urinary prostanoid metabolites in normal and hypertensive pregnant women. *Obstet Gynecol* 1995;**85**:353–356.

Kajihara T, Tanaka K, Oguro T, Tochigi H, Prechapanich J, Uchino S, Itakura A, Sućurović S, Murakami K, Brosens JJ *et al.* Androgens modulate the morphological characteristics of human endometrial stromal cells decidualized in vitro. *Reprod Sci* 2013;**21**:372–380.

Kaňová N, Bičíková M. Hyperandrogenic states in pregnancy. *Physiol Res* 2011; **60**:243–252.

Kent SC, Gnatuk CL, Kunselman AR, Demers LM, Lee PA, Legro RS. Hyperandrogenism and hyperinsulinism in children of women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab* 2008;**93**:1662–1669.

Khan GH, Galazis N, Docheva N, Layfield R, Atiomo W. Overlap of proteomic biomarkers between women with pre-eclampsia and PCOS: a systematic review and biomarker database integration. *Hum Reprod* 2015;**30**:133–148.

Kjerulff LE, Sanchez-Ramos L, Duffy D. Pregnancy outcomes in women with polycystic ovary syndrome: a meta-analysis. *Am J Obstet Gynecol* 2011;**204**:558.e1–558.e6.

Krishnaveni GV, Veena SR, Jones A, Srinivasan K, Osmond C, Karat SC, Kurpad AV, Fall CH. Exposure to maternal gestational diabetes is associated with higher cardiovascular responses to stress in adolescent Indians. *J Clin Endocrinol Metab* 2015;**100**:986–993.

Kühnert M, Schmidt S. Changes in lymphocyte subsets during pregnancy and post-partum in cases of beginning eclampsia. *J Perinat Med* 2000;**28**:389–398.

Lam KK, Chiu PC, Lee CL, Pang RT, Leung CO, Koistinen H, Seppala M, Ho PC, Yeung WS. Glycodelin-A protein interacts with Siglec-6 protein to suppress trophoblast invasiveness by down regulating extracellular signal-regulated kinase (ERK)/c-Jun signaling pathway. *J Biol Chem* 2011;**286**:37118–37127.

Larsen TB, Sørensen HT, Gislum M, Johnsen SP. Maternal smoking, obesity, and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case–control study. *Thromb Res* 2007;**120**:505–509.

Lautatzis ME, Goulis DG, Vrontakis M. Efficacy and safety of metformin during pregnancy in women with gestational diabetes mellitus or polycystic ovary syndrome: a systematic review. *Metabolism* 2013;**62**:1522–1534.

Lawlor DA, Relton C, Sattar N, Nelson SM. Maternal adiposity—a determinant of perinatal and offspring outcomes? *Nat Rev Endocrinol* 2012;**8**:679–688.

Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, Steinkampf MP, Coutifaris C, McGovern PG, Cataldo NA *et al.* Cooperative Multicenter Reproductive Medicine Network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;**356**:551–566.

Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, Welt CK. Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2013;**98**:4565–4592.

Legro RS, Wu X, Barnhart K, Niederberger C, Ng EH, Palomba S, Zhang H, Farquhar C, Rebar RW, Reindollar R *et al.* Improving the reporting of clinical trials of infertility treatments (IMPRINT): modifying the CONSORT statement. *Hum Reprod* 2014a; **29**:2075–2082.

Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, Christman GM, Huang H, Yan Q, Alvero R *et al.* NICHD Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. *N Engl J Med* 2014b;**371**:119–129.

Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:618–637.

Lorentzen B, Henriksen T. Plasma lipids and vascular dysfunction in preeclampsia. *Semin Reprod Endocrinol* 1998;**16**:33–39.

Lorentzen B, Birkeland KI, Endresen MJ, Henriksen T. Glucose intolerance in women with preeclampsia. *Acta Obstet Gynecol Scand* 1998;**77**:22–27.

