Review



# Reducing the Risk of Pre-eclampsia in Women with Polycystic Ovary Syndrome using a Combination of Pregnancy Screening, Lifestyle, and Medical Management Strategies

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# Reducing the Risk of Pre-Eclampsia in Women with Polycystic Ovary Syndrome Using a Combination of Pregnancy Screening, Lifestyle, and Medical Management Strategies

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**Abstract:** Polycystic ovary syndrome (PCOS) is a multisystem disorder that presents with a variety of phenotypes involving metabolic, endocrine, reproductive, and psychological symptoms and signs. Women with PCOS are at increased risk of pregnancy complications including implantation failure, miscarriage, gestational diabetes, fetal growth restriction, preterm labour, and preeclampsia (PE). This may be attributed to the presence of specific susceptibility features associated with PCOS before and during pregnancy, such as chronic systemic inflammation, insulin resistance (IR), and hyperandrogenism, all of which have been associated with an increased risk of pregnancy complications. Many of the features of PCOS are reversible following lifestyle interventions such as diet and exercise, and pregnant women following a healthy lifestyle have been found to have a lower risk of complications, including PE. This review summarizes the evidence investigating the risk of PE and the role of nutritional factors in women with PCOS. The findings suggest that the beneficial aspects of lifestyle management of PCOS, as recommended in the evidenced-based international guidelines, extend to improved pregnancy outcomes. Identifying high-risk women with PCOS will allow targeted interventions, early pregnancy screening, and increased surveillance for PE. Women with PCOS should be included in risk assessment algorithms for PE.

**Keywords:** PCOS; pre-eclampsia; pregnancy; lifestyle; nutrition; placenta; pathophysiology; angiogenic ratio; screening

## 1. Introduction

Polycystic ovary syndrome is a systemic metabolic and endocrine disorder that results from a disturbance of adaptive interdependent homeostatic survival networks (metabolic, immune, and neuroendocrine) [1–4]. The pathophysiology is characterized by chronic systemic inflammation, IR, and hyperandrogenism [3–9]. This results in a range of phenotypic presentations, that when studied together, have been shown to confer an increased risk of pregnancy complications, including PE [10–12]. When considered separately, different PCOS phenotypes present with clinical and biochemical features that range from mild to severe [2,13]. Nevertheless, women with PCOS inherit individual susceptibility features, independent of other co-existing morbidities such as obesity, that increase their risk of pregnancy complications and justify their inclusion in PE risk assessment algorithms [10,13,14].

Recent evolutionary models characterize PCOS as an evolutionary mismatch disorder that arises from an interaction between genetic and environmental factors [1,2]. Rapid cultural changes in the

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contemporary environment have outpaced genetic adaptation and resulted in a mismatch between modern dietary and environmental exposures and behaviours, and selective metabolic and reproductive traits [1]. The influence of these modern exposures on developmentally programmed susceptibility genes, programs the embryo and fetus to express the phenotypic features of PCOS during childhood, adolescence, and adulthood [15–19]. As a result, adaptive physiological survival pathways that result in activation of inflammation, variation in insulin sensitivity, preferential abdominal fat accumulation, and downregulation of reproduction, become pathological following exposure to lifestyle and environmental factors [1,2]. The development of chronic systemic inflammation, IR, and hyperandrogenism, predispose women with PCOS to a range of chronic diseases and pregnancy complications [20–24].

Polycystic ovary syndrome affects 10-13% of reproductive age women and can present with a wide range of symptoms including menstrual irregularity, hirsutism, acne, alopecia, anxiety, depression, and subfertility, resulting in reduced quality of life [25]. PCOS can be a progressive metabolic condition that leads to obesity, hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome, metabolic-associated hepatic steatosis, chronic kidney disease, cardiovascular disease, and cancer [1,22,26]. The population attributable risk of PCOS to type 2 diabetes is 19-28%, and the combined impact of PCOS makes a significant contribution to the chronic disease epidemic [22]. Multiple systematic reviews of large population-based studies over the past 40 years have reported a significantly increased risk of pregnancy complications, including PE, in women with PCOS [10,11,27–30].

Hypertensive disorders of pregnancy (HDP) (defined as chronic hypertension, gestational hypertension, preeclampsia-eclampsia and chronic hypertension with superimposed preeclampsia) are a leading cause of maternal-fetal morbidity and mortality worldwide [31,32]. Preeclampsia affects 3-5% of pregnancies and is responsible for 76,000 maternal and 500,000 fetal/neonatal deaths every year [31,33]. The definition of PE has evolved over time, in line with research developments into the underlying pathophysiology [34]. This has resulted in an increased awareness of factors involved in the prevention, prediction, diagnosis, treatment, and long-term consequences of PE. It has been estimated that over 300 million women are at risk of chronic health problems (neurodevelopmental, metabolic, cardiac) due to previous PE [35–37].

The International Society for the Study of Hypertension in Pregnancy (ISSHP) has defined PE as new-onset gestational hypertension at or after 20 weeks gestation accompanied by proteinuria, maternal organ involvement, or uteroplacental dysfunction [32]. The pathophysiology of PE is characterized by placental malperfusion that results in syncytiotrophoblast stress and release of soluble factors (pro-inflammatory cytokines, exosomes, extracellular vesicles, transcription factors, hormones, and anti-angiogenic factors), that cause maternal vascular endothelial injury resulting in hypertension and multi-organ involvement [38–40]. More recently, circulating angiogenic factors such as soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF), have been identified as markers of placental health and added to the diagnostic criteria in some countries [34]. In addition, advances in genetics, epigenetics, transcriptomics, metabolomics, artificial intelligence, organoid cultures of the endometrium and trophoblast, and stem cell research, have progressed our understanding of normal and pathological placentation [38,39].

It has long been appreciated that normal placental development requires a complex network of bidirectional communication signals (cytokines, metabolites, hormones, exosomes) between embryo-derived cells (trophoblast, macrophages) and maternal-derived cells (endometrial gland epithelium, stromal, macrophages, natural killer, dendritic, and T cells) [38,39]. Decades of epidemiological research has identified over 70 maternal risk factors that are associated with the development of PE [12,39]. This has resulted in a greater awareness of the possible role of pre-existing maternal pathophysiological features on the development of abnormal placentation and related complications, such as PE [38].

