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Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome

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BACKGROUND: Reproductive disorders and infertility are associated with the risk of obstetric complications and have a negative impact on pregnancy outcome. Affected patients often require assisted reproductive technologies (ART) to conceive, and advanced maternal age is a further confounding factor. The challenge is to dissect causation, correlation and confounders in determining how infertility and reproductive disorders individually or together predispose women to poor pregnancy outcomes.

METHODS: The published literature, to June 2015, was searched using PubMed, summarizing all evidences concerning the perinatal outcome of women with infertility and reproductive disorders and the potential mechanisms that may influence poor pregnancy outcome.

RESULTS: Reproductive disorders (endometriosis, adenomyosis, polycystic ovary syndrome and uterine fibroids) and unexplained infertility share inflammatory pathways, hormonal aberrations, decidual senescence and vascular abnormalities that may impair pregnancy success through common mechanisms. Either in combination or alone, these disorders results in an increased risk of preterm birth, fetal growth restriction, placental pathologies and hypertensive disorders. Systemic hormonal aberrations, and inflammatory and metabolic factors acting on endometrium, myometrium, cervix and placenta are all associated with an aberrant milieu during implantation and pregnancy, thus contributing to the genesis of obstetric complications. Some of these features have been also described in placentas from ART.

CONCLUSIONS: Reproductive disorders are common in women of childbearing age and rarely occur in isolation. Inflammatory, endocrine and metabolic mechanisms associated with these disorders are responsible for an increased incidence of obstetric complications. These patients

should be recognized as 'high risk' for poor pregnancy outcomes and monitored with specialized follow-up. There is a real need for development of evidence-based recommendations about clinical management and specific obstetric care pathways for the introduction of prompt preventative care measures.

Key words: polycystic ovary syndrome / endometriosis / uterine fibroids / unexplained infertility / assisted reproductive technologies / preterm birth / pre-eclampsia / placenta / inflammation / sex steroids

Introduction

A major challenge of modern women's health is to define maternal or fetal factors associated with the risk of adverse obstetric outcomes. A growing number of studies are revealing that infertility and reproductive disorders, such as endometriosis, adenomyosis, polycystic ovary syndrome (PCOS) and uterine fibroids, may have a negative impact on pregnancy, from implantation until term. In addition, many patients with reproductive disorders and/or infertility require assisted reproductive technologies (ART), which independently may affect pregnancy outcomes. Thus, it is a difficult task to distinguish the contribution of specific reproductive disorders or infertility to poor pregnancy outcomes relative to the interventions required for pregnancy success (Talaulikar and Arulkumaran, 2012). In addition, women are delaying commencement of a family until later in life, resulting in an increased rate of infertility due to advanced maternal age, which constitutes an additional obstetric risk factor (Balasch and Gratacós, 2012). Therefore, women with reproductive disorders often have multiple risk factors (advanced maternal age, use of ART) contributing to negative obstetric outcomes. It is important to understand the causes of this effect and develop new care pathways to ensure adequate management of their reproductive health.

Hormones and inflammatory mechanisms are implicated in the major events of female reproductive function, including ovulation, menstruation, embryo implantation and pregnancy. Increasing evidence shows that hormonal aberrations and a hyperinflammatory state may lead to derangements of the immune-endocrine cross talk among endometrium, myometrium and cervix, and between the decidua and trophoblast, predisposing to pregnancy complications. Therefore, the aim of the current review was to assess whether inflammatory mechanisms and hormonal and metabolic dysfunctions occurring in uterine (endometrium, myometrium, cervix) and placental tissues in women with uterine fibroids, endometriosis, adenomyosis, PCOS and unexplained infertility may contribute to pregnancy disorders. Since other uterine conditions associated with obstetric complications, such as uterine malformations (Chan *et al.*, 2011), synechiae (Tuuli *et al.*, 2012) and Asherman syndrome (March, 2011), work mainly through mechanisms other than inflammatory, endocrine and metabolic pathways, they are not part of the present review.

Methods

The published literature was searched using PubMed summarizing all evidence concerning the obstetric and neonatal outcome of women with infertility and reproductive disorders and the potential mechanisms that may influence pregnancy complications. In particular, the literature research, up to June 2015, was focused on endometriosis, adenomyosis, PCOS, uterine fibroids and ART, while the pathogenic mechanisms contributing to adverse pregnancy outcome were related to hormonal and neurohormonal aberration, inflammatory pathways and metabolic dysfunction.