Løvvik TS, Wikström AK, Neovius M, Stephansson O, Roos N, Vanky E. Pregnancy and perinatal outcomes in women with polycystic ovary syndrome and twin births: a population-based cohort study. *BJOG* 2015.

Magnussen EB, Vatten LJ, Myklestad K, Salvesen KÅ, Romundstad PR. Cardiovascular risk factors prior to conception and the length of pregnancy: population-based cohort study. *Am J Obstet Gynecol* 2011;**204**:526.e1–8.

Maheshwari A, Stofberg L, Bhattacharya S. Effect of overweight and obesity on assisted reproductive technology—a systematic review. *Hum Reprod Update* 2007; **13**:433–444.

Makieva S, Saunders PTK, Norman JE. Androgens in pregnancy: roles in parturition. *Hum Reprod Update* 2014;**20**:542–559.

Malchau SS, Loft A, Henningsen AK, Nyboe Andersen A, Pinborg A. Perinatal outcomes in 6338 singletons born after intrauterine insemination in Denmark, 2007 to 2012: the influence of ovarian stimulation. *Fertil Steril* 2014;**102**:1110–1116.

Maliqueo M, Sir-Petermann T, Pérez V, Echiburú B, de Guevara AL, Gálvez C, Crisosto N, Azziz R. Adrenal function during childhood and puberty in daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2009; **94**:3282–3288.

Maliqueo M, Galgani JE, Pérez-Bravo F, Echiburú B, de Guevara AL, Crisosto N, Sir-Petermann T. Relationship of serum adipocyte-derived proteins with insulin sensitivity and reproductive features in pre-pubertal and pubertal daughters of polycystic ovary syndrome women. *Eur J Obstet Gynecol Reprod Biol* 2012; **161**:56–61.

Maliqueo M, Lara HE, Sánchez F, Echiburú B, Crisosto N, Sir-Petermann T. Placental steroidogenesis in pregnant women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2013;**166**:151–155.

Maliqueo M, Sundstrom-Poromaa I, Vanky E, Fornes R, Benrick A, Akerud H, Stridsklev S, Labrie F, Jansson T, Stener-Victorin E. Placental STAT3 signaling is activated in women with polycystic ovary syndrome. *Hum Reprod* 2015; **30**:692–700.

Martin RM, Gunnell D, Smith GD. Breastfeeding in infancy and blood pressure in later life: systematic review and meta-analysis. *Am J Epidemiol* 2005;**161**:15–26.

McDonald SD, Han Z, Mulla S, Beyene J, Knowledge Synthesis Group. Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analysis. *Br Med J* 2010;**341**:c3428.

Messerlian C, Maclagan L, Basso O. Infertility and the risk of adverse pregnancy outcomes: a systematic review and meta-analysis. *Hum Reprod* 2013;**28**:125–137.

Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriages after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008;**91**:714–726.

Mikola M, Hiilesmaa V, Halttunen M, Suhonen L, Tiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. *Hum Reprod* 2001;**16**:226–229.

Misso ML, Costello MF, Garrubba M, Wong J, Hart R, Rombauts L, Melder AM, Norman RJ, Teede HJ. Metformin versus clomiphene citrate for infertility in non-obese women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2013;**19**:2–11.

Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. *Fertil Steril* 2009;**92**:1966–1982.

Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2010;**16**:347–363.

Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposityimpact. *Trends Endocrinol Metab* 2015;**26**:136–143.

Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A *et al.* Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Endocrinol Metab* 2012;**97**:1492–1500.

Murray AJ. Oxygen delivery and fetal-placental growth: beyond a question of supply and demand? *Placenta* 2012;**33**:e16–e22.

Mutsaerts MA, Groen H, ter Bogt NC, Bolster JH, Land JA, Bemelmans WJ, Kuchenbecker WK, Hompes PG, Macklon NS, Stolk RP *et al.* The LIFESTYLE study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. A randomised controlled trial. *BMC Womens Health* 2010; **10**:22.

