Reply: Polycystic ovary syndrome and pregnancy

Sir,

We thank Dr Galazis for his interest in our review (Palomba *et al.*, 2015) and for the issues raised about the increased risk of pregnancy complications in women with polycystic ovary syndrome (PCOS). Our comprehensive review demonstrated that women with PCOS have a 2-fold increased risk of gestational diabetes mellitus (GDM) and a 3–4-fold increased risk of pregnancy-induced hypertension (PIH) and pre-eclampsia (PE) when compared with non-PCOS controls (Palomba *et al.*, 2015). Notwithstanding the impact of PCOS on human reproduction, recent guidelines of the Endocrine Society (Legro *et al.*, 2013) suggested that fertility in patients with PCOS is impaired exclusively in the presence of oligoanovulation and that the reproductive outcomes in women with PCOS are not worse compared with non-PCOS controls. Indeed, the meta-analytic results were obtained including data from low-powered studies with retrospective/prospective design, and were not adjusted for several confounders which could affect the risk of pregnancy complications irrespective of PCOS. Moreover, considering the largest cohort studies, in which the specific odds ratios for pregnancy complications were adjusted for confounders, the resulting risk only slightly decreased. However, the most important message of our review (Palomba *et al.*, 2015) is that, although the exact mechanism(s) involved in the pathogenesis of the obstetric and neonatal complications in PCOS are currently unknown, women with PCOS should be considered as "high-risk patients" since they show genetic, environmental, clinical and biochemical characteristics that are associated with increased risks of pregnancy complications.

Considering the high incidence of GDM in PCOS, the Royal College of Obstetricians and Gynaecologists (Green-top Guidelines N. 33, 2014) stated that clinicians may consider offering screening for GDM before pregnancy and 2-hour post 75 g oral glucose tolerance test at 24–28 weeks of gestation to all pregnant women with PCOS. Moreover, specific data on the effect of an intensive strategy to diagnose GDM in women with PCOS on maternal and neonatal mortality/morbidity are lacking. There are few clinical studies with the aim to test preventive interventions on the risk of developing GDM in women with PCOS. Metformin has been proposed to improve insulin sensitivity in pregnant women with PCOS (Palomba *et al.*, 2009; Sivalingam *et al.*, 2014). Furthermore, the systematic review and meta-analysis by Zhuo *et al.* (2014) demonstrated a reduction of the risk of GDM in women with PCOS only in non-randomized controlled trials (RCTs). In addition, the reduction of about 80% of the GDM risk observed in non-RCTs, although statistically significant, should be considered as not clinically relevant since very far from a relative risk below 2 points, as suggested by epidemiologists (Sackett *et al.*, 1991).

On the other hand, patients with PCOS are at increased risk for a persistent impaired glucose metabolism after GDM (Palomba *et al.*, 2012) and probably need to be managed actively. To this regard, a recent placebo-controlled RCT (Aroda *et al.*, 2015) demonstrated that lifestyle intervention and metformin treatment in women with a history of GDM reduce the progression to type 2 diabetes by 35 and 40%, respectively, during a 10-year follow-up period.

Hypertensive disorders during pregnancy, including PIH and PE, may result in substantial maternal and neonatal/fetal morbidity, and in long-term increased cardiovascular risk. A recent study on placentas of women with PCOS demonstrated specific inflammatory and vascular alterations (Palomba *et al.*, 2015). Placental function could be assessed with umbilical artery Doppler velocimetry. However, currently, no scientific data in umbilical artery Doppler velocimetry are available for pregnant patients with PCOS. On the other hand, the evaluation of the uterine artery Doppler velocimetry during the first and mid-second trimester of pregnancy could be an useful technique for an early assessment of the risk of the development of PIH/PE in women with PCOS. One study demonstrated that the detection rate of the abnormal uterine artery Doppler indices was higher in women with PCOS compared with controls (Palomba *et al.*, 2010). This could mean that pregnant women with PCOS have a potential failure of trophoblastic invasion into the musculoelastic coat of the spiral arteries, which could result in incomplete vascular transformation and persisting increased impedance of the uterine arteries (Palomba *et al.*, 2015).

Unfortunately, no specific intervention is suggested to be useful for women with PCOS, despite when a woman is considered to be at high risk because of abnormal uterine artery Doppler velocimetry. In pregnant patients with PCOS the use of metformin failed to improve the uterine artery blood flow in a randomized placebo-controlled study (Stridsklev *et al.*, 2014), and the administration of low-dose aspirin could be considered only in cases of women with PCOS and a history of preterm PE or recurrent PE (Sibai, 2015).

In conclusion, considering the heterogeneous aetiological factors involved in the increased risk of pregnancy complications in women with PCOS, there remains a lot to be desired because of the complex selection of patients who need to be considered as 'high-risk' and the potential intervention strategies which should be multifactorial.

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