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REVIEW

Pregnancy complications in spontaneous and assisted conceptions of women with infertility and subfertility factors. A comprehensive review

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Abstract In the literature, there is growing evidence that assisted reproductive techniques increase the risk of pregnancy complications in subfertile couples. Moreover, many concomitant preconception risk factors for subfertility are frequently present in the same subject and increase the risk of pregnancy complications. This review aimed to summarize in a systematic fashion the best current evidence regarding the effects of preconception maternal factors on maternal and neonatal outcomes. A literature search up to March 2016 was performed in IBSS, SocINDEX, Institute for Scientific Information, PubMed, Web of Science and Google Scholar. An evidence-based hierarchy was used to determine which articles to include and analyse. Available data show that the risk of pregnancy complications in spontaneous and assisted conceptions is likely multifactorial, and the magnitude of this risk is probably very different according specific subgroups of patients. Notwithstanding the only moderate level and quality of the available evidence, available data suggest that the presence and the treatment of specific preconception cofactors of subfertility should be always taken into account both in clinical practice and for scientific purposes.

KEYWORDS: complications, infertility, obstetric, pregnancy, subfertility

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Introduction

Many investigations note increased risks of obstetric and/or neonatal complications in infertile patients or when pregnancy is achieved after medical or surgical treatment for enhancing fertility (Barnhart, 2013). The Centres for Diseases Control and Prevention (CDC) report on assisted reproductive techniques surveillance states that assisted reproductive procedures are associated with potential risks to the mother and fetus (Sunderam et al., 2015). However, available data are heterogeneous and complex because infertile couples often have preconception comorbid and potentially unrecognized risk factors for subfertility, and the underlying risk factors that lead to infertility may also lead to pregnancy complications and long-term maternal and offspring health problems. Multiple maternal factors associated with infertility may contribute to the adverse outcomes rather than the assisted reproductive procedures themselves (Hayashi et al., 2012). In fact, data adjusted for maternal age, parity, prepregnancy height and weight, smoking, alcohol consumption and pre-existing medical and gynaecologic diseases, revealed no difference in obstetric and/or neonatal complication rates among 242,715 women with singleton pregnancies that received different treatments for infertility (Hayashi et al., 2012). Thus, a substantial proportion of the increased risks in assisted reproductive techniques singleton pregnancies can be attributed to parental characteristics (Pinborg et al., 2013). A growing number of studies have shown that reproductive disorders can per se induce an increased risk of pregnancy complications with similar mechanism of action (Vannuccini et al., 2016). This is true for systemic diseases, such as obesity or polycystic ovary syndrome (PCOS), and for gynaecological conditions, such as uterine fibroids and polyps and endometriosis/adenomyosis.

Another difficulty is to distinguish the contribution of specific reproductive disorders or infertility/subfertility to poor pregnancy outcomes (regardless of fertility treatment) (Talaulikar and Arulkumaran, 2012) because reproductive disorders rarely occur alone (Holoch et al., 2014). The treatment of one or more subfertility factors before natural or assisted conception may be another crucial confounder influencing the pregnancy and neonatal outcomes. Thus, the overall obstetric risk includes the woman's characteristics and genetics, obstetric risks such as twins, and finally the potential impact of each element of assisted reproductive techniques.

Although meta-analyses and population-based studies have been conducted on the obstetric risks of infertility/subfertility and its treatments, there was no single comprehensive systematic review on the impact of subfertility and reproductive disorders on pregnancy outcomes independently from the use of assisted reproductive techniques. Thus, the aim of the current study was to review comprehensively and in a systematic fashion available evidence regarding the effects of preconception maternal factors on maternal and neonatal outcomes in spontaneous and assisted conceptions.

Materials and methods

Multiple strategies were used to search and identify relevant demographic, epidemiological, clinical and experimental studies. Sociological online libraries (IBSS, SocINDEX), Institute for Scientific Information, PubMed, Web of Science and Google Scholar were consulted. Only articles written in English were considered. Studies available up to March 2016, and reporting data about the relationship between obstetric and neonatal complications and conditions related to subfertility/infertility and their treatments were included.

Additional journal articles were identified from the bibliography of the studies initially included. Literature searches and abstract screening were performed by two researchers (SP and SS).

An evidence-based hierarchy was used to determine which articles were included. The study included meta-analyses for each specific issue, and updated them with more recent clinical studies. A priority was given for randomized controlled trials (RCT). Moreover, nonrandomized prospective, uncontrolled prospective, retrospective and finally experimental studies were considered sequentially. In cases when specific data for infertile patients were unavailable, data was reported from the general populations to provide a frame of reference. Any disagreement or uncertainty was resolved by discussion to reach a consensus.

An attempt to summarize the available best evidence about the relationships between each subfertility factor and main adverse obstetric and neonatal outcome was performed. Level and quality of evidence for each relationship was assessed. The level of evidence was evaluated according to The Oxford Centre for Evidence-Based Medicine (OCEM)–Levels of Evidence 2011 guidelines (2011) (http://www.cebm.net/index.aspx?o=5653). The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al., 2011).

Infertility

Infertility is usually defined as the failure to achieve a clinically detectable pregnancy after more than 12 months of regular unprotected intercourses (the time to pregnancy [TTP] longer than 12 months) (Boivin et al., 2007). It is common, affecting at least one out of six couples (Boivin et al., 2007). Irrespective of the cause of infertility, the TTP is an important factor influencing the risk of pregnancy complications after conception. Saunders et al. (1988) first reported that infertility is an independent risk factor for subsequent problems during pregnancy. Subsequently, many studies suggested that infertility itself, regardless of treatment, is associated with an elevated risk of adverse pregnancy outcome. As infertility is a heterogeneous condition, it is possible that some of the mechanisms leading to infertility also play a role in the aetiology of these adverse outcomes.

A systematic review with meta-analysis (Messerlian et al., 2013) analysed the effect of TTP of more than 12 months on pregnancy and neonatal complications. The study included a total sample size of 1,269,758 births, including 19,983 in the exposed/infertile group and 1,249,775 in the unexposed/fertile group, and 68,885 preterm births (PTB). When only five studies including matched or stratified participants were analysed, pregnancies with TTP longer than 12 months had an odds ratio (OR) of 1.39 (95% confidence interval [CI] 1.20 to 1.62) for PTB. If the eight studies where regression models were used are pooled, the result was modestly attenuated

(OR 1.31, 95%CI 1.21 to 1.42) with very low heterogeneity (Messerlian et al., 2013). Women conceiving after long TTP also had increased odds of giving birth to children with low birth weight (LBW) (OR 1.30, 95%CI 1.16 to 1.45; OR 1.5, 95%CI 1.27 to 1.78; and OR 1.34, 95%CI 1.21 to 1.48, for crude pooling, pooling of studies matching data and pooling of regression-adjusted studies, respectively) (Messerlian et al., 2013). In contrast, long TTP was not associated with a small for gestational age (SGA) fetus (Jaques et al., 2010).

These data were confirmed in a subsequent systematic review that aimed to clarify factors responsible for the increased risk of adverse neonatal outcomes in assisted reproductive treatment pregnancies (Pinborg et al., 2013). Specifically, the risk of PTB was 35% higher in spontaneous conception singletons of couples with TTP longer than 12 months than in spontaneous conception singletons of couples with TTP shorter or equal to 12 months (adjusted OR [aOR] 1.35, 95%CI 1.22 to 1.50) (Pinborg et al., 2013).