Adverse maternal and neonatal outcomes in pregnant women with reproductive disorders

Polycystic ovary syndrome

PCOS, one of the most common disorders in women of reproductive age (affecting 4–7% of women), is characterized by hyperandrogenism and ovarian dysfunction (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Approximately 50% of women with PCOS are overweight or obese and have reduced insulin sensitivity (Norman *et al.*, 2004). Growing evidence demonstrates that PCOS has a negative impact on fertility and pregnancy outcome (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Roos *et al.*, 2011; Fauser *et al.*, 2012; Qin *et al.*, 2013). An increased risk of pregnancy and neonatal complications, including early pregnancy loss, gestational diabetes (GDM), gestational hypertensive disorders, preterm birth (PTB), low birthweight (LBW) and need for Cesarean section, independent of obesity, has been demonstrated (Fig. 1) . The severity of adverse pregnancy outcome is related to the different phenotypes and features of PCOS (Toulis *et al.*, 2009; Palomba *et al.*, 2010; De Frène *et al.*, 2014).

Women with PCOS and glucose intolerance may develop GDM (5–40% risk; Toulis *et al.*, 2009). PTB affects 6–15% of pregnancies of women with PCOS (Yamamoto *et al.*, 2012) and in hyperandrogenic women with PCOS a 2-fold increased risk of PTB and pre-eclampsia (PE) occurs, suggesting the role of androgens in the pathogenesis in these complications, although metabolic abnormalities must also be considered (Naver *et al.*, 2014). Furthermore, in a large cohort of pregnant women with PCOS, a surprisingly high frequency of cervical insufficiency, particularly in South Asian and African women, is described (Feigenbaum *et al.*, 2012).

Neonates of women with PCOS are at greater risk of neonatal complications, including perinatal mortality, prematurity and higher neonatal intensive care unit admission (Roos *et al.*, 2011).

Endometriosis and adenomyosis

Endometriosis is a benign, chronic, inflammatory disease that affects 10% of reproductive age women and up to 50% of women with infertility (Burney and Giudice, 2012). The incidence of obstetric complications in patients with endometriosis, achieving pregnancy spontaneously or through ART, is controversial. Patients with an ovarian endometrioma achieving pregnancy by ART are twice as likely to have PTB or a small for gestational age (SGA) neonate (Fernando *et al.*, 2009), when compared with other forms of endometriosis. Patients with endometriosis requiring IVF treatment have a higher risk of placenta previa and postpartum hemorrhage (Healy *et al.*, 2010; Takemura *et al.*, 2013), while in those women who conceived spontaneously, there was a higher incidence of miscarriage, PTB and placental complications (Vercellini *et al.*,