National Institute of Health. Evidence-based Methodology Workshop on Polycystic Ovary Syndrome. December 3–5, 2012. https://prevention.nih.gov/docs/programs/pcos/FinalReport.pdf (15 June 2015, date last accessed).

Naver KV, Grinsted J, Larsen SO, Hedley PL, Jørgensen FS, Christiansen M, Nilas L. Increased risk of preterm delivery and pre-eclampsia in women with polycystic ovary syndrome and hyperandrogenaemia. *BJOG* 2014;**121**:575–581.

Ngai I, Govindappagari S, Neto N, Marji M, Landsberger E, Garry DJ. Outcome of pregnancy when gestational diabetes mellitus is diagnosed before or after 24 weeks of gestation. *Obstet Gynecol* 2014;**123**(Suppl 1):162–163.

Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. *Hum Reprod Update* 2004;**10**:267–280.

Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. *Cochrane Database Syst Rev* 2000;**4**:CD000410.

O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic review. *Epidemiology* 2003;**14**:368–374.

Orio F, Palomba S. Reproductive endocrinology: new guidelines for the diagnosis and treatment of PCOS. *Nat Rev Endocrinol* 2014;**10**:130–132.

Orio F, Palomba S, Cascella T, De Simone B, Di Biase S, Russo T, Labella D, Zullo F, Lombardi G, Colao A. Early impairment of endothelial structure and function in young normal-weight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004;**89**:4588–4593.

Orio F, Palomba S, Cascella T, Di Biase S, Manguso F, Tauchmanovà L, Nardo LG, Labella D, Savastano S, Russo T *et al*. 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* 2005;**90**:2–5.

Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG. Infant feeding and blood cholesterol: a study in adolescents and a systematic review. *Pediatrics* 2002;**110**:597–608.

Palomba S. Aromatase inhibitors for ovulation induction. *J Clin Endocrinol Metab* 2015; **100**:1742–1747.

Palomba S, Falbo A, Zullo F. Management strategies for ovulation induction in women with polycystic ovary syndrome and known clomiphene citrate resistance. *Curr Opin Obstet Gynecol* 2009a;**21**:465–473.

Palomba S, Falbo A, Zullo F, Orio F. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocr Rev* 2009b;**30**:1–50.

Palomba S, Falbo A, Orio F, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril* 2009c;**92**:1646–1658.

Palomba S, Falbo A, Russo T, Tolino A, Orio F, Zullo F. Pregnancy in women with polycystic ovary syndrome: the effect of different phenotypes and features on obstetric and neonatal outcomes. *Fertil Steril* 2010a;**94**:1805–1811.

Palomba S, Falbo A, Russo T, Battista L, Tolino A, Orio F, Zullo F. Uterine blood flow in pregnant women with polycystic ovary syndrome: relationships with clinical outcomes. *BJOG* 2010b;**117**:711–721.

Palomba S, Marotta R, Di Cello A, Russo T, Falbo A, Orio F, Tolino A, Zullo F, Esposito R, La Sala GB. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case–control study. *Clin Endocrinol (Oxf)* 2012a;**77**:898–904.

Palomba S, Falbo A, Russo T, Rivoli L, Orio M, Cosco AG, Vero R, Capula C, Tolino A, Zullo F *et al*. The risk of a persistent glucose metabolism impairment after gestational diabetes mellitus is increased in patients with polycystic ovary syndrome. *Diabetes Care* 2012b;**35**:861–867.

Palomba S, Marotta R, Di Cello A, Russo T, Falbo A, Orio F, Tolino A, Zullo F, Esposito R, La Sala GB. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case–control study. *Clin Endocrinol (Oxf)* 2012c;**77**:898–904.

Palomba S, Russo T, Falbo A, Di Cello A, Amendola G, Mazza R, Tolino A, Zullo F, Tucci L, La Sala GB. Decidual endovascular trophoblast invasion in women with polycystic ovary syndrome: an experimental case–control study. *J Clin Endocrinol Metab* 2012d;**97**:2441–2449.