One large retrospective trial (Tobias et al., 2013) of 40,773 pregnancies demonstrated a moderate association between a TTP longer than 12 months and the incidence of developing gestational diabetes mellitus (GDM). The risk ratio (RRa) for GDM with TTP longer than 12 months adjusted for age was 1.50 (95%CI 1.34 to 1.69), for pre-pregnancy body mass index (BMI) was 1.38 (95%CI 1.23 to 1.55) and for pre-pregnancy lifestyle characteristics 1.39 (95%CI 1.24 to 1.57) (Tobias et al., 2013). Secondary analyses evaluating the incidence of GDM stratified by causes of infertility demonstrated increased risk with ovulation disorders (RRa 1.52, 95%CI 1.23 to 1.87), tubal infertility (RRa 1.83, 95%CI 1.20 to 2.77) and unexplained infertility (RRa 1.44, 95%CI 1.14 to 1.84) (Tobias et al., 2013). Also more recently, infertility per se, rather than infertility treatment, was confirmed to be closely related with increased risk of adverse outcomes in singleton pregnancies (DoPierala et al., 2015). No differences in adverse pregnancy and neonatal outcomes were detected between the treated and untreated subfertile couples, whereas pre-eclampsia (adjusted relative risk [aRR] 1.18, 95%CI 1.02 to 1.37), antepartum hemorrhage (AH) (aRR 1.32, 95%CI 1.18 to 1.47) and very early preterm birth (VEPTB) (aRR 1.96, 95%CI 1.53 to 2.49) resulted higher in subfertile women. Moreover, infertility was defined not only as a TTP higher than 12 months despite regular unprotected sexual intercourse but also in cases of amenorrhoea, polycystic ovaries or tubal damage.

Finally, other specific and partially unknown factors should ideally always be included for adjusting the analyses. For example, a large hospital-based cohort study (Messerlian et al., 2015) demonstrated that parity modified the aRR of complicated pregnancy in infertile patients who did not received any treatment when compared with fertile women who had spontaneous conception.

Advanced maternal age

In literature, the advanced maternal age has not had a univocal definition. Among women with proven prior fertility, the probability of infertility increased from 10%–20% after 35 years of age and to 45% in the early forties with particular regard for women who have never conceived (Steiner and Jukic, 2016). However, women over 35 years old are having more babies in developed countries (Martin et al., 2013). A cohort study (Laopaiboon et al., 2014) evaluated the association between maternal age and adverse maternal and perinatal outcomes using the 2010–2011 World Heaalth Organization (WHO) Multicountry Survey on Maternal and Newborn Health (WHOMCS) data set. This is comprised of over 314,000 deliveries from 29 countries, the majority developing nations. A total number of 276,291 women were included; 238,504 women 20–34 years old were considered as a reference group, whereas 29,245 women 35–39 years old, 7,015 women 40–44 years old and 1,527 women 45 years old or older were study groups (Laopaiboon et al., 2014). The increase of the maternal age was linearly associated with an increased risk for maternal near miss events, with an adjusted OR (aOR) of 1.5 (95%CI 1.3 to 1.8), 2.2 (95%CI 1.7 to 2.8) and 3.5 (95%CI 2.2 to 5.5) for 35–39, 40–44 years, and >45 years, respectively. The aOR for maternal death were 1.7 (95%CI 1.2 to 2.6), 2.6 (95%CI 1.4 to 4.7) and 4.3 (95%CI 1.5 to 12.1) for the same three groups. Risks for adverse perinatal outcomes, such as PTB, stillbirth, early neonatal mortality, perinatal mortality, LBW (<2500 g) and neonatal intensive care unit (NICU) admission, were also increased in the three age groups in a 'dose-dependent' fashion (Laopaiboon et al., 2014).

Similar findings were noted in a recent study (Barton et al., 2014) that stratified analysis based on obesity. This cohort included 53,480 nulliparous women; 1,231 women ≥40 years old were compared with a reference group of 52,249 20–29 years of age (Barton et al., 2014). Both obese and non-obese women older than 40 years old had an increased risk of Caesarean deliveries (CDs), GDM, PTB and LBW when compared with younger patients (Barton et al., 2014). In women over 40, the negative effect of obesity on the risk of pregnancy induced hypertension (PIH), VPTB and NICU admission seemed to be more evident (Barton et al., 2014). Another large retrospective cohort study (Jacquemyn et al., 2014) confirmed these findings. Data regarding the pregnancy outcomes were analysed by age (22,586 women aged 25, 15,206 women aged 30, 3,405 women aged 40 and 421 women aged 45 or older). With advancing maternal age and irrespective of confounders, a significant linear increase for LBW (<2.500 g), PTB (<37, <35 weeks and <29 weeks), PIH, GDM and CD was noted. Perinatal mortality was also more than doubled across age groups shifting from 4.9‰ to 9.5‰ pregnancies (Jacquemyn et al., 2014). More recently, an extremely advanced maternal age (equal to or higher than 50 years), when compared with a reference age of 20–34 years, resulted in a five- and three-fold increase in the risk of severe maternal morbidity (RR 5.08, 95%CI 1.65 to 15.6) and of NICU admission (RR 3.1, 95%CI 2.2 to 4.4) in spontaneous conception, respectively (Osmundson et al., 2016). The risk of CD (RR 2.42, 2.11 to 2.78) and placenta previa (RR 6.86, 95%CI 3.32 to 14.19) also resulted two- and six-fold higher (Osmundson et al., 2016). Also data, restricted to primiparae women and adjusted for multiple confounders including chronic diseases and the use of a young oocyte donor, confirmed that an advanced age (higher than 45 years) is an independent risk factor for GDM (aOR 2.4, 95%CI 1.3 to 4.3), PIH (aOR 5.8, 95%CI 2.7 to 12.6) and pre-eclampsia (aOR 2.5, 95%CI 1.0 to 5.9) (Ben-David et al., 2016). That effect disappeared in multiple pregnancies (Ben-David et al., 2016). Finally, in a Japanese cohort, the OR of PIH in assisted reproductive treatment pregnancies when compared with spontaneous conceptions were lower in women aged 40 years and

older (three-fold versus six-fold), even if the absolute values resulted higher than in women aged 30–34 years (Toshimitsu et al., 2014).

Abnormal BMI

An abnormal BMI can be a crucial co-factor for both infertility and pregnancy complications. In addition, changes in BMI before or during infertility treatment or during pregnancy also are important confounders.

The effect of obesity on human reproduction is well known (Michalakis et al., 2013). Obese women experience a longer TTP and an increased rate of infertility (Gesink Law et al., 2007). Two recent analyses of the Society for Assisted Reproductive Technology (SART) register on 239,127 fresh autologous (Provost et al., 2016a) and 22,317 fresh donor/recipient (Provost et al., 2016b) IVF cycles demonstrated a progressive worsening of the reproductive outcomes with BMI increase with a reduction of the live birth risk from −6% to −48% and from −10% to −59%, respectively, from overweight (BMI 25.0–29.9) to superobese (BMI > 50). This effect is potentially due to lower oocyte (Jungheim et al., 2013) and/or endometrial (Dessolle et al., 2009) competence.

Weight loss could reduce the need for ARTs in obese women with anovulatory infertility (Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive Endocrinology and Infertility, 2013), and improve the rate of spontaneous and assisted conceptions (Chavarro et al., 2012; Domar et al., 2012; Ramezanzadeh et al., 2012; Twigt et al., 2012). Recently, a large multicentre RCT (Mutsaerts et al., 2016) confirmed the beneficial effect of a six-month lifestyle intervention programme in obese women with anovulatory infertility on the rate of spontaneous conception, although it failed to demonstrate the efficacy of lifestyle modification programmes before infertility treatment versus immediate infertility treatment on the rate of vaginal birth of a healthy singleton at 37 weeks or more (primary endpoint) or on maternal and neonatal outcome, both after intention-to-treat and per-protocol analysis (Mutsaerts et al., 2016).