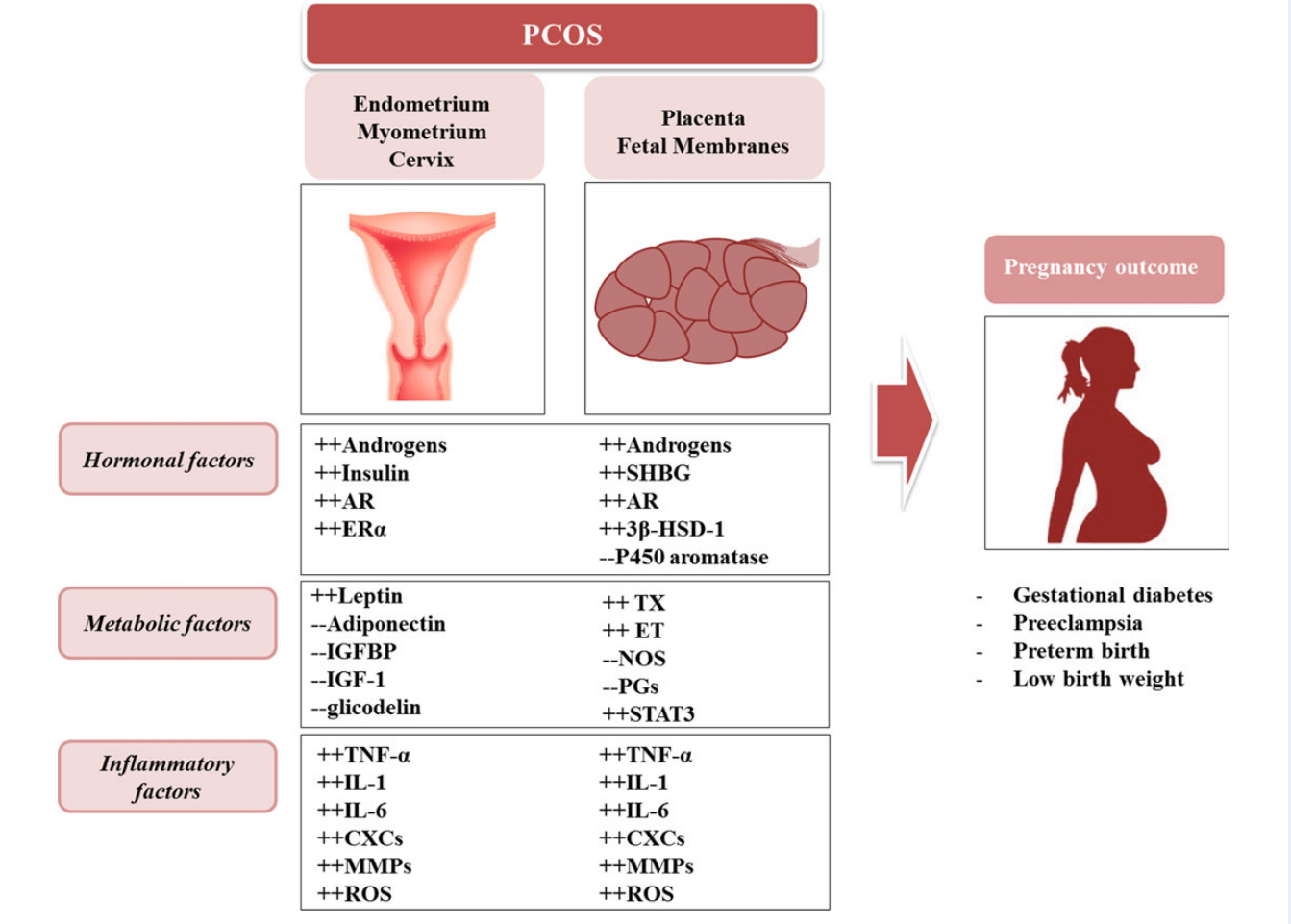

Figure 1 Hormonal, inflammatory and metabolic factors occurring in the uterus (endometrium, myometrium, cervix) and in placental tissues (trophoblast and membranes) mediate the mechanisms of pregnancy complications in women with PCOS. AR, androgen receptor; ERα, estrogen receptor alpha; SHBG, sex hormone-binding globulin; 3β-HSD-1, 3beta-hydroxysteroid dehydrogenase type 1; IGFBP, insulin-like growth factor-binding protein; IGF-1, insulin-like growth factor type 1; TX, thromboxane; ET, endothelin; NOS, nitric oxide synthase; PGs, prostaglandins; STAT3, signal transducer and activator of transcription 3: TNF-α, tumor necrosis factor-alpha; IL-1, interleukin 1; IL-6, interleukin 6; CXCs, chemokines; MMPs, matrix metalloproteinases; ROS, reactive oxygen species.

2012). In particular, women with endometriosis in their first pregnancy have greater risk of SGA babies, GDM, premature preterm rupture of membranes (pPROMs) and PTB, with longer hospitalization for mother and neonate (Conti *et al.*, 2014). Also women with adenomyosis have increased risk of PTB and pPROM (Juang *et al.*, 2007). In large population studies, including both spontaneous and ART pregnancies, an increased rate of PTB in women with endometriosis has been described (Stephansson *et al.*, 2009; Fig. 2). Regarding neonatal outcome, endometriosis increases the incidence of stillbirth, irrespective of the use of ART (Aris, 2014). Conversely, a lack of negative pregnancy outcome in women with endometriosis has been shown in other studies (Kortelahti *et al.*, 2003; Benaglia *et al.*, 2012; Mekaru *et al.*, 2014).

Uterine fibroids

Uterine fibroids (leiomyomas) are the most common benign tumors of the female reproductive tract, affecting 30–70% of reproductive-age women and therefore are common in pregnancy (from 0.1 to 12.5% of all pregnancies) (Cooper and Okolo, 2005).

Current evidence suggests that fibroids are associated with adverse obstetric outcomes, with antepartum, intrapartum and post-partum complications. Uterine fibroids are related to PTB (Coronado *et al.*, 2000; Qidwai *et al.*, 2006; Conti *et al.*, 2013), and large fibroids (>5 cm) have been shown to be significantly associated with earlier delivery (Shavell *et al.*, 2012). Uterine fibroids are also associated with fetal malpresentations, fetal growth restriction (FGR), placenta previa or placental abruption (Koike *et al.*, 1999; Ouyang *et al.*, 2006; Somigliana *et al.*, 2007; Klatsky *et al.*, 2008; Deveer *et al.*, 2012; Lam *et al.*, 2014) and a higher incidence of post-partum hemorrhage (Coronado *et al.*, 2000; Andreani *et al.*, 2009).

The most common cause of neonatal morbidity in pregnant women with fibroids is preterm delivery (Lai *et al.*, 2012), with a longer neonatal hospitalization (Conti *et al.*, 2013), but this should be adjusted for confounding factors, such as maternal age and the use of ART (Khalaf *et al.*, 2006; Luyckx *et al.*, 2014).