Although there may be differences in the pathogenesis of early (<34 weeks gestation) and late-onset PE, the pathophysiology and maternal/fetal consequences can be similar [38]. Pre-existing maternal pathological features such as chronic systemic inflammation [41], insulin resistance [42],

 doi:10.20944/preprints202312.2120.v1



and hyperandrogenemia [43], as occur in women with PCOS [3], may alter normal placental development, metabolism, and physiology, at all stages of pregnancy [44,45]. In addition, many of the metabolic, endocrine, reproductive, and neuroimmune disturbances that occur in women with PCOS, have been shown to be reversed following lifestyle interventions such as diet and exercise [1,25,46].

Comprehensive international guidelines recommend lifestyle interventions as the first line of management for all women with PCOS [25]. Healthy maternal dietary patterns have been associated with a lower risk of developing PE (odds ratio (OR): 0.78, 95% confidence interval (CI) 0.7-0.86) and increased consumption of ultra-processed foods confer a higher risk (OR: 1.28, CI 1.15-1.42) [47]. Evidenced-based reviews and prospective cohort studies have demonstrated the effectiveness of lifestyle interventions for reducing the risk of PE in women with PCOS [47,48]. In addition, over 75 randomized controlled trials have demonstrated the value of aspirin in the prevention of PE [49].

The following sections of this review will outline the evidence for the increased risk of PE in women with PCOS. The evidence supporting lifestyle and medical interventions will also be discussed and recommendations made for screening and medical therapy in pregnancy.

## 2. Evidence for Increased Risk of PE in Women with PCOS

Many observational studies, systematic reviews, and meta-analyses have reported an increased risk of pregnancy complications in women with PCOS over the past 40 years. These include miscarriage, gestational diabetes mellitus (GDM), intrauterine growth restriction, preterm birth, low birth weight, gestational hypertension, and PE [10,27–30]. In total, 8 systematic reviews published between 2006 and 2023, reported an increased relative risk of PE in women with PCOS of between 1.87 and 4.23 (Table 1) [10,27–30,50–52]. The most recent 2023 meta-analysis included 36 studies that compared rates of PE in women with and without PCOS [52]. Pooled meta-analysis of 34 studies in women not taking metformin, showed a significantly increased risk of PE in women with PCOS (OR: 2.35, 95% CI 1.93-2.86). Subgroup analysis of high-quality studies, after removal of low and medium quality studies, showed a significantly higher risk of PE in women with PCOS (OR: 3.05, 95% CI 1.20-7.8). Subgroup analysis in 7 body mass index (BMI) matched studies, showed that women with PCOS retained an increased risk of developing PE (OR: 2.39, 95% CI 1.14-4.99) [52]. These findings are in agreement with 2 previous meta-analyses that showed a higher prevalence of PE in BMI-matched women with and without PCOS [50,51]. Overall, these data suggest that women with PCOS have an increased risk of PE that is independent of BMI.

**Table 1.** Systematic reviews of studies investigating the risk of pre-eclampsia in women with PCOS.

| Author (Year) | Odds Ratio (95% CI) [1] | Studies | Reference |
|---|---|---|---|
| Boomsma et al (2006) | 3.47 (1.95-6.17) | 8 | (27) |
| Kjerulff et al (2011) | 4.23 (2.77-6.46) | 12 | (28) |
| Qin et al (2013) | 3.28 (2.06-5.22) | 15 | (29) |
| Yu et al (2016) | 2.79 (2.29-3.38) | 25 | (30) |
| Khomami (2019) | 1.87 (1.55-2.25) | 26 | (10) |
| Pan (2021) | 2.07 (1.91-2.24) | 20 | (50) |
| Riestenberg (2022) | 2.03 (1.43-2.87) | 15 | (51) |
| Mousa (2023) | 2.28 (1.88-2.77) | 36 | (52) |

[1] CI = confidence interval.

In addition, a large study from the United States National Inpatient Database of 71,436,308 weighted hospitalizations for deliveries, analyzed 195,675 women with PCOS for their risk of pregnancy complications [11]. Women with PCOS had a higher risk of PE, eclampsia, peripartum cardiomyopathy, and heart failure, during delivery hospitalizations. The risk of developing PE was significantly increased in women with PCOS after adjustment for age, race, demographic variables, and comorbidities, including BMI (OR: 1.56, 95% CI 1.54-1.59). In addition, delivery hospitalizations were associated with increased length and cost of hospitalization in women with PCOS [11]. Despite

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this large body of evidence, PCOS is not generally recognized as a risk factor for pregnancy complications and PE and is not included in national or international risk assessment models.

There is international consensus that women should be assessed for risk factors associated with PE in early pregnancy [12,32,53]. There is ongoing debate regarding which risk factors to include and the type of measures that should be part of risk assessment strategies [53]. Clinical practice guidelines (CPG) recommend a combination of predictive assessments that include clinical risk factors, biophysical markers such as mean arterial blood pressure and mean uterine artery pulsatility index (UtAPI), and biochemical markers such as pregnancy-associated plasma protein A (PAPP-A) and/or PlGF [54,55]. Various combinations of these measures are advised by different national bodies and professional societies [31,53,56]. Recent reviews and commentaries have highlighted the fact that PE risk factors in current CPG are poorly aligned with the evidence [12,57]. A recent review by an expert working group identified PCOS as a probable risk factor for the development of PE, having a similar relative risk and level of evidence to many other risks that are currently included in risk assessment models [12]. None of the current CPG include PCOS as a risk factor. More recent studies add further weight to this evidence and support the need for a review of strategies advocated by CPG [11].

The international evidenced-based guidelines for the assessment and management of PCOS recommend screening, monitoring, and management of risk profiles in women with PCOS, preconception, during pregnancy, and postpartum, in accordance with the recommendations for the general population [25,58]. These recommendations include assessment of blood glucose, body weight, blood pressure, smoking, alcohol consumption, diet, exercise, sleep, and emotional health. There are no specific recommendations for the identification, screening, and management of women with PCOS in pregnancy.