Obesity is also a major risk factor for virtually all pregnancy complications (Cedergren, 2004; Lawlor et al., 2012; Marchi et al., 2015). It increased the general risk of pregnancy loss (Metwally et al., 2008) and of congenital malformations (Cai et al., 2014; Knight et al., 2010; Rasmussen et al., 2008; Sirimi and Goulis, 2010). Maternal obesity was closely related to fetal macrosomia/large for gestational age (LGA) infants (Yogev and Catalano, 2009), PTB (Cnattingius et al., 2013; McDonald et al, 2010), stillbirth (Chu et al., 2007), admission of newborns to the NICU (Yogev and Catalano, 2009) and perinatal mortality (Salihu et al., 2007). The risk of thromboembolism (Guelinckx et al., 2008; Larsen et al., 2007), GDM (Yogev and Catalano, 2009) and PIH/pre-eclampsia (Abdollahi et al., 2003; Sattar et al., 2001) was also increased in obese mothers. Specific factors related to the increased risk of pregnancy complications in obese patients are visceral obesity (Abdollahi et al., 2003; Sattar et al., 2001), pre-pregnancy BMI (Frederick et al., 2006; Torloni et al., 2009) and excessive gestational weight gain (Barau et al., 2006; Dietz et al., 2005; Graves et al., 2006; Guelinckx et al., 2008; Seligman et al., 2006; Yu et al., 2006).

A meta-analysis (Aune et al., 2014) including 38 cohort studies of good quality and reporting data on very large number of events, demonstrated a linear correlation between BMI and risk of fetal death, stillbirth and infant death. A further systematic review (Meehan et al., 2014) demonstrated, after synthesis of data from 11 cohort studies, greater odds of having an infant death (OR 1.4, 95%CI 1.2 to 1.6) in obese mothers. The effects of preconception maternal height and weight on the risk of PTB were studied in a large retrospective cohort of 60,232 singletons and 24,111 twin live births resulting from assisted reproductive techniques (Dickey et al., 2013). Morbidly obese women had an aRR of 2.6 (95%CI 1.8 to 3.6), 2.2 (95%CI 1.8 to 2.6) and 1.5 (95%CI 1.4 to 1.7) for singleton VEPTB (≥20 and <28 completed weeks), early PTB (EPTB; ≥20 and <32 completed weeks) and PTB (≥20 and <37 completed weeks), respectively, compared with normal weight women (Dickey et al., 2013). Similar, albeit less profound effects, were noted with twins. Morbid obesity led to an aRR of 2.4 (95%CI 1.8 to 3.0), 1.5 (95%CI 1.3 to 1.8) and 1.1 (95%CI 1.0 to 1.1) for VEPTB, EPTB and PTB, respectively (Dickey et al., 2013). It may be that the adverse effect of obesity in twin pregnancies is partially masked by the much greater effect of twinning itself. More than 1.5 million deliveries from the Swedish Medical Birth Register showed that the highest risk of overweight and obesity was for VEPTB (22–27 weeks' gestation) (Cnattingius et al., 2013). The risk for VEPTB increased from 26% in women with a BMI of 25–30 (OR 1.3, 95%CI 1.2 to 1.4) to 58% in women with a BMI of 30–35 (OR 1.58, 95%CI 1.39 to 1.79) (Cnattingius et al., 2013). In women with a BMI of 35–40 (OR 2.0, 95%CI 1.7 to 2.5) and of 40 or greater (OR 3.0, 95%CI 2.3 to 3.9) the risk of VEPTB was at least two-fold higher (Cnattingius et al., 2013).

More recently, a retrospective cohort study of 11,726 women demonstrated that the clinical presentation of PTB changed according to the BMI subgroup (Lynch et al., 2014). Spontaneous PTB resulted less frequently in class I obese women (aOR 0.7, 95%CI 0.5 to 1.0), and the risk of PTB due to preterm premature rupture of the membranes (PPRM) was increased in class II women (aOR 1.7, 95%CI 1.1 to 2.7) while medically indicated PTB were increased both in class III obese (aOR 2.2, 95%CI 1.4 to 3.4) and moderately underweight (aOR 2.9, 95%CI 1.3 to 6.3) patients (Lynch et al., 2014). However, after adjustment for gestational age at birth, PPRM was not associated independently to maternal obesity or its severity (Faucett et al., 2016). On the other hand, although the increase in maternal weight was also related with pre-eclampsia with severe features, no difference among overweight (aOR 1.4, 95%CI 1.0 to 2.1), obese (aOR 2.0, 95%CI 1.4 to 2.8) and morbidly obese (aOR 2.0, 95%CI 1.3 to 2.9) women compared with normal-weight women (Durst et al., 2016). A large cohort study (Declercq et al., 2016) including 6,419,836 singleton births and 36,691 infant deaths demonstrated a close relationship between prepregnancy BMI and infant death that resulted from 30% to 70% higher considering obese I and II category, respectively. The deleterious effects of prepregnancy overweight and obesity on the perinatal risk could be mediated by the higher rates of LGA (OR 1.5, 95%CI 1.4 to 1.6; and OR 2.1, 95%CI 1.9 to 2.2, respectively), high neonatal body weight (OR 1.5, 95%CI 1.4 to 1.6; and OR 2.00; 95%CI 1.8 to 2.2, respectively) and macrosomia (OR 1.7, 95%CI 1.4 to 2.0; and OR 3.2, 95%CI 2.4 to 4.4, respectively) (Yu et al., 2013).

The effect of gestational weight gain or loss in patients with abnormal BMI are more controversial and limited to special populations of obese pregnant women (Thangaratinam et al., 2012). According to international guidelines (Institute of Medicine and National Research Council, 2009), a gestational weight gain in obese women of 5 kg to 9 kg is the recommended range. At the moment, two meta-analyses demonstrated a slightly increased risk of PTB when the weight gain is above (aOR 1.5, 95%CI 1.1 to 2.2) (Faucher et al., 2016) or below (aOR 1.5, 95%CI 1.1 to 2.0) the recommended range (Kapadia et al., 2015). Moreover, a gestational weight gain below the recommendations seems to be related to lower odds of PIH (aOR 0.7, 95%CI 0.5 to 0.9) and pre-eclampsia (aOR 0.9, 95%CI 0.8 to 1.0) (Kapadia et al., 2015). Also more recently the risk of infant death was confirmed to be related to pregnancy weight gain; however, a pregnancy weight gain less or more than recommendations was significantly and clinically less important than prepregnancy BMI (Declercq et al., 2016).

The effect of a low BMI on reproduction is less studied and controversial data are available in literature. The leanness is frequently associated with oligoamenorrhoea/amenorrhoea and anovulatory infertility with particular regard for patients with anorexia nervosa and/or functional hypothalamic amenorrhoea, although data from the SART register showed no significant difference in reproductive outcomes between lean and normal weight patients (Provost et al., 2016a, 2016b). However, the prepregnancy underweight increased the risk of SGA (OR 1.8, 95%CI 1.8 to 1.9) and of LBW (OR 1.5, 95%CI 1.3 to 1.7) (Yu et al., 2013). Having as reference women with a BMI of 20, a meta-analysis failed to demonstrated a significant increase of the incidence of fetal death, stillbirth and infant death in patients with a lower BMI (Aune et al., 2014). A two-fold increased incidence (aOR 2.4, 95%CI 1.2 to 4.7) of spontaneous PTB was also observed in underweight women (Lynch et al., 2014).

The risk of congenital anomalies is overall increased in obese women (Marchi et al., 2015; Stothard et al., 2009), whereas no increased risk was detected in lean women with the exclusion of aortic valve stenosis (OR 1.5, 95%CI 1.0 to 2.2) (Cai et al., 2014).

The reason for the relationship between BMI and adverse pregnancy outcomes is uncertain. In obese women, insulin resistance and adipokines may play a role and the ovary and/or the endometrium can be the final targets (Pasquali et al., 2003). Another factor may be maternal sleep-breathing disorders. These are common in obese women and are independently associated with GDM and hypertensive disorders of pregnancy (Bisson et al., 2014; Pamidi et al., 2014). On the other hand, chronic maternal under-nutrition, low concentrations of macro- or micronutrients in the diet, endocrine/psychosocial factors, placental growth restriction and infection/inflammation from alterations in the immune system may increase risks in underweight women (Bloomfield, 2011; Lynch et al., 2014).