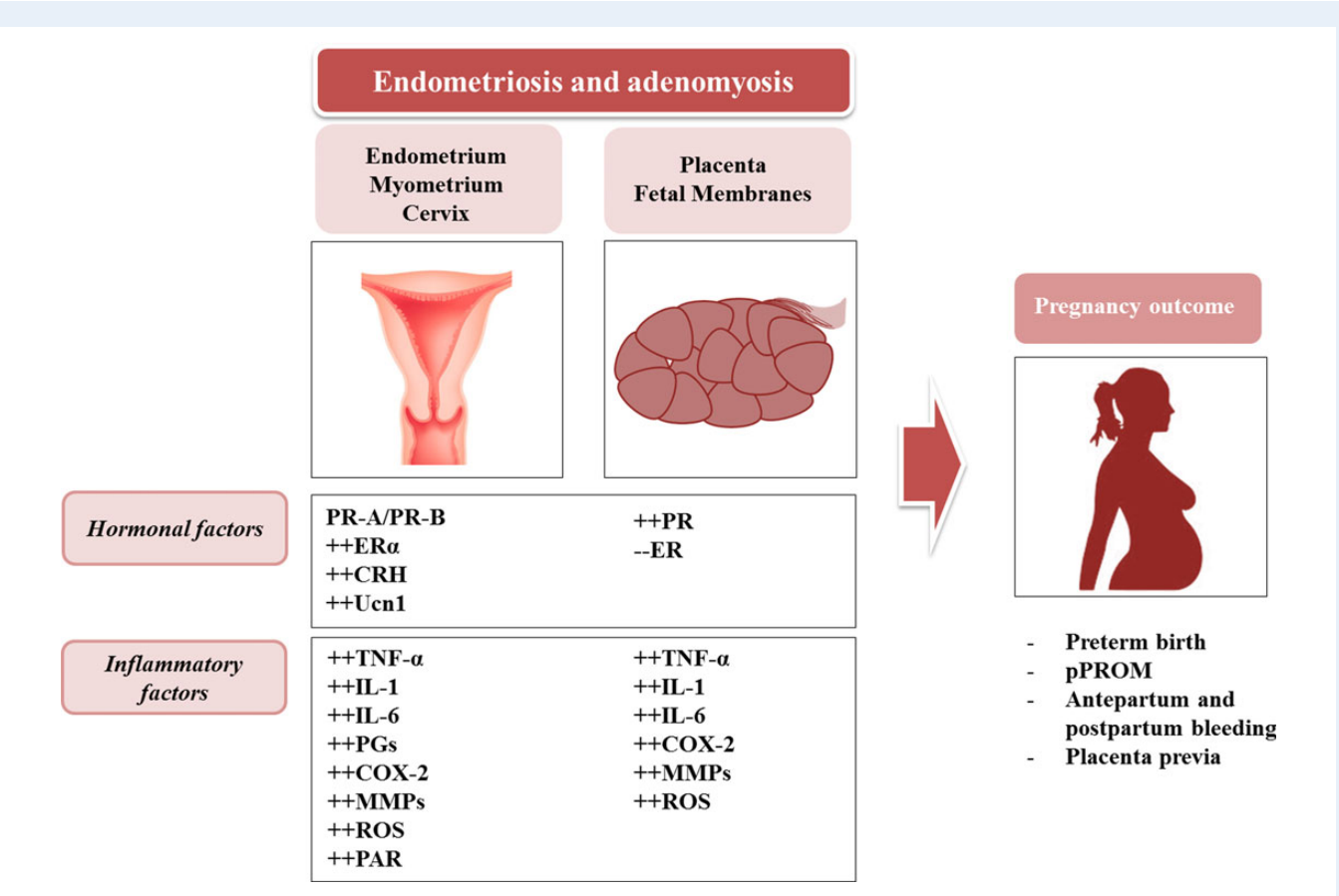

Figure 2 Hormonal and inflammatory factors occurring in uterus (endometrium, myometrium, cervix) and in placental tissues (trophoblast and membranes) mediate the mechanisms of pregnancy complications in women with endometriosis and adenomyosis. PR-A, progesterone receptor isoform A; PR-B, progesterone receptor isoform B; CRH, corticotropin-releasing hormone; Ucn1, urocortin 1; COX-2, cyclooxygenase 2; PAR, protease-activated receptor.

Unexplained infertility and ART

Unexplained infertility affects 10–20% of women (Sunderam *et al.*, 2012), and regardless of treatment, is associated with an increased risk of pregnancy-induced hypertension (PIH) and PE, antepartum hemorrhage, PTB and Caesarean delivery (Pandian *et al.*, 2003; Thomson *et al.*, 2005; Jaques *et al.*, 2010; Raatikainen *et al.*, 2012; Messerlian *et al.*, 2013). Risks for these disorders are also increased in pregnancies conceived by ART (Schieve *et al.*, 2002; Kovalevsky *et al.*, 2003; Helmerhorst *et al.*, 2004; Romundstad *et al.*, 2008; Klemetti *et al.*, 2010). Note that twin pregnancies, irrespective of mode of conception, are associated with an increased risk of morbidity and mortality for mother and babies (Geisler *et al.*, 2014), and thus only singleton ART should to be compared with spontaneously conceived singleton pregnancies in risk assessment. In fact, singleton pregnancies achieved by IVF or ICSI show an increased risk of antepartum hemorrhage, hypertensive disorders, GDM, FGR, induction of labor, pPROM, PTB and Caesarean section (Helmerhorst *et al.*, 2004; Jackson *et al.*, 2004; Pinborg *et al.*, 2013; Fig. 3). The increased risk persists even when the effect of stimulation is removed (in frozen embryo transfers) and single embryo transfer is performed (Pandey *et al.*, 2012). An increased risk for other maternal complications, including placenta praevia, placental abruption and vaginal bleeding, is also observed (Jackson *et al.*, 2004; Romundstad *et al.*, 2006; Healy *et al.*, 2010).