## 3. Evidence for the Role of Nutritional Factors in the Pathophysiology of PE

Maternal nutrition has been suspected to play a role in the pathogenesis of PE for over 100 years [59–61]. The "dietary" hypothesis was proposed by advocates in the United Kingdom (Theobald) and United States (Dieckmann) in the early 1900's [60]. A 1926 review summarized the literature up to this time on the possible pathological effects of dietary macronutrients and their metabolites (protein and urea, fat and ketosis, carbohydrate restriction and ketosis) in patients with PE [61]. Although dietary management was common (milk, bread, rice, eggs, and fruit, with salt restriction) it was noted that there were "no series of experiments in which the effect of various diets in PE has been deliberately tested" [61]. Nevertheless, it was noted that the incidence of eclampsia fell significantly during the first and second world wars and increased in the post-war years in Germany and the Netherlands, respectively, and this was attributed to dietary restriction during the war years [60]. In addition, there were numerous publications between 1922 and 1957 that reported differences in the rates of PE and eclampsia in indigenous versus European and urban populations (Algeria 1922, India 1938, Ceylon 1946, South Africa 1947, New Guinea 1949, Fiji 1950, Indonesia 1952, Belgian Congo 1956) [59,60]. Indigenous diets were noted to consist of "wholefoods" containing starchy root vegetables, leafy greens, home-pounded grains, fruit, and small quantities of milk, fish, and meat, if they were available. This was contrasted with European and urban diets that were high in refined grains (white rice and flour), sugar, and salt, and low in meat, milk, vegetables, and fruit [60].

According to the Global Burden of Disease Study, poor quality diet is one of the leading risk factors for morbidity and mortality globally [62]. International guidelines for the assessment and management of PCOS have recommended that lifestyle interventions, such as diet and exercise, should be discussed with all women diagnosed with PCOS [63]. More recent observational and intervention studies provide contemporary evidence to support the role of nutritional factors in PE [64]. Evidence-based summaries from systematic reviews, meta-analyses, and representative PE expert groups (PRECISE), recommend healthy maternal dietary patterns to reduce the risk of PE [47,64–66].

A recent comprehensive evidenced-based expert review of nutritional factors that may protect or exacerbate the risk of PE by the PRECISE Conceptual Framework Working Group, highlighted the importance of focusing on research related to healthy diet patterns rather than single nutrients [47].

 doi:10.20944/preprints202312.2120.v1



Nevertheless, they identified 25 nutritional factors in two umbrella reviews and twenty-two meta-analyses. Of these, 14 were found to be significantly associated with an increased incidence of PE. Healthy maternal diets containing fruits, vegetables, whole-grain foods, fish, and chicken, such as Mediterranean and New Nordic diets, were associated with 22% reduced odds of developing PE (OR: 0.78, 95% CI 0.70-0.86) [66]. In contrast, maternal diets high in ultra-processed foods and added sugars increased the odds of developing PE by 28% (OR: 1.28, 95% CI 1.15-1.42) [67]. Long-term longitudinal studies have shown that higher ultra-processed food intake in women is associated with increased cardiovascular risk and hypertension [68], as can occur in women with a history of PE [69]. These data support the recommendations of other expert reviews and the World Health Organization, on promoting healthy maternal diets [47,70,71].

Prospective cohort studies and observational research suggest that following a healthy lifestyle and diet prior to pregnancy is associated with reduced risk of PE. The multicenter prospective SCOPE study enrolled 5628 apparently healthy nulliparous women with singleton pregnancies, to examine the association of PCOS (354 women) with pregnancy complications, including PE [48]. The investigators reported that in this low-risk population the proportion of women with PE was similar in women with PCOS to those without PCOS (5.9% vs 6.7%; OR: 0.88, 95% CI 0.56-1.4). Pregnant women with PCOS were following a healthier lifestyle, including increased fruit and vegetable intake, more frequent vigorous exercise, lower alcohol consumption, and lower rates of smoking [48]. Analysis of data from the complete SCOPE cohort of 5628 women showed that lower intake of fruit and higher intake of fast food in the preconception period were associated with longer time to pregnancy [72]. A recent large meta-analysis of 21 cohort studies, showed that following a healthy lifestyle (diet and high physical activity) can also reduce the risk of developing GDM [73]. The authors highlighted the need for more randomized intervention trials. Taken together, these data suggest that nutritional factors may have an impact on fertilization, implantation, and placentation.

Intervention trials currently underway should help clarify the impact of lifestyle modification prior to pregnancy on in-utero metabolic factors and neonatal outcomes [74]. Recent developments in endometrial organoid research should provide insights into the molecular mechanisms involved in mediating the effects of metabolic and immune disturbances in women with PCOS with adverse pregnancy outcomes [75]. A recent endometrial organoid study compared cell-type-specific disease signatures and molecular pathways for PCOS-specific endometrial dysfunction in women with and without PCOS [76]. The investigators examined 248,694 nuclei from 6 endometrial cell subtypes. They reported a range of differentially expressed genes in cells and pathways related to processes involved in placentation. Women with PCOS were treated with either metformin or lifestyle management for 16 weeks, followed by repeat endometrial biopsy and establishment of a second endometrial organoid. Both treatments, either metformin or lifestyle intervention alone, restored multiple differentially expressed genes in each cellular subtype. This study provides new mechanistic insight into PCOS-specific endometrial dysfunction and the potential for reversibility with medical or lifestyle interventions.

Diet is a modifiable risk factor, and a balanced healthy diet has been shown to reduce the risk of PE [48]. Pregnant women should eat a diet rich in fruit, vegetables, and whole-grains, and healthy sources of fat and protein [65,71]. Women with PCOS should receive lifestyle-oriented counselling and advice, before, during, and after pregnancy, and be considered for inclusion in risk assessment algorithms for the prediction and assessment of PE as previously discussed.