PCOS

PCOS is the most common endocrine disease of reproductive aged women occurring in up to 15–20% (Dumesic et al., 2015). Historically defined as a syndrome related to anovulatory infertility, hirsutism and metabolic syndrome, only recently has attention been focused on an increased risk of obstetric complications (Palomba et al., 2015a).

Data on rates of pregnancy loss are conflicting (Fauser et al., 2012). A meta-analysis of women with and without PCOS undergoing assisted reproductive techniques demonstrated no difference in pregnancy loss (Heijnen et al., 2006). This result was confirmed in a large cohort study (Liu et al., 2014). On the other hand, a recent study examining long-term health usage and hospitalization in women with PCOS reported an increased risk of pregnancy loss in women with PCOS compared with women without the condition (Hart and Doherty, 2015). Albeit the excess risk for pregnancy loss observed in women with PCOS seemed to be influenced by BMI and not independently related to PCOS (Joham et al., 2014), recent data adjusted for many confounders including BMI demonstrated an increased (aOR1.7, 95%CI 1.6 to 1.8) risk of miscarriage in women with a diagnosis of PCOS (Rees et al., 2016). However, maternal factors resulting in endometrial disorders are more likely to be responsible for the increased risk of miscarriage in patients with PCOS since the risk of embryonic chromosome aneuploidy was lower in women with PCOS than in controls (Wang et al., 2016). In addition, many women with PCOS conceive using ovulation stimulation protocols that can influence the risk of pregnancy loss (Palomba et al., 2015a).

Several meta-analyses on pregnancy complications in women with PCOS (Palomba et al., 2015a) report at least a three-fold increased risk of both PIH/pre-eclampsia and GDM. However, these data were obtained retrospectively and from few small prospective cohorts, and not adjusted for the several confounders (BMI, multiple pregnancies, parity, assisted reproductive techniques and prepregnancy diseases/comorbidities). A large longitudinal case-control study including only singleton spontaneous conception (Palomba et al., 2014b) confirmed the increased risk of PIH (12.7 versus 5.2%) and pre-eclampsia (8 versus 2%) in women with PCOS compared with healthy controls. Similarly, the increased risk of GDM, occurring in 6–15% of women with PCOS, was significantly increased (Palomba et al., 2014b, 2014c). A very recent retrospective cohort study (Sterling et al., 2016) on singleton births from women with and without PCOS after fresh IVF/ICSI cycles demonstrated, after adjusting for several confounders including the TTP and BMI, a higher risk of developing GDM (aOR 3.2, 95%CI 1.4 to 7.3), PIH (aOR 4.3, 95%CI 1.9 to 9.3) and PTB (aOR 2.3, 95%CI 1.1 to 5.0). Of note, the increased risk of PTB was not significant after adjusting for development of PIH (Sterling et al., 2016).

Data on the risk of CD, as well as those on the risk for adverse fetal outcomes, in women with PCOS are conflicting (Boomsma et al., 2006; Kjerulff et al., 2011; Qin et al., 2013). PCOS women had a two-fold increased risk of PTB, even if confined to hyperandrogenic subjects (Naver et al., 2014). Another study noted a higher risk of PTB, EPTB and LBW in twin pregnancies of women with PCOS than in controls, although this effect was lost after adjusting for BMI and gestational age (Løvvik et al., 2015).

Neonates born to women with PCOS had a two-fold increased risk for admission to the NICU (Qin et al., 2013) and their mortality was increased three-fold (Boomsma et al., 2006). In a very recent Australian population-based study (Doherty et al., 2015), 2,566 women with a history of PCOS were age-matched to 25,660 women without PCOS.

Perinatal mortality was associated with maternal PCOS (2.3% versus 0.7%) with an aOR 1.5 (95%CI 1.0 to 2.2) (Doherty et al., 2015). The offspring of PCOS women were more likely (14.1% versus 7.9%) to require admission to a NICU (aOR 1.2, 95%CI 1.1 to 1.4) (Doherty et al., 2015). One meta-analysis found no increased risk for SGA neonates in PCOS pregnancies (Boomsma et al., 2006). However, a more recent one reported an almost two-fold increased risk of SGA and no risk of LGA neonates (Qin et al., 2013). Two studies confirmed an increased risk of SGA of four- (Han et al., 2011) and more than two- (Palomba et al., 2014b) fold in neonates of women with PCOS, whereas another study showed no effect of PCOS on the risk of SGA (Naver et al., 2014). On the other hand, an increased incidence of LGA in PCOS patients was observed in a retrospective (Roos et al., 2011) and prospective (Palomba et al., 2014b) study. The incidence of macrosomia, however, was similar in PCOS women when compared with controls in assisted reproductive treatment populations (Boomsma et al., 2006). An increased risk of LGA in children born from a mother with PCOS who received assisted reproductive treatment was recently observed (aOR 2.8, 95%CI 1.2 to 6.4); that data did not change after adjusting for GDM status (Sterling et al., 2016). Given these mixed results, the relationship between PCOS and birth-weight remains uncertain.

A large case-control study (Rees et al., 2016) including 9,068 women with PCOS matched one-to-two for age and BMI with controls, and adjusted for other confounders such as multiple gestations, parity and smoking history, confirmed that PCOS is associated with an increased risk of pre-eclampsia (aOR 1.3, 95%CI 1.2 to 1.5), GDM (aOR 1.4, 95%CI 1.2 to 1.7) and PTB (aOR 1.3, 95%CI 1.1 to 1.4). The risk of CD was also higher (aOR 1.1, 95%CI 1.1 to 1.2), and babies born to mothers with PCOS had an increased risk of neonatal jaundice (aOR 1.2; 1.0 to 1.4) and respiratory complications (aOR 1.2, 95%CI 1.1 to 1.4) (Rees et al., 2016). Interestingly, the treatment with metformin increased significantly the incidence of pre-eclampsia of about 50% (Rees et al., 2016); however, it is unclear whether those data represent a true adverse effect of metformin administration or is more likely a reflection of residual confounding due to preferential prescribing in higher risk pregnancies.

Recent data report an association between congenital abnormalities and maternal PCOS. Specifically, one group noted an increase in congenital anomalies among all births and those reported up to six years of age in children born to a mother with PCOS (Doherty et al., 2015). These data were somewhat limited because they did not include congenital abnormalities that led to a termination of pregnancy. The increased risk of congenital abnormalities in children born to a mother with PCOS may be due to the increased prevalence of GDM and obesity, and to their related treatments (Joham et al., 2016).

It is very difficult to define whether the increased obstetric risk in women with PCOS is specific for the syndrome or is entirely due to comorbidities, such as obesity and/or insulin resistance. Some authors detected a higher risk in women with hyperandrogenism and oligo-anovulation (Palomba et al., 2010), perhaps due to the effect of hyperandrogenaemia on placenta function and/or on cervical remodelling and myometrial function (Makieva et al., 2014; Palomba et al., 2015a), and of oligo-amenorrhoea on TTP (see before) and/or on endometrial function (Brosens and Benagiano, 2015; Palomba and La Sala, 2016a). On the other hand, the increased risk of pregnancy complications was not a specific prerequisite of any of these phenotypes. They were associated with PCOS irrespective of the diagnostic criteria adopted (Kollmann et al., 2015). In conclusion, the increased incidence of pregnancy complications in women with PCOS appears to be the result of several factors such as fertility treatment, multiple pregnancies, obesity, insulin resistance, metabolic dysfunction, inflammation and placental alterations (Palomba et al., 2015a). Accordingly, PCOS patients should be given individual counselling regarding their pregnancy risks (Palomba and La Sala, 2016b).

Uterine fibroids

Uterine fibroids are reported in up to 2.4% of subfertile women without any other cause of infertility (Donnez and Jadoul, 2002). However, the association between fibroids and early or late pregnancy complications is controversial.