In the last decade, oocyte donation has enabled couples to overcome infertility due to advanced maternal age, diminished ovarian reserve, primary ovarian insufficiency and surgical menopause (Luk *et al.*, 2010). Controversial results are reported in infertile women undergoing IVF with donor oocytes. Similar rates of prematurity, hypertensive disorders of pregnancy, GDM and placental abnormalities were found when donor oocyte cycles were compared with IVF cycles with autologous oocytes in women with advanced maternal age (Krieg *et al.*, 2008; Malchau *et al.* 2013). Conversely, donor oocyte recipients are at higher risk for untoward obstetric outcomes than their IVF counterparts, with the highest rate of PIH (Keegan *et al.*, 2007; Le Ray *et al.*, 2012). Moreover, in women who conceive twin pregnancies using IVF, oocyte donation increases the risk of PIH and PE, independent of age, BMI and parity (Sekhon *et al.*, 2014). However, oocyte donation has no impact on the overall perinatal outcome (Stoop *et al.*, 2012).

Neonates from women with unexplained infertility have a higher risk of perinatal morbidity even without the use of ART. An increased rate of prematurity, SGA and 'poor neonatal health' was observed as the time to conception (without medical assistance) increased beyond 6 months (Jaques *et al.*, 2010; Raatikainen *et al.*, 2010). The same adverse neonatal