## 4. Mechanisms of Action of Nutritional Factors in the Pathophysiology of PE

Advances in the understanding of normal placental development have paved the way for improved understanding of the pathogenesis and pathophysiology of abnormal placentation in PE [38]. The syndrome of PE may have multiple underlying causes that differ in early or late-onset presentations, all of which could be influenced by maternal nutritional disturbances [45,77]. Normal development of the placenta involves a complex network of communication signals between fetal-derived trophoblast and a broad range of maternal-derived endometrial cells [39]. The fetal-derived precursor cells of the placenta are affected by sperm-derived signals to endometrial cells prior to

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fertilization [78,79], paternal and maternal genetics [80], imprinted genes [81], epigenetic reprogramming following fertilization [82], nutritional components of oviduct fluid from cells lining the Fallopian tube prior to implantation [38,83], histotrophic nutrition during the first trimester [84], and haemotrophic nutrition following the establishment of significant blood flow into the placental intervillous space [85]. Disturbances of normal physiology in any of these components could lead to abnormal trophoblast-decidual dialogue and contribute to deficient trophoblast invasion into the uterus and impaired spiral artery remodeling, resulting in placental hypoperfusion and syncytiotrophoblast stress, as is known to occur in PE (Figure 1) [77].

It has been proposed that placental development, is independent of, and precedes, embryogenesis, because of a two-way feed-forward dialogue between trophoblast cells and endometrial glands [38]. Hormones from trophoblast (human chorionic gonadotrophin, human placental lactogen) and decidual cells (prolactin) stimulate glandular epithelial cells to upregulate production of nutrients (glucose, lipid droplets, glycoproteins) and growth factors (epidermal growth factor), that in turn feedback on trophoblast cells and promote further proliferation and growth of the placenta [38]. This new understanding has focused attention on the role of pre- and post-conception maternal pathophysiology, such as occurs in women with PCOS [3], altered nutrient supply, impaired bidirectional signalling, defective decidualization, and abnormal placentation in PE (Figure 1) [45,86–89].

Epigenetic processes also play an important role in the development and progression of PE [90] and a wide range of epigenetic changes involving methylation, histone deacetylation, and microRNA, have been identified in the placentas of women with PE [90,91]. Epigenetic processes are the mechanism by which environmental influences alter gene expression without changing the structure of DNA. In PE, reduced placental blood flow causes hypoxia and results in epigenetic changes that activate adaptive responses in the placenta and maternal circulation [92,93]. Nutrition, diet, and metabolism regulate epigenetic mechanisms and integrate environmental cues and exposures with cellular responses [94]. Cellular metabolites (acetyl coenzyme A, adenosine triphosphate, nicotinamide adenine dinucleotide) act as nutrient sensors and contribute to the regulation of gene expression via epigenetic mechanisms [95]. Reciprocal crosstalk between epigenetics and metabolism determines molecular programing and cellular function [94]. Maternal obesity can lead to placental dysfunction via chronic inflammation, dysregulation of metabolic pathways, and epigenetic changes in gene expression [96,97]. Unbalanced diets can alter normal metabolic and epigenetic processes and lead to disturbed cellular function and disease [98]. Recent research in nutritional epigenomics explains how lifestyle interventions (diet and exercise) can restore metabolic and epigenetic homeostasis [99,100]. The interaction between cellular metabolism and the epigenome is a fundamental process in placental development and PE that is influenced by maternal nutritional and environmental exposures [45,90,101–108].

The accumulating molecular, endocrine, metabolic, and epigenetic evidence provides detailed mechanistic explanations for the role of nutritional factors in the pathophysiology of PE that support the evidenced-based research and recommendations previously discussed. The following sections provide a brief discussion of the pathophysiological components of PCOS that may be involved in the pathogenesis of altered placental development and function in PE.

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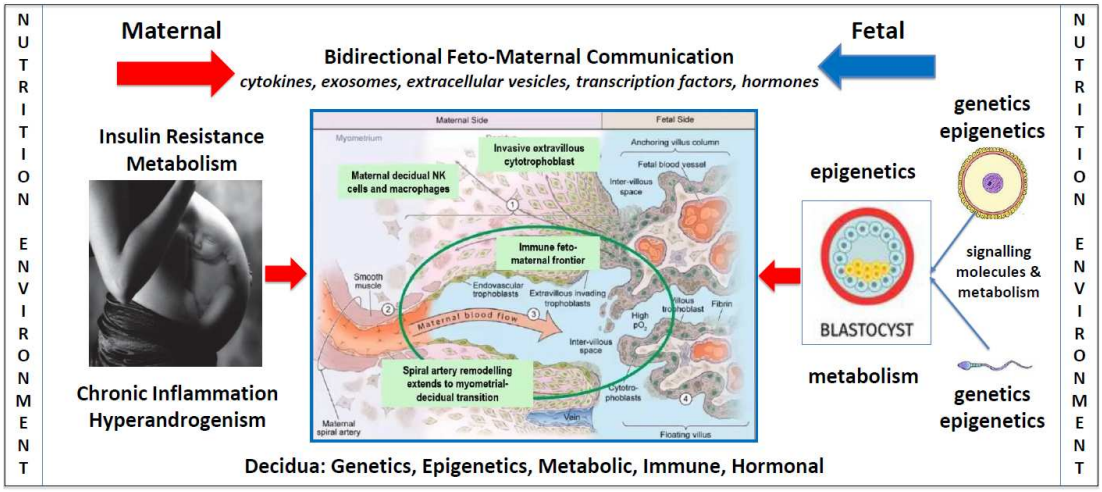