Palomba S, Russo T, Falbo A, Di Cello A, Tolino A, Tucci L, La Sala GB, Zullo F. Macroscopic and microscopic findings of the placenta in women with polycystic ovary syndrome. *Hum Reprod* 2013a;**28**:2838–2847.

Palomba S, Falbo A, La Sala GB. Effects of metformin in women with polycystic ovary syndrome treated with gonadotrophins for in vitro fertilisation and intracytoplasmic sperm injection cycles: a systematic review and meta-analysis of randomised controlled trials. *BJOG* 2013b;**120**:267–276.

Palomba S, Chiossi G, Falbo A, Orio F, Tolino A, Colao A, La Sala GB, Zullo F. Low-grade chronic inflammation in pregnant women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2014a;**99**:2942–2951.

Palomba S, Falbo A, Chiossi G, Muscogiuri G, Orio F, Tolino A, Colao A, La Sala GB, Zullo F. Lipid profile in pregnant women with polycystic ovary syndrome. *Steroids* 2014b;**88C**:36–43.

Palomba S, Falbo A, Chiossi G, Tolino A, Tucci L, La Sala GB, Zullo F. Early trophoblast invasion and placentation in women with different polycystic ovary syndrome phenotypes. *Reprod Biomed Online* 2014c;**29**:370–381.

Palomba S, Falbo A, La Sala GB. Metformin and gonadotropins for ovulation induction in patients with polycystic ovary syndrome: a systematic review with meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol* 2014d;**12**:3.

Pamidi S, Pinto LM, Marc I, Benedetti A, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2014;**210**:52.e1–52.e14.

Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. *Hum Reprod Update* 2012;**18**:485–503.

Parchim NF, Wang W, Iriyama T, Ashimi OA, Siddiqui AH, Blackwell S, Sibai B, Kellems RE, Xia Y. Neurokinin 3 receptor and phosphocholine transferase: missing factors for pathogenesis of C-reactive protein in preeclampsia. *Hypertension* 2015;**65**:430–439.

Peterson C, Grosse SD, Li R, Sharma AJ, Razzaghi H, Herman WH, Gilboa SM. Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. *Am J Obstet Gynecol* 2015;**212**: 74.e1–74.e9.

Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update* 2013a;**19**:87–104.

Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Söderström-Anttila V, Nygren KG, Hazekamp J, Bergh C. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Hum Reprod Update* 2013b;**19**:87–104.

Polotsky AJ, Allshouse A, Crawford SL, Harlow SD, Khalil N, Santoro N, Legro RS. Relative contributions of oligomenorrhea and hyperandrogenemia to the risk of metabolic syndrome in midlife women. *J Clin Endocrinol Metab* 2012;**97**: 868–877.

Polotsky AJ, Crawford SL, Harlow SD, Khalil N, Kazlauskaite R, Santoro N, Legro RS. Hyperandrogenic oligomenorrhea and metabolic risks across menopausal transition. *J Clin Endocrinol Metab* 2014;**99**:2120–2127.

Poolsup N, Suksomboon N, Amin M. Effect of treatment of gestational diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2014;**9**:e92485.

Qin JZ, Pang LH, Li MJ, Fan XJ, Huang RD, Chen HY. Obstetric complications in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 2013;**11**:56.

Ramidi G, Khan N, Glueck CJ, Wang P, Goldenberg N. Enoxaparin-metformin and enoxaparin alone may safely reduce pregnancy loss. *Transl Res* 2009;**153**:33–43.

Rao A, Sairam S, Shehata H. Obstetric complications of twin pregnancies. *Best Pract Res Clin Obstet Gynaecol* 2004;**18**:557–576.

Rasmussen SA, Chu SY, Kim SY, Schmid CH, Lau J. Maternal obesity and risk of neural tube defects: a metaanalysis. *Am J Obstet Gynecol* 2008;**198**:611–619.

Ray JG, Diamond P, Singh G, Bell CM. Brief overview of maternal triglycerides as a risk factor for pre-eclampsia. *BJOG* 2006;**113**:379–386.