A systematic review with meta-analysis (Pritts et al., 2009) highlighted that infertile women with submucous fibroids had an increased risk of pregnancy loss (RR 1.7, 95%CI 1.4 to 2.1), lower risk of implantation (RR 0.3, 95%CI 0.1 to 0.7) and of ongoing pregnancy/live birth rate (RR 0.3, 95%CI 0.1 to 0.9) compared with those without fibroids. The mechanisms whereby submucous fibroids impact fertility remain uncertain. There is some evidence that such lesions may contribute to a global molecular impact that inhibits the receptivity of the endometrium to implantation (AAGL: Advancing Minimally Invasive Gynecology Worldwide, 2012). A reduction in the levels of endometrial HOXA factor expression, both over the myoma and the normal myometrium, was detected only in women with submucous fibroids (Rackow and Taylor, 2010).

Despite limited evidence, subserosal fibroids do not seem to have a significant effect on fertility and/or on pregnancy complications risk with good agreement among studies (Metwally et al., 2011; Pritts et al., 2009; Somigliana et al., 2007; Sunkara et al., 2010).

Unlike submucous and subserosal fibroids, there is still debate regarding the effects of intramural fibroids on reproductive outcomes. Intramural fibroids had an adverse effect on pregnancy loss rates in one meta-analysis (Pritts et al., 2009) but not in another (Sunkara et al., 2010) (RR 1.9, 95%CI 1.5 to 2.4 and RR 1.2, 95%CI 1.0 to 1.6, respectively). In both meta-analyses (Pritts et al., 2009; Sunkara et al., 2010), intramural fibroids had a deleterious effect on live birth rates (RR 0.7, 95%CI 0.6 to 0.8 and RR 0.8, 95%CI 0.7 to 0.9; respectively). In assisted reproductive treatment patients, a reduction in implantation rate in women with intramural fibroids was noted in one meta-analysis (RR 0.8, 95%CI 0.7 to 0.9) (Pritts et al., 2009). Also, in patients aged less than 37 years undergoing assisted reproductive treatment, intramural fibroids were associated with a reduction in live births (RR 0.8, 95%CI 0.6 to 0.9) (Sunkara et al., 2010). On the other hand, a more recent systematic review and meta-analysis (Metwally et al., 2011) found no effect of intramural fibroids with no cavity distortion on any fertility outcome in either spontaneous or assisted conceptions.

There also is conflicting evidence on the impact of fibroids on obstetric outcomes as well as uncertainty

regarding mechanisms (Somigliana et al., 2007). Although most available evidence supports an association between fibroids and some pregnancy complications, there is considerable variation among studies (Klatsky et al., 2008; Lam et al., 2014; Stout et al., 2010). Prospective cohort studies suggest that women with large fibroids are at increased risk for pregnancy complications (Michels et al., 2014; Shavell et al., 2012). Women with fibroids measuring more than 5 cm had an excess of about 10% in PTB when compared with those with smaller fibroids or without fibroids (35% versus 24.5% versus 25.5%, respectively) (Shavell et al., 2012). An increased risk of CD was also detected (aRR 1.2, 95%CI 1.1 to 1.3) for women with a single leiomyoma 3 cm or more in diameter (Michels et al., 2014).

Fibroids are also associated with PTB (Klatsky et al., 2008; Lai et al., 2012; Lam et al., 2014; Stout et al., 2010) and fetal death (aOR 2.7, 95%CI 1.0 to 6.9), although the body of literature was mainly based on retrospective observational studies. The association between fibroids and fetal death was in losses <32 weeks gestation (<32 weeks: aOR 4.2, 95%CI 1.2 to 14.7 versus >32 weeks: aOR 0.8, 95%CI 0.1 to 6.2) (Lai et al., 2012). There are no consistent data about the relationship between fibroids and PPRM, IUGR, placenta previa and placenta abruption (Ciavattini et al., 2015; Klatsky et al., 2008). In particular, placental abruption, that represents a rare but severe neonatal outcome, was inconsistently associated with fibroids (Klatsky et al., 2008). The closest association was detected with submucosal or retroplacental fibroids, even if the risk remained low and myomectomy was not effective to reduce the risk (Coronado et al., 2000; Sheiner et al., 2004).

Even more uncertainty exists about the effect of myomectomy on fertility outcomes. Myomectomy for intramural fibroids had no significant effect on pregnancy (Pritts et al., 2009). No benefit of myomectomy on the rate of pregnancy loss was detected for women with submucous fibroids compared with women with other fibroids (Pritts et al., 2009). In infertile women, no difference in fertility was observed between women who had myomectomy compared with women with no fibroids (Pritts et al., 2009; Kroon et al., 2011). This observation suggests that hysteroscopic myomectomy has no detrimental effect upon implantation. A recent Cochrane review (Bosteels et al., 2015) captured only one RCT comparing hysteroscopic myomectomy compared with timed intercourse in women aged less than 37 years with unexplained subfertility and submucous fibroids of diameter ≤40 mm with or without associated intramural fibroids (Casini et al., 2006). No effect on the rates of pregnancy loss and of clinical pregnancies was observed between the two strategies. However, the small number of women studied and the high risk of bias preclude definitive conclusions (Bosteels et al., 2015).

Few data are available about the effect of myomectomy on the obstetric risk and perinatal outcomes. Uterine rupture is a rare complication after myomectomy. Fortunately, it is a rare event, occurring after 0.2% and 0.26% of myomectomies after laparotomy and laparoscopy, respectively (Parker et al., 2010; Sizzi et al., 2007; Zhang and Hua, 2014). Available systematic reviews with meta-analysis comparing different surgical approaches to uterine fibroids are characterized by a paucity of data on obstetric and perinatal complications (Palomba et al., 2015b; Pundir et al., 2013). A retrospective observational study compared perinatal outcomes after laparoscopic myomectomy versus abdominal myomectomy, and found no difference in the rates of emergency CD, PTB, placental abnormalities, PIH, low Apgar score, non-reassuring fetal heart rate patterns and intrauterine fetal death (Fukuda et al., 2013).

At the moment, the effects of other new medical (i.e. ulipristal acetate) and surgical (i.e. focused ultrasound/radiofrequency ablation) treatments for uterine fibroids on pregnancy and neonatal complications are confined to case series and/or uncontrolled retrospective studies.

Endometrial polyps

The prevalence of endometrial polyps in infertile women is variable, ranging from 1% to 41% (Silberstein et al., 2006). A prospective study on 1,000 patients undergoing hysteroscopic evaluation of the uterine cavity prior to an assisted reproductive treatment cycle, found endometrial polyps in 32% (Hinckley and Milki, 2004). The high prevalence of endometrial polyps in infertile women could suggest a relationship between the two entities (Pérez-Medina et al., 2005). Endometrial polyps may adversely affect fertility by mechanical interference with gamete transport or anatomical interference with embryo implantation (Taylor and Gomel, 2008). Also, the glands and stroma in endometrial polyps are unresponsive to hormonal stimulation, leading to impaired implantation at the site of the polyp (Mittal et al., 1996). Finally, endometrial polyps may induce local inflammatory changes, which can interfere with normal implantation and/or embryonic development (Afifi et al., 2010; Spiewankiewicz et al., 2003).

A systematic review (Afifi et al., 2010), based on only one RCT and two case-control studies, concluded that data regarding the efficacy and safety of endometrial polypectomy in subfertile women are scarce and yield conflicting results. In one RCT (Pérez-Medina et al., 2005) of suboptimal quality, 28% of women undergoing intrauterine insemination achieved clinical pregnancy with a simple diagnostic hysteroscopy compared with 63% (OR 4.4, 95%CI 2.5 to 8.0) after the hysteroscopic removal of the endometrial polyps (Bosteels et al., 2015). On the contrary, a recent retrospective cohort study found that newly diagnosed endometrial polyps less than 20 mm during ovarian stimulation were associated with an increased biochemical pregnancy rate, without adversely impacting clinical pregnancy or live birth rates after fresh assisted reproductive treatment cycles (Elias et al., 2015). The reasons for this observation are unclear. If a polyp is suspected during the course of ovarian stimulation or prior to fresh embryo transfer, further management should be individualized based on the number of embryos created, prior reproductive history of the patient and the individual clinics' success rates for their frozen embryo programme (Afifi et al., 2010).