**Figure 1. Factors influencing bidirectional feto-maternal placentation.** A schematic model showing the potential impact of nutritional and environmental factors at all stages of pregnancy, including gametogenesis, decidualization, implantation, and placental and fetal development. The blue arrow represents the paternal, maternal, and fetal components. Nutritional and environmental factors influence sperm maturation and development in males [109]. Once sperm enter the reproductive tract, they release signalling molecules that interact with decidual cells prior to fertilization [78]. Human oocytes develop in the mother during embryonic development and are subject to nutritional and environmental factors that influence epigenetic developmental programming [110]. Maternal and paternal nutritional and environmental factors can therefore influence sperm and oocytes prior to fertilization and have the potential to alter bidirectional communication signals during placentation. The red arrow represents the effect of nutritional and environmental factors in maternal pathophysiology and their impact on decidualization, placentation, and embryogenesis. Following fertilization, the zygote and morula receive nutrition from maternal secretions in the Fallopian tube [38]. During implantation and throughout the first trimester, both the placenta and embryo obtain nutrition from histotroph fluid that is derived from maternal endometrial gland secretions [38]. These secretions provide glucose, lipids, glycoproteins, and growth factors that stimulate rapid proliferation of villous trophoblast, extravillous trophoblast invasion, spiral artery remodeling, and normal development of the placenta [85,111]. At the start of the second trimester blood enters the intervillous space resulting in haemotrophic nutritional exchange between the maternal and fetal circulations [112]. Accumulating evidence suggests that pathophysiological changes in women with PCOS, such as insulin resistance, chronic inflammation, and hyperandrogenism, may influence the composition and quality of histotrophic and haemotrophic nutrition, alter bidirectional communication between decidual and placental cells, and effect normal placentation and fetal development. Central diagram in blue is adapted with permission from Kingdom and Drewlo 2011 [113].

### *4.1. Insulin Resistance*

Insulin is a pleotropic hormone that has multiple cellular and tissue-specific actions such as regulation of glucose uptake in some cells (muscle, adipose, vascular endothelium) [114], increased production of endothelial nitric oxide resulting in vasodilation in systemic and cardiac blood vessels [115], reduced excretion of urate [116], enhanced sodium absorption in the kidney [117], and multiple metabolic effects [118]. Many of these physiological processes are known to be involved in the pathophysiology of both PCOS and PE [3,39].

Insulin resistance can be defined as an altered cellular response to insulin stimulation that occurs in selective cells and tissues throughout the body [118]. The development of physiological IR is a normal adaptation to pregnancy to ensure adequate placental growth and nutrient supply to the fetus [119]. All women develop progressive IR and hyperinsulinemia throughout pregnancy in response to various hormones (human placental growth hormone, human chorionic gonadotrophin, human placental lactogen) [120,121] and adipokines (adiponectin) produced by the placenta and maternal

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adipose tissue [122]. Pancreatic insulin secretion can increase by up to 250% during pregnancy to maintain euglycaemia [123]. Gestational diabetes is diagnosed if hyperglycaemia develops, as defined by national and international reference ranges, and is known to be associated with increased maternal and fetal complications [124,125]. Hyperinsulinaemia and/or hyperglycaemia related to GDM or PCOS may therefore be involved in pathological placental and fetal responses. Nutritional management is the cornerstone of treatment for both GDM and PCOS [25,126].

Most women diagnosed with PCOS prior to pregnancy have reduced insulin sensitivity, hyperinsulinaemia, and normoglycaemia [3,127]. Glucose metabolism has been shown to be important for preparation of the endometrium for embryo implantation. Pre-existing IR and hyperinsulinaemia have been associated with dysregulated decidualization and are thought to increase the risk of PE [128]. The expression of placental insulin receptors increases with gestational age, along with changes in the tissue distribution [129]. Although insulin sensitive glucose transporters are expressed in the placenta, the majority are not responsive to insulin stimulation [45]. Glucose transporters on the microvillous membrane of the syncytiotrophoblast move glucose into the cytoplasm by facilitated diffusion down the concentration gradient [85]. As a result, placental glucose transport to the fetus is mostly insulin independent. This may explain why maternal hyperglycaemia results in fetal hyperglycaemia and hyperinsulinaemia, which can be associated with adverse fetal (macrosomia) and placental effects [126]. Nevertheless, IR can interrupt glucose homeostasis and cause dysfunctional lipid metabolism and excessive inflammation, both of which are associated with PE [45].

Insulin resistance in early pregnancy has been shown to be predictive for the development of PE [130]. Pre-existing IR, coupled with the effects of chronic inflammation and hyperandrogenemia, is likely to have additive pathological effects on placental development and may be involved in the pathogenesis of PE [86,119]. Insulin has been shown to inhibit the activity of aromatase in human trophoblasts [131], which may provide a mechanism for connecting hyperinsulinaemia with placental androgen excess in women with PCOS. Elevated insulin levels were found to cause increased DNA damage, apoptosis, and decreased cell survival in cultured first trimester trophoblasts from healthy pregnancies [42]. Transcriptome signatures in placental trophoblasts exposed to insulin showed that the many biological processes (hormonal, cytokine, cell cycle, metabolic) were either up- or downregulated by insulin [132]. Trophoblast cells from the placenta of obese women were 30-times less sensitive to insulin than cells from normal-weight women. The investigators proposed that the enhancement of placental-specific genes supports the concept that insulin promotes both endocrine and growth functions in the placenta, and that IR and obesity can affect the structure and function of the placenta in early pregnancy [132]. Obese women have greater placental lipid accumulation (lipotoxicity and “fatty placenta”) than normal weight women [133]. Excess placental lipid may be due to changes in fatty acid uptake, decreased fatty acid oxidation, or increased esterification, and may contribute to increased lipid supply to the fetus and fetal adiposity [134]. These data support previous reports that show placental size and volume are strongly related to maternal insulin secretion in early pregnancy [135]. Nevertheless, obesity is often associated with hyperinsulinaemia, hyperglycaemia, and hypertriglyceridemia, which makes it difficult to separate the effects that may be driven by obesity from those caused by GDM or PCOS in women who have some or all these problems [134].