Reynolds RM, Allan KM, Raja EA, Bhattacharya S, McNeill G, Hannaford PC, Sarwar N, Lee AJ, Bhattacharya S, Norman JE. Maternal obesity during pregnancy and premature mortality from cardiovascular event in adult offspring: follow-up of 1 323 275 person years. *Br Med J* 2013;**347**:f4539.

Romualdi D, De Cicco S, Gagliano D, Busacca M, Campagna G, Lanzone A, Guido M. How metformin acts in PCOS pregnant women: insights into insulin secretion and peripheral action at each trimester of gestation. *Diabetes Care* 2013;**36**: 1477–1482.

Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, Vatten LJ. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* 2008;**372**:737–743.

Roos N, Kieler H, Sahlin L, Ekman-Ordeberg G, Falconer H, Stephansson O. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population-based cohort study. *Br Med J* 2011;**343**:d6309.

Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;**19**:41–47.

Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med* 2008;**358**:2003–2015.

Sabour S, Franx A, Rutten A, Grobbee DE, Prokop M, Bartelink ML, van der Schouw YT, Bots ML. High blood pressure in pregnancy and coronary calcification. *Hypertension* 2007;**49**:813–817.

Sacks GP, Studena K, Sargent K, Redman CW. Normal pregnancy and preeclampsia both produce inflammatory changes in peripheral blood leukocytes akin to those of sepsis. *Am J Obstet Gynecol* 1998;**179**:80–86.

Sacks GP, Seyani L, Lavery S, Trew G. Maternal C-reactive protein levels are raised at 4 weeks gestation. *Hum Reprod* 2004;**19**:1025–1030.

Salihu HM, Dunlop A, Hedayatzadeh M, Alio AP, Kirby RS, Alexander GR. Extreme obesity and risk of stillbirth among black and white gravidas. *Obstet Gynecol* 2007; **110**:552–557.

Salvesen KA, Vanky E, Carlsen SM. Metformin treatment in pregnant women with polycystic ovary syndrome—is reduced complication rate mediated by changes in the uteroplacental circulation? *Ultrasound Obstet Gynecol* 2007;**29**:433–437.

Sattar N, Berry C, Greer IA. Essential fatty acids in relation to pregnancy complications and fetal development. *BJOG* 1998;**105**:1248–1255.

Sattar N, Clark P, Holmes A, Lean ME, Walker I, Greer IA. Antenatal waist circumference and hypertension risk. *Obstet Gynecol* 2001;**97**:268–271.

Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. *Hypertension* 2003;**42**:39–42.

Seely EW, Solomon CG. Insulin resistance and its potential role in pregnancy-induced hypertension. *J Clin Endocrinol Metab* 2003;**88**:2393–2398.

Seneviratne SN, Parry GK, McCowan LM, Ekeroma A, Jiang Y, Gusso S, Peres G, Rodrigues RO, Craigie S, Cutfield WS *et al.* Antenatal exercise in overweight and obese women and its effects on offspring and maternal health: design and rationale of the IMPROVE (Improving Maternal and Progeny Obesity Via Exercise) randomised controlled trial. *BMC Pregnancy Childbirth* 2014;**14**:148.

Seppälä M, Taylor RN, Koistinen H, Koistinen R, Milgrom E. Glycodelin: a major lipocalin protein of the reproductive axis with diverse actions in cell recognition and differentiation. *Endocr Rev* 2002;**23**:401–430.

Serin IS, Kula M, Başbuğ M, Unlühizarci K, Güçer S, Tayyar M. Androgen levels of preeclamptic patients in the third trimester of pregnancy and six weeks after delivery. *Acta Obstet Gynecol Scand* 2001;**80**:1009–1013.

Sharma S, Ghosh S, Singh S, Chakravarty A, Ganesh A, Rajani S, Chakravarty BN. Congenital malformations among babies born following letrozole or clomiphene for infertility treatment. *PLoS One* 2014;**9**:e108219.