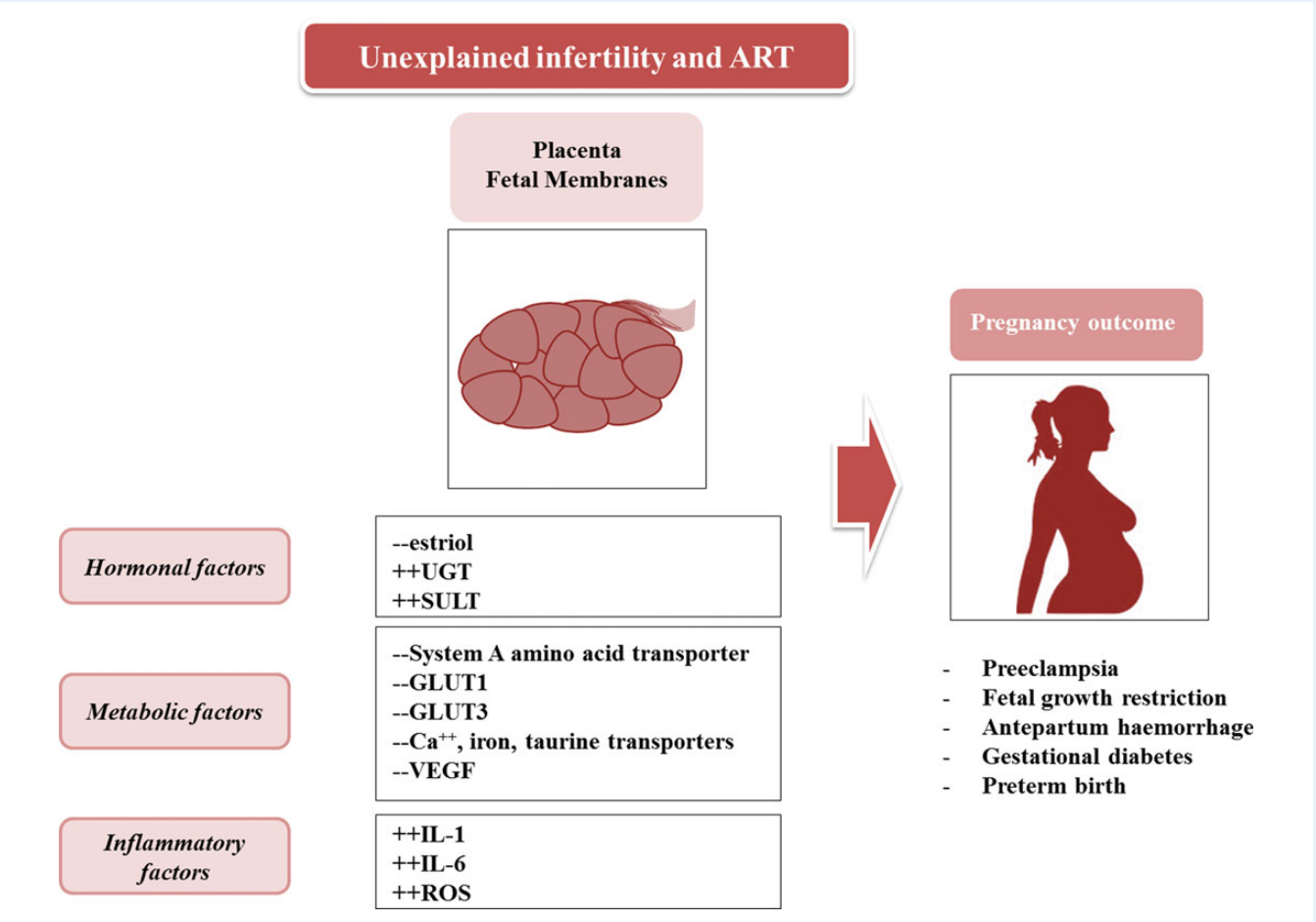

Figure 3 Hormonal, inflammatory and metabolic factors occurring in placental tissues (trophoblast and membranes) mediate the mechanisms of pregnancy complications in women with unexplained infertility and requiring ART. UGT, uridine 5′-diphospho (UDP)-glucuronosyltransferase; SULT, sulfotransferase; GLUT1, glucose transporter type 1; GLUT3, glucose transporter type 3; VEGF, vascular endothelial growth factor.

outcomes are observed in singleton IVF neonates (Moini *et al.*, 2012; Kawwass *et al.*, 2013; Kondapalli and Perales-Puchalt, 2013). Singletons born after intrauterine insemination (IUI) had a higher risk of adverse perinatal outcomes compared with spontaneously conceived children, similar to ICSI, but more favorable outcomes compared with IVF. Stimulation with clomiphene citrate is associated with higher risk of SGA compared with natural-cycle IUI, but FSH treatment is not associated with adverse outcomes (Malchau *et al.*, 2014).

Pathogenic mechanisms contributing to adverse pregnancy outcome in women with reproductive disorders

Pathogenic mechanisms that contribute to uterine fibroids, endometriosis, adenomyosis, PCOS and unexplained infertility may impair pregnancy outcome through common pathways associated with hormonal aberrations, inflammation, metabolic disorders, decidual dysfunction and vascular disorders. As mentioned, either in combination or alone, these disorders result in an increased risk of PTB, FGR, GDM, placental pathologies and/or hypertensive disorders, which are also collected as a syndrome (Romero *et al.*, 2014). Endometrium, myometrium, cervix or placenta may be the anatomical sites where an aberrant milieu predisposes to the onset of specific obstetric complications.

Endometrium

Endometrial alterations are in part responsible for infertility and suboptimal uterine receptivity linked to uterine fibroids, endometriosis/adenomyosis and PCOS (Cakmak and Taylor, 2011; Fauser *et al.*, 2012; Lessey *et al.*, 2013) and the abnormal endometrial milieu may contribute to adverse pregnancy outcome through hormonal, metabolic and inflammatory mechanisms. The establishment and development of pregnancy requires the coordinated implantation of the embryo and trophoblast invasion into the receptive maternal decidua, followed by remodeling of the spiral arteries. Proliferation, migration and invasion of trophoblastic cells into the maternal endometrium are essential steps, and failure of one of these due to endometrial dysfunction may be the basis for developing obstetric complications.

Hormonal abnormalities, including altered endometrial receptor expression, are present in PCOS and endometriosis and drive endometrial dysfunction leading to altered trophoblast decidual invasion. Endometrial

growth and differentiation in women with PCOS are influenced by hyperandrogenism, in view of overexpression of androgen and estrogen receptors (ER) (Makieva *et al.*, 2014). Endometrium of PCOS also shows altered progesterone receptor (PR) gene expression (Piltonen *et al.*, 2015). Indeed, endometrial stromal fibroblasts from women with PCOS have impaired progesterone-mediated decidualization. A proinflammatory cytokine profile, chemokine and matrix metalloproteinase (MMP) release and immune cell chemoattraction are also observed (Piltonen *et al.*, 2015). These gene abnormalities may induce a significant impairment of decidual endovascular trophoblast invasion, responsible for increased incidence of PTB, FGR and hypertensive disorders in pregnancy (Fig. 1).

Similarly, endometriosis is characterized by abnormal ER- and PR-mediated signaling pathways associated with progesterone resistance (Al-Sabbagh *et al.*, 2012; Lessey and Young, 2014). In case of pregnancy in Fkbp52−/− mice, characterized by progesterone resistance, decidualization is inhibited and inefficiency in maintaining pregnancy to full term are observed (Tranguch *et al.*, 2007; Yang *et al.*, 2012; Fig. 2).