Maternal metabolism and cardiovascular physiology are altered in pregnancy in response to the increasing demands of placental and fetal growth [136]. Maternal vascular endothelial dysfunction is a classic feature of PE that is thought to be secondary to reduced placental blood flow and release of pro-inflammatory cytokines, reactive oxygen species, extracellular vesicles, and imbalance of angiogenic and anti-angiogenic factors [39,137]. Experimental studies have shown that women with PCOS have endothelial dysfunction (impaired endothelium-dependent vasodilation) and reduced response to the vasodilation effect of insulin [138–141]. The observed endothelial dysfunction may be related to both elevated androgen levels and IR [138,140]. In addition, PCOS is often associated with chronic hypertriglyceridemia [142], which is a known risk factor for endothelial dysfunction and may cause arteriolar vasoconstriction by altering the regulation of prostaglandins [143]. A systematic

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review and meta-analysis showed that women that develop PE had elevated serum lipids and triglycerides during all trimesters of pregnancy [88]. Both maternal and placental factors may therefore converge on the maternal endothelium to produce the observed pathological manifestations of PE [86]. Women with PCOS may be at increased risk of PE due to the combined effects of inflammation, hyperandrogenemia, hypertriglyceridemia, and IR, on vascular endothelial function.

In summary, accumulating evidence suggests that IR can affect normal placental development and may contribute to the pathophysiology of PE via a variety of mechanisms. Future research involving molecular techniques, computational advances, multiomics data, and endometrial organoids, should help our understanding of the effect of maternal IR on placental nutrient and energy utilization, growth pathways, and placental physiology. The investigation of maternal nutritional insults on placental development and function may open the way for interventions that mitigate the impact on adverse pregnancy-related outcomes, such as those that occur in PE.

### *4.2. Chronic Systemic Inflammation*

Pregnancy is characterized by a state of chronic low-grade inflammation due to systemic release of a variety of placental cytokines that are required for normal placental development and function [132,144]. PCOS is also characterized by chronic inflammation that is thought to be secondary to poor-quality nutrition, nutritional excess and other environmental factors that affect metabolic and inflammatory signal transduction pathways [3,145,146]. Women with PCOS also have a chronic low-grade inflammatory state during pregnancy that has been found to be associated with a higher risk of adverse obstetric outcomes [147–149]. Abnormal maternal inflammation has been associated with altered uteroplacental development and function [150], although the precise mechanisms are largely unknown.

Women with PCOS appear to have a proinflammatory state that is intrinsic to the underlying pathophysiology [3]. This may contribute to altered endometrial immune cell (natural killer cells, macrophages, T cells) and cytokine profiles (interleukin 15 and 18, chemokine ligand 10), that compromise normal implantation [151,152]. Women with PE have a heightened inflammatory state with elevated proinflammatory cytokines and chemokines, both systemically and in the placenta [150,153]. Studies in rodents and non-human primates have provided evidence of mechanistic links between maternal inflammation and PE [150,154]. Lipopolysaccharide-induced inflammation in pregnant rats showed that inflammation was associated with deficient trophoblast invasion and spiral artery remodeling [150]. In addition, inflammation increased maternal mean arterial pressure and was associated with structural changes in the kidney and proteinuria, as is found in PE [150]. Wilson et al demonstrated increased syncytiotrophoblast inflammation in a testosterone-induced primate model of PCOS using a novel contrast-enhanced ultrasound technique [154].

Maternal diet during pregnancy can also influence systemic and placental inflammation and may provide a mechanistic link between PCOS and PE [155,156]. Diet quality has been found to influence insulin signaling and inflammatory pathways in rodents and humans [157]. Higher quality diet was shown to improve insulin signaling in the placenta using a mouse model of maternal obesity [157]. Francis et al examined the effect of consuming a healthy diet on a range of placental proteins involved in metabolic pathways and inflammation [156]. They assessed diet quality using the Healthy Eating Index, which is based on consumption of vegetables, fruit, dairy, protein, whole grains, and unsaturated fats, with lower intakes of red and processed meat, and added sugar [158]. They found that proteins of the p38MAPK inflammatory signaling pathway were lower in placental villi of pregnant women consuming a healthier diet. Placental p38MAPK is upregulated by proinflammatory stimuli and has been linked to placental angiogenesis and further production of proinflammatory cytokines [159]. Taken together, these data support the findings of observational studies linking healthy diets to improved pregnancy outcomes, and lower rates of PE, as previously discussed.

Pathological levels of maternal inflammation may result in altered decidual and placental inflammatory responses that affect placental development and function [41,150,160]. Inflammatory processes can contribute to, and exacerbate, the effects of insulin resistance and hyperandrogenism

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[1]. Previous reviews have discussed the role of chronic low-grade inflammation and altered immune function in PCOS [3] and PE [41].

### *4.3. Hyperandrogenism*

The presence of hyperandrogenism in non-pregnant women with the PCOS is associated with increased metabolic and cardiovascular risk [161–164]. Although not all studies report increased adverse pregnancy outcomes in different PCOS phenotypes [165], the majority of published reports demonstrate an association between hyperandrogenism and complications such as gestational diabetes, preterm delivery, and PE [166–168]. PCOS is associated with altered histological structure of the placenta, including microscopic alterations in trophoblast invasion [169,170], that may be increased in women with hyperandrogenism [171]. Maternal hyperandrogenism has also been found to be an independent predictor of PE [168].

The relationship between androgens and maternal cardiovascular and placental function has been investigated in human and animal models [172]. Placental androgen receptor gene expression is increased and placental aromatase mRNA and protein expression are decreased, in the placenta of women with PE [173]. Serum testosterone levels of preeclamptic women are elevated (2-3 fold) and are correlated with vascular dysfunction [172]. Elevated androgens in pregnant rats are involved in gestational hypertension (reduced uterine arterial blood flow) [174], endothelial dysfunction (impaired nitric oxide-mediated relaxation in systemic and uterine vessels) [174,175], heightened vasoconstriction in response to angiotensin II [175], decreased spiral artery remodeling (inhibition of angiogenesis, reduced radial and spiral artery diameters, increased UtAPI) [176], placental hypoxia (increase in hypoxia-inducible factor) [176], and altered nutrient transport (reduced amino acid transport) [173]. All of these factors are known to be involved in the pathophysiology of PE.