Shaw LJ, Merz CNB, Azziz R. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the national institutes of health—national heart, lung, and blood institute sponsored women's ischemia syndrome evaluation. *J Clin Endocrinol Metab* 2008;**93**:1276–1284.

Shobel HP, Fischer T, Heuszer K, Geiger H, Schmieder RE. Preeclampsia: a state of sympathetic overactivity. *N Engl J Med* 1996;**335**:1480–1485.

Shreeve N, Cagampang F, Sadek K, Tolhurst M, Houldey A, Hill CM, Brook N, Macklon N, Cheong Y. Poor sleep in PCOS; is melatonin the culprit? *Hum Reprod* 2013;**28**:1348–1353.

Silver R. Infertility trial outcomes: healthy moms and babies. *Fertil Steril* 2014; **101**:1209–1216.

Sirimi N, Dimistrios GC. Obesity in pregnancy. *Hormones (Athens)* 2010;**9**:299–306.

Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol* 2013;**6**:1–13.

Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Pérez-Bravo F, Recabarren SE. Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. *Hum Reprod* 2002; **17**:2573–2579.

Sir-Petermann T, Hitchsfeld C, Maliqueo M, Codner E, Echiburú B, Gazitúa R, Recabarren S, Cassorla F. Birth weight in offspring of mothers with polycystic ovarian syndrome. *Hum Reprod* 2005;**20**:2122–2126.

Sir-Petermann T, Maliqueo M, Codner E, Echiburu B, Crisosto N, Perez V, Pérez-Bravo F, Cassorla F. Early metabolic derangements in daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2007;**92**:4637–4642.

Sir-Petermann T, Codner E, Pérez V, Echiburú B, Maliqueo M, Ladrón de Guevara A, Preisler J, Crisosto N, Sánchez F, Cassorla F *et al.* Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2009;**94**:1923–1930.

Sivalingam VN, Myers J, Nicholas S, Balen AH, Crosbie EJ. Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications. *Hum Reprod Update* 2014;**20**:853–868.

Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;**357**:2002–2006.

Society of Obstetricians and Gynaecologists of Canada. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can* 2014;**36**:64–83.

Spaan J, Peeters L, Spaanderman M, Brown M. Cardiovascular risk management after a hypertensive disorder of pregnancy. *Hypertension* 2012;**60**:1368–1373.

Sridhar SB, Darbinian J, Ehrlich SF, Markman MA, Gunderson EP, Ferrara A, Hedderson MM. Maternal gestational weight gain and offspring risk for childhood overweight or obesity. *Am J Obstet Gynecol* 2014;**211**:259.e1–259.e8.

Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, Teede HJ. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. *Hum Reprod* 2013;**28**:777–784.

Stothard KJ, Tennant PW, Ruth B, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *J Am Med Assoc* 2009;**301**:636–650.

Stuebe AM, Landon MB, Lai Y, Spong CY, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ *et al.* Maternal BMI, glucose tolerance, and adverse pregnancy outcomes. *Am J Obstet Gynecol* 2012;**207**:62.e1–62.e7.

Sun M, Maliqueo M, Benrick A, Johansson J, Shao R, Hou L, Jansson T, Wu X, Stener-Victorin E. Maternal androgen excess reduces placental and fetal weight, increases placental steroidogenesis, and leads to long-term health effects in their female offspring. *Am J Physiol Endocrinol Metab* 2012;**303**:E1373–E1385.

Sween LK, Althouse AD, Roberts JM. Early-pregnancy percent body fat in relation to preeclampsia risk in obese women. *Am J Obstet Gynecol* 2015;**212**:84.e1–84.e7.

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2012; **5**:CD003053.

Tarlatzis BC, Fauser BC, Legro RS, Norman RJ, Hoeger K, Pasquali R, Franks S, Messinis IE, Casper RF, Homburg R *et al.* Consensus on infertility treatment related to polycystic ovary syndrome. *Fertil Steril* 2008;**89**:505–522.