No data are available on the effects of polyps on obstetric complications.

Congenital uterine anomalies

Congenital uterine anomalies are the result of alterations of the development, fusion and resorption of Müllerian ducts. They are present in 3.5–6.3% of infertile women (Raga et al., 1997) and potentially associated with a negative effect on reproductive outcomes.

Patients with congenital vaginal and uterine agenesis can achieve a child only using assisted reproductive techniques and gestational carriers or uterus transplantation. Thus, data on pregnancy and neonatal complications did not regard the affected patient in the first case or are very limited in the latter (de Ziegler et al., 2016). A systematic review with meta-analysis (Chan et al., 2011) including nine observational studies with 3,805 patients highlighted the impact that different anomalies, classified according to the American Society for Reproductive Medicine (ASRM) criteria (Buttram et al., 1988), have on reproductive outcomes. In particular, women with canalization defects had the worst reproductive outcomes with lower clinical pregnancy rates (RR 0.9%, 95%CI 0.8 to 1.0), an increased incidence of first-trimester pregnancy loss (RR 2.9, 95%CI 2.0 to 4.1), of PTB (RR 2.1, 95%CI 1.5 to 3.1) and malpresentation at delivery (RR 6.2, 95%CI 4.1 to 9.6). Meta-analysis revealed no effect on second-trimester pregnancy loss rates for overall canalization defects, with the exception of septate uteri (RR 3.7, 95%CI 1.6 to 8.9) (Chan et al., 2011).

Unification defects were not related to decreased fertility. In fact, women with bicornuate, unicornuate or didelpys uterus had similar pregnancy and first-trimester pregnancy loss rates as those with 'normal' uteri. A higher risk of second trimester loss (RR 2.3, 95%CI 1.1 to 5.2), PTB (RR 3.0, 95%CI 2.1 to 4.2) and fetal malpresentation at delivery (RR 3.9, 95%CI 2.4 to 6.2) was noted in the subgroup of patients with bicornuate uteri (Chan et al., 2011). Finally, arcuate uterus only had a modest effect on reproductive function; it was only associated with an increased risk of second trimester pregnancy loss (RR 2.4, 95%CI 1.3 to 4.3) and malpresentation (RR 2.5, 95%CI 1.5 to 4.2) (Chan et al., 2011).

Of note, the hypoplastic uterus is frequently associated with gonadal dysgenesis. Infertile patients with hypoplastic uterus and gonadal dysgenesis seem to have no increased risk of pregnancy complications when pregnancies are achieved with the use of oocyte donation. Moreover, in case of Turner syndrome, the risk of pregnancy complications, including miscarriage, PIH/pre-eclampsia, aortic dissection and thyroid diseases, is very high (de Ziegler et al., 2016).

In summary, congenital uterine anomalies are associated with poor reproductive outcomes and malpresentation at delivery. However, the effect is most pronounced in women with septate uterus and outcomes are good with most other abnormalities. There are still no high-quality RCT on the efficacy of hysteroscopic treatment of uterine anomalies (Bosteels et al., 2015).

Endometriosis

Endometriosis is a major cause of subfertility and the use of assisted reproductive techniques is common in women with endometriosis. Moreover, the presence of endometriosis itself is a risk factor for adverse obstetric outcomes (Brosens et al., 2012; Petraglia et al., 2012). As with other conditions, epidemiological studies yield mixed results and there are few well-designed prospective trials (Leone Roberti Maggiore et al., 2016). Nonetheless, endometriosis has been linked to pregnancy loss (Santulli et al., 2016), spontaneous hemoperitoneum in pregnancy, obstetrical bleeding and PTB (Brosens et al., 2012; Leone Roberti Maggiore et al., 2016; Petraglia et al., 2012).

Many uncontrolled studies reported an increased incidence of early pregnancy loss in patients with endometriosis and a beneficial effect of surgical treatment (Brosens et al., 2012). Recently, a nested case-control study (Hansen et al., 2014) compared 24,667 women with endometriosis with 98,668 age-matched women without endometriosis, reported an increased rate of pregnancy loss (RR 1.2, 95%CI 1.2 to 1.3) and ectopic pregnancy (RR 1.9, 95%CI 1.8 to 2.1). However, the few available RCTs showed no reduction in pregnancy loss after surgery for endometriosis (Gruppo Italiano per lo Studio dell'Endometriosi, 1999; Marcoux et al., 1997; Parazzini et al., 1994). Data are also conflicting with regard to the link between endometriosis and pregnancy loss in assisted reproductive treatment cycles. Two meta-analyses comparing assisted reproductive treatment outcomes in women with and without endometriosis demonstrated a small increase in the risk of pregnancy loss among pregnant women with endometriosis ranging from 26% (OR 1.3, 95% CI 0.9 to 1.7) (Hamdan et al., 2015) to 31% (RR 1.3, 95% CI 1.1 to 1.6) (Barbosa et al., 2014).

Some cases of severe and acute bowel, urinary and adnexa complications have been reported in patients with endometriosis during pregnancy (Leone Roberti Maggiore et al., 2016; Petraglia et al., 2012; Viganò et al., 2015). Similarly, cases of uterine ruptures and complications for extrapelvic endometriosis in pregnancy are anecdotal (Leone Roberti Maggiore et al., 2016). Their exact prevalence of these complications is unknown. Impairment of the bowel wall, due to extensive decidualization, and the associated adhesions that might cause trauma during uterine growth can induce a spontaneous perforation (Setubal et al., 2014; Viganò et al., 2015).

Another rare but serious complication in pregnant women with endometriosis is spontaneous hemoperitoneum. It is probably due to the rupture of a rapidly growing endometrioma, but it can also be due to bleeding from the peritoneal implants (Brosens et al., 2012) or from vessel walls due to the intrusion of decidualized endometriotic tissue with and/or without subsequent necrosis (Leone Roberti Maggiore et al., 2016; Viganò et al., 2015). The overall prevalence of endometriosis-related hemoperitoneum was estimated to be 0.4%, and the risk is significantly increased among women with endometriosis who conceive by means of assisted reproductive techniques (Viganò et al., 2015). In addition, cases of gastrointestinal bleeding and perforation of the appendix have also been described (Brosens et al., 2012). The diagnosis of an acute event involving the appendix, such as acute appendicitis or bleeding of appendiceal endometriosis, is more challenging in pregnancy because symptoms like nausea and vomiting are common in normal pregnancy and pain may be in variable locations due to upward displacement of the appendix by the growing uterus (Leone Roberti Maggiore et al., 2016).

In the case of endometriosis-related complications during pregnancy, no significant effect on obstetric risk was reported for bowel complications, albeit a 36% perinatal mortality rate and gestational age significantly and clinically lower were observed for spontaneous hemoperitoneum (Leone Roberti Maggiore et al., 2016).