Apart from sex steroids, an abnormal decidual/trophoblast interaction may also be driven by metabolic dysfunction. Indeed, adiponectin, leptin and other fat tissue hormones, mainly related to obesity and PCOS, may have an impact on decidua/trophoblast interaction in PCOS and obese patients (Crujeiras and Casanueva, 2015). Furthermore, PCOS patients in the first trimester of pregnancy show a reduction of serum insulin-like growth factor-binding protein 1 and glycodelin that significantly correlate with reduced trophoblast invasion (Palomba *et al.*, 2012). Moreover, lower glycodelin may contribute to a more proinflammatory environment in women with PCOS or endometriosis during early gestation, further impairing trophoblast invasiveness (Irwin *et al.*, 2001; Alok and Karande, 2009). These alterations may lead to epigenetic changes in endometrium that persist long after the insult is removed or corrected. Widespread alterations in endometrial gene methylation, and therefore gene expression, affect endometrial function (Lee *et al.*, 2009, Naqvi *et al.*, 2014; Fig. 1).

The activation of inflammatory pathways could be subsequently associated with immune and vascular dysfunction in placenta/decidua interactions, leading to FGR, PE and PTB. PCOS is associated with a state of chronic low-grade inflammation shown by increased serum concentrations of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-1, adhesion molecules, follistatin and C-reactive protein (Piltonen *et al.*, 2013; Palomba *et al.*, 2014). Moreover, in PCOS, an increased oxidative stress index activated by inflammatory transcription factor NF-kappa B has been observed (Agarwal *et al.*, 2012; Fig. 1).

Increased local and systemic inflammatory pathways and reactive oxygen species are considered a major causal factor for explaining the poor pregnancy outcomes in women with endometriosis (Reis *et al.*, 2013). Altered cell proliferation and apoptosis, increased oxidative stress, increased endometrial prostaglandin (PG) production (PGE2 and PGF2α) and expression of cyclooxygenase 2 (COX-2) (Burney *et al.*, 2007; Tamaresis *et al.*, 2014) ultimately impact decidualization, reducing endometrial receptivity and thereby influencing pregnancy outcomes (Brosens *et al.*, 2012; Vilella *et al.*, 2013; Tamaresis *et al.*, 2014). Inflammation may be enhanced by the altered ratio of PR isoform A (PR-A) to PR isoform B (PR-B) in eutopic endometrium. The hyperinflammatory state in endometriosis influences the decidua/trophoblast interactions early in gestation as well as chorion–decidua interactions that could activate mechanisms of PTB later in pregnancy (Petraglia *et al.*, 2012; Tamaresis *et al.*, 2014; Marcellin *et al.*, 2015) (Fig. 2).

The same mechanisms may affect decidual/trophoblast invasion in women with adenomyosis, who showed increased expression of MMP-2 and MMP-9, E-cadherin, HOXA-10 and leukemia inhibitory factor (Fischer *et al.*, 2011; Benagiano *et al.*, 2012; Galliano *et al.*, 2015; Fig. 2).

Corticotropin-releasing hormone (CRH) and urocortin (Ucn) are examples of neurohormones/neuropeptides related to stress and inflammation in reproductive organs and women with endometriosis share deranged CRH and Ucn mRNA expression associated with an impaired CRH receptor (CRH-R1) activity in modulating the process of decidualization (Novembri *et al.*, 2011).

Uterine cavities containing leiomyomas also show excess inflammation, with up-regulation of MMPs and inflammatory cytokines such as IL-1, transforming growth factor-β and TNF-α, possibly contributing to the increased incidence of PTB (Horne and Critchley, 2007; Sinclair *et al.*, 2011; Tamaresis *et al.*, 2014; Doherty and Taylor, 2015). Indeed, endometrium of women with submucosal and intramural fibroids displays significantly higher macrophage infiltration and increased expression of the chemokine CCL2 and PGF2 compared with women without fibroids (Miura *et al.*, 2006). These molecular alterations lead to impaired decidualization and may contribute to adverse pregnancy outcomes.

Myometrium

Myometrium is a major reproductive tissue involved in pregnancy maintenance as well as in labor onset and progression: a very complex biomolecular communication system exists within myometrium which is actively coordinated through endocrine, paracrine and immunoregulatory factors (Challis *et al.*, 2009; Hirota *et al.*, 2010). Progesterone is essential for the maintenance of pregnancy by regulating myometrial quiescence and the withdrawal of this hormone from the maternal circulation, or at the receptor level, may lead to the onset of labor (Patel *et al.*, 2015). An increased myometrial cell PR-A to PR-B ratio, through an epigenetic mechanism, eliminates PR-B-mediated inhibition (Chai *et al.*, 2014; Patel *et al.*, 2015) and up-regulates pro-inflammatory genes in myometrial cells. The same PR myometrial expression changes are evident in women with preterm labor and endometriosis, supporting that this aberrant hormonal milieu may predispose women to increased risk of PTB.