Teede HJ, Misso ML, Deeks AA, Moran LJ, Stuckey BG, Wong JL, Norman RJ, Costello MF, Guideline Development Groups. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. *Med J Aust* 2011;**195**:65–112.

Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, Kunz R, Mol BW, Coomarasamy A, Khan KS. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *Br Med J* 2012;**344**:e2088.

Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod* 2008;**23**:462–477.

Tian L, Shen H, Lu Q, Norman RJ, Wang J. Insulin resistance increases the risk of spontaneous abortion after assisted reproduction technology treatment. *J Clin Endocrinol Metab* 2007;**92**:1430–1433.

Tobias DK, Chavarro JE, Williams MA, Buck Louis GM, Hu FB, Rich-Edwards J, Missmer SA, Zhang C. History of infertility and risk of gestational diabetes mellitus: a prospective analysis of 40,773 pregnancies. *Am J Epidemiol* 2013; **178**:1219–1225.

Torloni MR, Betrán AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review and meta-analysis. *Obes Rev* 2009;**10**:194–203.

Urman B, Sarac E, Dogan L, Gurgan T. Pregnancy in infertile PCOD patients. Complications and outcome. *J Reprod Med* 1997;**42**:501–505.

Valsamakis G, Kumar S, Creatsas G, Mastorakos G. The effects of adipose tissue and adipocytokines in human pregnancy. *Ann N Y Acad Sci* 2010;**1205**:76–81.

Vanky E, Isaksen H, Moen MH, Carlsen SM. Breastfeeding in polycystic ovary syndrome. *Acta Obstet Gynecol Scand* 2008;**87**:531–535.

Vanky E, Stridsklev S, Heimstad R, Romundstad P, Skogøy K, Kleggetveit O, Hjelle S, von Brandis P, Eikeland T, Flo K *et al.* Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. *J Clin Endocrinol Metab* 2010;**95**:448–455.

Veltman-Verhulst SM, Van Rijn BB, Westerveld HE. Polycystic ovary syndrome and early-onset preeclampsia: reproductive manifestations of increased cardiovascular risk. *Menopause* 2010;**17**:990–996.

Veltman-Verhulst SM, Fauser BC, Eijkemans MJ. High singleton live birth rate confirmed after ovulation induction in women with anovulatory polycystic ovary syndrome: validation of a prediction model for clinical practice. *Fertil Steril* 2012;**98**:761–768.

Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twickler MB. Maternal lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study. *J Clin Endocrinol Metab* 2012;**97**:3917–3925.

Wang YA, Nikravan R, Smith HC, Sullivan EA. Higher prevalence of gestational diabetes mellitus following assisted reproduction technology treatment. *Hum Reprod* 2013; **28**:2554–2561.

Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, Lobo R, Norman RJ, Talbott E, Dumesic DA. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab* 2010; **95**:2038–2049.

Williams D. Pregnancy: a stress test for life. *Curr Opin Obstet Gynecol* 2003;**15**:465–471.

Wolf M, Sandler L, Hsu K, Vossen-Smirnakis K, Ecker JL, Thadhani R. First-trimester C-reactive protein and subsequent gestational diabetes. *Diabetes Care* 2003; **26**:819–824.

Xu N, Chua AK, Jiang H, Liu NA, Goodarzi MO. Early embryonic androgen exposure induces transgenerational epigenetic and metabolic changes. *Mol Endocrinol* 2014; **28**:1329–1336.

Yogev Y, Catalano PM. Pregnancy and obesity. *Obstet Gynecol Clin North Am* 2009; **36**:285–300.

Yu CK, Teoh TG, Robinson S. Obesity in pregnancy. *BJOG* 2006;**113**:1117–1125.

Zhuo Z, Wang A, Yu H. Effect of metformin intervention during pregnancy on the gestational diabetes mellitus in women with polycystic ovary syndrome: a systematic review and meta-analysis. *J Diabetes Res* 2014;**2014**: 381231.