Both IR and chronic inflammation can cause and exacerbate hyperandrogenism in women with PCOS [1,3]. Insulin stimulates androgen production in theca cells of normal ovaries and likely contributes to elevated maternal testosterone levels [172,177,178]. Insulin inhibits the aromatase enzyme in human trophoblasts which may result in a placental contribution to maternal hyperandrogenemia [131]. Chronic inflammation can cause hyperandrogenism via a number of mechanisms including disruption of signaling pathways, alteration to epigenetic processes, and posttranscriptional regulatory effects [9]. Hyperandrogenism in PCOS may be due to the synergistic actions of IR and chronic ovarian and systemic inflammation [3,179]. The degree of hyperandrogenism in women with PE varies depending on the sex of the fetus, with higher levels in pregnancies with a male fetus [173]. Therefore, women with PE may have elevated androgen levels due to a combination of fetal, maternal, and placental sources.

A detailed discussion of the effects of hyperandrogenism on maternal vascular and placental function and the implications for the pathogenesis of PE are beyond the scope of the present report and can be found in previous comprehensive reviews [172,180]. Taken together, these data strongly suggest that many androgen-mediated actions are important contributors to the pathophysiology of PE. The majority of women with PCOS have hyperandrogenemia [181] that may contribute to dysregulated androgen signaling in the placenta and increase the frequency of maternal-fetal complications associated with PE [172].

## 5. Identification, Assessment, and Management of Women with PCOS in Pregnancy

Early identification of women at increased risk of developing PE has been advocated to help reduce the associated maternal and perinatal morbidity and mortality [34,53]. There has been a general lack of awareness of the significant association between PCOS and adverse pregnancy outcomes, including PE. Healthcare professionals do not usually identify women with PCOS during antenatal care, delivery, or post-partum [182]. This is reflected in the absence of inclusion of PCOS in risk assessment algorithms for PE, and lack of specific recommendations for screening, monitoring, and treatment of women with PCOS during pregnancy [58]. The 2023 international guidelines include a meta-analysis of 109 studies that explored the relationship between PCOS and adverse pregnancy outcomes [63]. As previously discussed, women with PCOS had a significantly increased risk of

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developing PE on pooled analysis (OR: 2.28, 95% CI 1.88-2.77), that was even greater when only high-quality studies were assessed (OR: 3.05, 95% CI 1.20-7.8) [52].

Accumulated evidence from 8 systematic reviews over the past 40 years, therefore report a significantly increased risk of PE in women with PCOS [52]. These data, coupled with the increasing availability of early pregnancy screening for PE [34], suggest that women with PCOS should be included in risk assessment algorithms and be considered for screening and possible treatment to reduce the risk of developing PE.

Screening may include measurement of mean arterial blood pressure, ultrasound with mean UtAPI, and maternal serum biochemical markers (PAPP-A and/or PlGF) [54,183,184]. Several prospective studies have demonstrated the predictive value of measurements of the serum sFlt-1/PlGF ratio for diagnosis, monitoring, and management of women at high-risk of developing PE [34,53,185–187]. Low-dose aspirin treatment starting before 16 weeks and continued to 37 weeks, has been shown to significantly reduce the likelihood of preterm pre-eclampsia (62% reduction), preterm birth, and other associated complications [49]. Low-dose aspirin (<300mg per day) selectively inactivates endothelial cyclooxygenase and inhibits the biosynthesis of placental thromboxane A [33,188]. The mechanism by which aspirin prevents PE is unknown but may include improvements in placentation, inhibition of platelet aggregation, and anti-inflammatory effects [188–191]. Women with PCOS identified as high-risk on first trimester screening, could be offered low-dose aspirin prophylaxis followed by repeated angiogenic ratio measurements starting at 22 weeks gestation, as per established protocols (Figure 2) [53].

Low-dose aspirin has been co-administered with a variety of other medications for ovulation induction in women with PCOS-related infertility. These include clomid [192], letrozole [193], tamoxifen [194], and Chinese medicine [195]. When considered together, these studies report improved oocyte quality, higher pregnancy rates, and increased endometrial thickness. It is not possible to determine the impact of aspirin on placentation or pregnancy outcomes from these studies due to the combined administration with other medications. Nevertheless, aspirin is a non-steroidal anti-inflammatory medication with known hemodynamic and immunomodulatory effects and may have beneficial effects on placentation in high-risk women when initiated in the periconception period. A randomized trial sought to investigate this possibility by comparing low-dose aspirin monotherapy with placebo [196]. Preconception aspirin resulted in a non-significant increase in live birthrate among a large cohort of women with a history of pregnancy loss. A secondary analysis of women who were adherent to low-dose aspirin for at least 4 days per week showed improved reproductive outcomes [197]. A further secondary analysis in women with a history of low-grade inflammation, assessed by elevated high-sensitivity C-reactive protein (hsCRP), found that women in the lowest hsCRP tertile had increased live birth rates (RR: 1.35, 95% CI 1.08-1.67). Taken together, these studies raise some important issues for the management of women with PCOS as most women with PCOS have low-grade chronic inflammation and increased risk of pregnancy-related complications. Future studies are required to evaluate the impact of periconception aspirin in women with a history of adverse pregnancy outcomes and/or PCOS. In the meantime, the beneficial effects of lifestyle and postconception aspirin treatment are supported by a significant body of evidence, as previously discussed.

Recent studies have suggested that it may be possible to stop aspirin at 28 weeks gestation if the angiogenic ratio (sFlt-1:PlGF) and/or the UtAPI are normal [198,199]. Mendoza et al performed a multicentre, open label, randomized trial of 968 pregnant women who were at high-risk of preterm PE on first trimester screening (StopPRE trial) [198]. All women were commenced on aspirin 150mg per day before 16 weeks and 6 days gestation, followed by an sFlt-1:PlGF ratio at 24 to 28 weeks. Participants with a ratio less than 38 were randomized to either continue aspirin (control group) or discontinue aspirin treatment (intervention group). The incidence of preterm PE and delivery before 37 weeks gestation was 1.48% (7/473) in the intervention group and 1.73% (8/463) in the control group (absolute difference -0.25%; 95% CI: -1.86% to 1.36%) [198]. Aspirin commenced in high-risk women before 16 weeks and 6 days and discontinued at 24-28 weeks, was not inferior to aspirin continued to

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37 weeks for preventing preterm PE in women who had a normal sFlt-1:PlGF ratio at 24-28 weeks. There were no significant differences in any other adverse pregnancy or neonatal outcomes.