Endometriosis, irrespective of acute pregnancy complications, could negatively affect the pregnancy outcome. Some evidence suggests a relationship between endometriosis and PTB, although it is difficult to draw definitive conclusions because of low quality data. A large retrospective cohort study conducted on 1,436,069 singleton births using the Swedish Medical Birth Register (Stephansson et al., 2009) found an increased risk of PTB among women with endometriosis compared with women without the disease (6.8% versus 5%, respectively) with an aOR of 1.3 (95%CI 1.2 to 1.4). The data about an increased risk of PTB (OR 2.1, 95%CI 1.0 to 4.2) in women with endometriosis have also been very recently confirmed in a retrospective study where cases and controls were matched for several confounders; an increased risk (OR 2.5, 95%CI 1.1 to 5.5) of neonatal hospitalization was also recorded (Jacques et al., 2016). Endometriosis was not associated with PTB only in assisted reproductive treatment patients, but was in women who conceived without assisted reproductive techniques (aOR 1.4, 95%CI 1.3 to 1.5) (Stephansson et al., 2009). In contrast, the risk of PTB was found to be both directly and inversely related to ovarian endometriosis (Fernando et al., 2009; Vercellini et al., 2012). The opposite conclusion was obtained in a 12-year cohort study including 31,068 women (Aris, 2014). The incidence of PTB in women with endometriosis was higher than in those without (10.5% versus 9.2%, respectively) but this trend was not significant (Aris, 2014). A recent retrospective study compared 996 women with endometriosis (subdivided into 406 who achieved pregnancy by assisted reproductive techniques and 590 who did not undergo assisted reproductive treatment cycles) to 297,987 fertile women who had spontaneous conceptions. An increased rate of PTB was found for the endometriosis non-assisted reproductive treatment group (aOR 1.7, 95%CI 1.3 to 2.2), but not for the endometriosis assisted reproductive treatment group (Stern et al., 2015).

The association between endometriosis and other adverse pregnancy outcomes are still a matter of debate. An increased risk of pre-eclampsia (aOR 1.1, 95%CI 1.0 to 1.3) was observed in the Swedish register study (Stephansson et al., 2009). Although this analysis (Stephansson et al., 2009) included a very large population of 1,442,675 singleton births, it had two limitations: the analysis was stratified by assisted reproductive techniques only for PTB outcome (and not for pre-eclampsia), and the birth register did not allow verification of the endometriosis diagnosis (Leone Roberti Maggiore et al., 2016). Other studies obtained contrasting results (Brosens et al., 2013; Saraswat et al., 2016).

Data regarding the association between endometriosis and SGA baby risk are also mixed, and limited to retrospective analyses. Some studies (Conti et al., 2015; Fernando et al., 2009) demonstrated a possible relationship (especially for ovarian endometriosis) whereas others (Benaglia et al., 2012; Lin et al., 2015; Saraswat et al., 2016; Stephansson et al., 2009; Vercellini et al., 2012) found none.

In a large multicentre study (Healy et al., 2010) in assisted reproductive treatment patients, the risks of placenta previa (OR 1.7, 95%CI 1.2 to 2.4) and postpartum hemorrhagia (PA) (OR 1.3, 95%CI 1.1 to 1.6) were increased in women with endometriosis. More recently, endometriosis (aOR 2.01, 95%CI 1.21 to 3.33) was an independent risk factor for placenta previa in a retrospective cohort study involving 4,007 women with singleton assisted reproductive technique births (Rombauts et al., 2014). Although most of the available evidence is from data on assisted reproductive techniques, a recent retrospective cohort study (Lin et al., 2015) on 498 women with and without endometriosis who achieved spontaneous conception showed a higher risk of placenta previa in women with endometriosis (aOR 4.5, 95%CI 1.2 to 16.5). That increased risk seems to be confined to patients with recto-vaginal endometriosis (OR 5.8, 95%CI 1.5 to 22.0, versus ovarian/peritoneal endometriosis), as observed in primiparae who conceived spontaneously (Vercellini et al., 2012).

Recently, increased odds of early and late pregnancy complications, such as neonatal complications, was observed in singleton pregnancies from 5,375 women with surgically confirmed endometriosis in comparison with 8,710 women without endometriosis who were pregnant during the same time period (Saraswat et al., 2016). In particular, after adjusting data for age, parity, socio-economic status and year of delivery, women with endometriosis had a higher risk of miscarriage (aOR 1.8, 95%CI 1.4 to 2.2), ectopic pregnancy (aOR 2.7, 95%CI 1.1 to 6.7), placenta previa (aOR 2.2, 95%CI 1.5 to 3.3), AH (aOR 1.7, 95%CI 1.4 to 2.0), PH (aOR 1.3, 95%CI 1.6 to 1.5) and PTB (aOR 1.3, 1.1 to 1.5) (Saraswat et al., 2016). Unfortunately, laparoscopy was not performed in control patients in order to exclude asymptomatic endometriosis, and data were not adjusted for crucial confounders such as BMI, longer TTP or exposure to fertility treatments.

Endometriosis has consistently shown no association with GDM (Aris, 2014; Stern et al., 2015; Tobias et al., 2013). One exception is a recent retrospective cohort study on both natural and assisted reproductive treatment pregnancies that found an association between endometriosis and GDM only in primiparous women (OR 2.1, 95%CI 1.3 to 3.4) (Conti et al., 2015).

Most studies report an increased risk of CD in women with endometriosis (Leone Roberti Maggiore et al., 2016). However, most studies are limited by small sample size and a failure to specify the principal indication for CD. Thus, secondary causes such as previous surgery, may have influenced the choice of CD in these women (Leone Roberti Maggiore et al., 2016).

At the moment, there are few data indicating that treatment of endometriosis could reduce these obstetric risks. Moreover, it is difficult to anticipate complications of endometriosis during pregnancy because there is no correlation between the stage of endometriosis and the prevalence of complications (Viganò et al., 2015). Accordingly, surgical treatment of endometriosis before pregnancy to prevent disease-related complications does not seem justified (Leone Roberti Maggiore et al., 2016; Viganò et al., 2015).

The increased risk in pregnancy complications observed in endometriosis patients could be the result of defective trophoblast invasion and placentation due to impaired decidualization for endometrial resistance to progesterone, increased and specific inflammatory pattern and/or a thicker uterine junctional zone (Benagiano et al., 2014; Brosens et al., 2012, 2013; Exacoustos et al., 2013; Leone Roberti Maggiore et al., 2016; Petraglia et al., 2012; Viganò et al., 2015). The endometriosis-related inflammatory state can also exert a direct effect on cervix remodelling, myometrium contractility and membrane rupture (Petraglia et al., 2012). Moreover,

at the moment no study has directly demonstrated that speculative mechanism of action.

Adenomyosis

Few data are available about the correlation between adenomyosis and pregnancy complications. One study noted an increased risk of miscarriage in women with histologically confirmed adenomyosis (Levgur et al., 2000). The risk in these women was 58.8%; not significantly different than patients with adenomyosis and fibroids (47.4%), but significantly higher than patients with fibroids alone or no uterine disease (20.5% and 22.2%, respectively) (Levgur et al., 2000). These data suggest a potential contribution of misdiagnosed adenomyosis on the risk of pregnancy complications in patients with intramural fibroids.

A case-control study (Juang et al., 2007) including 104 PTB cases and 208 controls showed an association between adenomyosis (diagnosed by magnetic resonance imaging or ultrasound) and PTB (aOR 2.0, 95%CI 1.2 to 4.5). Adenomyosis increased the risk for spontaneous PTB (aOR 1.8, 95%CI 1.3 to 4.3) and PPRM (aOR 2.0, 95%CI 1.4 to 3.2) (Juang et al., 2007). A retrospective cohort study recently confirmed the increased risk for PTB (OR 5.0, 95%CI 2.2 to 11.4) and PPRM (OR 5.5, 95% CI 1.7 to 17.7) (Mochimaru et al., 2015). Adenomyosis was also linked to other pregnancy complications, such as CD (OR 4.5, 95%CI 2.1 to 9.7), SGA (OR 4.3, 95%CI 1.8 to 10.3), PH (OR 6.5, 95%CI 2.2 to 19.0) and malpresentation (OR 4.2, 95% CI 1.6 to 10.8) (Mochimaru et al., 2015).

There are no data regarding the effect of the treatments of adenomyosis on pregnancy outcomes.

The same pathogenic mechanisms suggested for endometriosis was proposed for adenomyosis (Brosens et al., 2013) with particular regard for disregulation of inflammatory pathways with hypersecretion of inflammatory cytokines and chemokines (Petraglia et al., 2012).

Conclusions and future perspective

Notwithstanding the quality of evidence is generally suboptimal for the different confounders and limitations present in the available studies, the level of evidence seems to be sufficient to suggest a direct relationship between infertility, subfertility factors and many adverse obstetric and neonatal outcomes (**Table 1**).

Available data on infertility demonstrate that it is not a dichotomous state but a continuum ranging from complete sterility to mild subfertility with a variable impact on pregnancy outcomes (Habbema et al., 2004). There is a consistent detrimental effect on pregnancy of a long TTP (12 months or more), advanced maternal age and of obesity and/or excessive weight gain during pregnancy. The mechanisms whereby PCOS influences pregnancy complications remain unclear. There is still uncertainty about the role of intramural fibroids, as well as the efficacy of myomectomy, on obstetric risk. Endometriosis itself is a consistent risk factor for adverse pregnancy outcomes, whereas data on adenomyosis and endometrial polyps are unclear.

Current comprehensive review underlines that it is very difficult to precisely determine the risk of specific reproductive disorders on individual adverse pregnancy outcomes due to a lack of high-quality data and knowledge gaps remain. The heterogeneity of the studied populations, often mixing assisted reproductive techniques and spontaneous conceptions, as well as different reproductive disorders, and a lack of data concerning long-term effects on mother and infant are also a limitation. Future trials need to consider whether assisted reproductive techniques were used to conceive, the stage/severity of each disease (fibroids/polyps dimensions and/or ovarian or deep endometriosis), the association with other gynaecological abnormalities and previous surgical and/or medical treatments performed for improving fertility. It is critical that future studies isolate, as much as possible, the contribution of infertility alone as well as the effect of treatment on obstetric risks. Infertility itself is a bias that cannot be corrected with statistical analysis or quantitated, but it is crucial to assess the direction and potential magnitude of its influence on the results (Barnhart, 2014). One approach is to evaluate women with underlying reproductive disorders who spontaneously conceive. Of course, these women are more difficult to ascertain than those undergoing assisted reproductive treatment. Similarly, infertile patients often have comorbid conditions such as obesity and metabolic syndrome or multiple reproductive disorders. Adenomyosis and endometriosis could be reciprocally potential confounding factors (Viganò et al., 2015). The risk of endometriosis is increased in women with PCOS (Holoch et al., 2014) and the risk of endometrial polyps is increased in women with endometriosis (RR 2.8, 95%CI 2.5 to 3.2) (Zheng et al., 2015).

At the moment, the effect of several subfertility factors, such as hydrosalpinges, intrauterine adhesions and chronic endometritis, on pregnancy and neonatal complications is unknown (de Ziegler et al., 2016), albeit they certainly alter the uterine anatomy and physiology, and thus the normal process of implantation and placentation (Fox and Eichelberger, 2015). Similarly, the effect on the risk of pregnancy and neonatal complications of each intervention for treating/managing the subfertility factors is generally unknown.

The risk of pregnancy complications is multifactorial and the magnitude of this risk varies among subgroups. Unfortunately, it is very difficult to define appropriate control groups given the multiple potential biases such as infertility, factors of subfertility, drugs and techniques employed. In addition, confounding factors cannot always be adequately controlled through multivariate analysis because in many studies they are not clinically available, missing or not collected.

Finally, it is also important to assess not only the RR of pregnancy complications for each specific factor but also the effect of their combination/coexistence in terms of relative and absolute risk in order to optimally stratify risk for individual patients. Moreover, although obstetricians should be cognizant about the increased risk of pregnancy complications in subfertile populations and/or with factors of subfertility, they should avoid causing harm with unproven, costly and morbid interventions such as elective PTB or CD.

Table 1 Levels and quality of the best available evidence about the relationships between each subfertility factor and its treatment and risk of the main obstetric and neonatal adverse outcomes.

Factor	*Main adverse outcome*	*Evidence*	
		Level[a]	*Quality*[b]
Infertility (TTP longer than 12 months)	GDM	2	Moderate
	PIH/PE	1	Moderate
	AH	2	Moderate
	PTB	1	High
	VPTB	2	Moderate
	LBW	1	High
	Congenital anomalies	2	Moderate
Advanced maternal age (more than 35, 40 or 45 years)	Miscarriage	2	High
	GDM	2	High
	PIH/PE	2	High
	Placenta praevia	2	Moderate
	CD	2	High
	Severe maternal morbidity/death	2	High
	PTB	2	High
	VEPTB	2	Moderate
	LBW	2	High
	NICU admission	2	High
	Stillbirth/perinatal mortality/early neonatal mortality	2	High
	Congenital anomalies	1	High
Obesity (BMI higher than 30)	Miscarriage	1	High
	GDM	2	Moderate
	Thromboembolism	2	Moderate
	PIH/PE	2	Moderate
	Severe maternal morbidity/death	2	Moderate
	PTB	1	High
	EPTB	1	Moderate
	VEPTB	1	High
	Macrosomia/LGA	2	Moderate
	PPRM	2	High
	NICU admission	2	High
	Stillbirth/perinatal mortality/early neonatal mortality	1	High
	Congenital anomalies	1	High
Leanness (BMI lower than 18 or 18.5)	PTB	2	High
	SGA	1	Moderate
	LBW	1	Moderate
	Congenital anomalies[c]	1	Moderate
PCOS[d]	Miscarriage	1	Moderate
	GDM	1	Moderate
	PIH/PE	1	Moderate
	CD	1	Low
	PTB	1	Low
	EPTB	1–2[e]	Low–moderate[e]
	LBW	2[e]	Moderate[e]
	SGA	1	Low
	Macrosomia/LGA	1	Low
	Neonatal jaundice	2	Moderate
	Respiratory complications	2	Moderate
	NICU admission	1	Moderate
	Stillbirth/perinatal mortality/early neonatal mortality	1	Moderate
	Congenital anomalies	2	Moderate

(*continued on next page*)

Table 1 (*continued*)

Factor	*Main adverse outcome*	*Evidence*	
		Level[a]	*Quality*[b]
Uterine fibroids	Miscarriage	1	Moderate
	CD	2	Moderate
	PTB	3	Moderate
Endometrial polyps	NA	NA	NA
Congenital uterine anomalies	Miscarriage[f]	1	Low
	PTB	1	Low
	Malpresentation	1	Low
Endometriosis	Miscarriage	1	Moderate
	Ectopic pregnancy	2	Moderate
	PIH/PE	2	Moderate
	GDM	3	Low
	Acute maternal complications	1	Low
	Placenta praevia	2	Moderate
	AH	2	Moderate
	PH	2	Moderate
	PTB	2	Moderate
	SGA	3	Low
	Neonatal hospitalization	3	Moderate
Adenomyosis	Miscarriage	2	Low
	CD	3	Low
	PTB	2	Moderate
	SGA	3	Low
	PPRM	2	Moderate
	PH	3	Low
	Malpresentation	3	Low

AH = antepartum hemorrhage; BMI = body mass index; CD = Caesarean delivery; EPTB = early preterm birth; GDM = gestational diabetes mellitus; LBW = low birth weight; LGA = large for gestational age; NA = not available data; NICU = neonatal intensive care unit; PCOS = polycystic ovary syndrome; PE = preeclampsia; PH = postpartum hemorrhage; PIH = pregnancy-induced hypertension; PPRM = preterm premature rupture of the membranes; PTB = preterm birth; SGA = small for gestational age; TTP = time-to-pregnancy; VEPTB = very early preterm birth.
[a]Assessed following The Oxford Centre for Evidence-Based Medicine (OCEM)–Levels of Evidence 2011 guidelines (2011) (http://www.cebm.net/index.aspx?o=5653).
[b]Assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (Guyatt et al., 2011).
[c]Aortic valve stenosis.
[d]According to the Rotterdam criteria (Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004).
[e]For twin pregnancies.
[f]Canalization and unification defects are associated with first-trimester and second-trimester pregnancy loss, respectively.

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