Bonacina et al performed a post-hoc analysis of the StopPRE trial described above [199]. In the secondary analysis women with a UtAPI >90$^{th}$ percentile were excluded. A total of 836 women were randomized to continue (control group 416) or discontinue aspirin treatment (intervention group 420). Preterm PE occurred in 0.7% (3/409) in the intervention group and 1.3% (5/395) of the control group (absolute difference -0.53; 95% CI: -1.91 to 0.85). Discontinuation of aspirin at 24-28 weeks gestation in women with a UtAPI index <90$^{th}$ percentile was non-inferior to continuing aspirin treatment until 36 weeks for preventing preterm PE. Women in the intervention group had significantly less minor bleeding complications than women in the control group [199]. These findings are consistent with previous cohort studies showing that low-dose aspirin use during pregnancy may be associated with increased postpartum bleeding and haematoma [200].

The authors of the secondary analysis of the StopPRE trial concluded that high-risk women commenced on aspirin at <16 weeks gestation who had either a sFlt-1:PlGF ratio <38 or UtAPI <90$^{th}$ percentile, could discontinue aspirin at 24-28 weeks [199]. If further large trials confirm these findings, ceasing aspirin at 24-28 weeks could result in increased compliance and reduced bleeding risk, without loss of treatment efficacy.

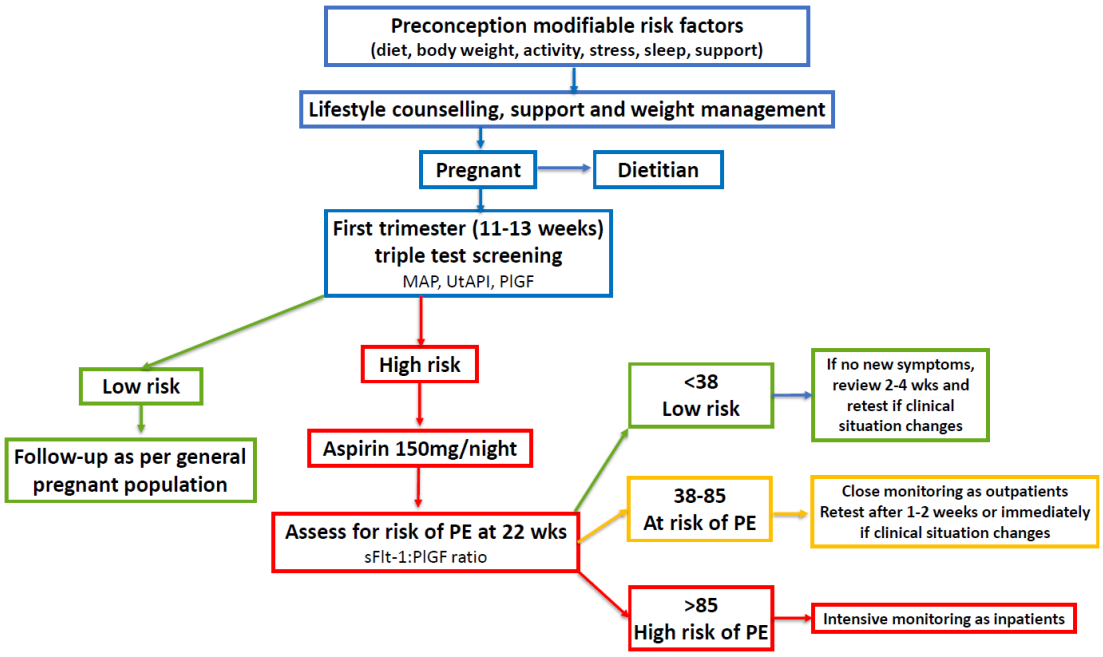


**Figure 2.** Risk assessment and management of women with PCOS before and during pregnancy.

First trimester triple test screening is based on references [54,184]. Use of aFlt-1:PIGF ratio is based on references [34,53]. Mean Arterial Pressure (MAP; Uterine Artery Pulsatility Index (UtAPI); Placental Growth Factor (PlGF); soluble fms-like tyrosine kinase-1 (sFlt-1).

In summary, the diagnosis of PCOS can reliably be made on history at first presentation in early pregnancy [201,202]. Women with PCOS should be offered nutritional advice from a dietitian and considered for prophylactic aspirin treatment as per Fetal Medicine Foundation or local guideline recommendations [183,203]. Women identified as high risk on screening should be offered low-dose aspirin (100-150mg/day, taken at night) starting before 16 weeks of pregnancy then followed by repeat angiogenic ratio measurement from 22 weeks gestation (Figure 2) [53,204]. In addition, health practitioners involved in antenatal care should be educated about the risk of pregnancy complications and PE in women with PCOS. Future research should be directed at investigating the underlying pathophysiology that predisposes women with PCOS to an increased risk of PE.

## 6. Conclusions

Polycystic ovary syndrome is a multisystem metabolic and endocrine disorder that is associated with an increased risk of pregnancy-related complications, including PE. International guidelines recommend lifestyle treatment, including diet and exercise, as the first line of management for all women with PCOS. A significant body of evidence supports the recommendations of expert advisory groups that healthy diet patterns reduce the risk of PE. PCOS is usually diagnosed in adolescence or early adulthood and presents an ideal opportunity for preventative lifestyle interventions that can be implemented prior to conception to reduce the risk of pregnancy complications. Women with a history of PCOS can also be assessed in early pregnancy and given lifestyle advice and support. In addition, women with PCOS can also be evaluated with first trimester triple test screening and advised about their eligibility for prophylactic medical therapy to reduce the risk of PE. Implementation of preventative intervention strategies have the potential to reduce pregnancy-related complications and future development of transgenerational chronic disease-related morbidity and mortality in women with PCOS and their offspring.

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