Several metabolic factors may influence the myometrium in reproductive disorders. For example, obesity, often associated with PCOS, is characterized by systemic vascular endothelial dysfunction, common to PE as well. In particular, vasoconstriction and vasodilatation are impaired in myometrial arteries from obese women, probably involving prothrombotic, proinflammatory and vasoactive (leptin, TNF, IL-6 and IL-8) and vasoprotective (adipokines) factors (Denison *et al.*, 2010). These changes may stimulate utero- and fetoplacental vascular endothelial dysfunction also via an imbalance in nitric oxide bioavailability and increased oxidative stress (Crujeiras and Casanueva, 2015; Fig. 1).

Pro-inflammatory cytokines and PGs are crucial in laboring myometrium (Smith, 2007; Challis *et al.*, 2009). Of note, the uterus with fibroids is characterized by a chronic inflammatory milieu and decreased oxytocinase activity (Ciavattini *et al.*, 2013), potentially predisposing women with uterine fibroids to PTB and pPROM, especially if multiple fibroids are present or if placentation occurs adjacent to or overlying a fibroid. In addition, dysfunctional uterine contractility, anatomical distortion of the uterine cavity and subsequent poor placentation may contribute to premature activation of parturition (Cakmak and Taylor, 2011).

Also in endometriosis inflammation may play a major role in activating premature uterine contractility. TNF-α and IL-1β increase the expression of COX-2 and the production of PGE2 by myometrial cells, while IL-6 up-regulates the expression of oxytocin receptors in the myometrial cells *in vitro* (Benagiano *et al.*, 2014). CRH and CRH-R play a role for priming and preparing myometrium for the onset of labor by regulating cell adaptation to increasing activity of inflammatory cytokines and switch to a procontractile phenotype with increased responsiveness to hormonal signals and mechanical forces (Markovic *et al.*, 2013; You *et al.*, 2014).

Another inflammatory pathway involved in causing threatening preterm contractions leading to PTB in endometriosis may be mediated by protease-activated receptor 2 (PAR-2) that during pregnancy is associated with production/release of COX pathway products activating thromboxane (TX)/PGH2 receptors and TXA2/PGH2 receptors (Freerksen *et al.*, 2005). The observation that uterine deletion of transformation-related protein (TRp53) increases the incidence of PTB, a condition corrected by oral administration of the selective COX2 inhibitor celecoxib, further supports the findings that PGs are essential for myometrial contraction (Hirota *et al.*, 2010; Fig. 2).

Cervix

Uterine cervix is the other uterine compartment that undergoes extensive changes through gestation and parturition acting as a gatekeeper, and collagens, elastin, proteoglycans and hyaluronate are responsible for the full tensile strength (Gonzalez *et al.*, 2011).

Hormonal dysfunction and inflammatory mechanisms associated with gynecological disorders may play an important role in degrading the cervical extracellular matrix and promoting cervical insufficiency. Indeed, the altered hormonal milieu of women with PCOS may influence the mechanical properties of the cervix by destabilizing cervical collagen, resulting in cervical insufficiency (Feigenbaum *et al.*, 2012). In this context, increased androgens and dehydroepiandrosterone sulfate may have a role in promoting cervical modifications by enhancing collagenase activity and thus decreasing fibril collagen organization (Makieva *et al.*, 2014). Although the mechanism of this action is not well established, there is some evidence that it is likely mediated via metabolism of 5α-reductase type 1 (which converts testosterone to dihydrotestosterone (DHT)), the predominant enzyme expressed by cervix at term (Mahendroo, 2012). Notably DHT, which cannot be metabolized to estrogens, promotes cervical ripening, implying an androgen-specific effect in remodeling throughout pregnancy (Makieva *et al.*, 2014).

Cervical ripening is induced by PGE2, IL-1, platelet-activating factor, by mechanical stretch and migration of macrophages and neutrophils (Mahendroo, 2012) and may explain the high incidence of PTB by cervical incompetence in PCOS (Feigenbaum *et al.*, 2012; Fig. 1).

Placenta and membranes

Abnormal placentation is considered crucial for poor obstetric outcomes and the potential placental mechanisms underlying the association between adverse pregnancy outcomes and reproductive disorders is a new area of investigation.

The endometrial–myometrial junctional zone (JZ) plays a critical role in human placentation and women with endometriosis or adenomyosis have defective deep placentation because of defective remodeling of the spiral arteries (Brosens *et al.*, 2010). In the absence of adequate decidual transformation, endovascular trophoblast cells arrest at the level of the endometrial–myometrial JZ and fail to progress into the myometrial spiral arteries, explaining the vascular resistance in pPROM and PTB (Brosens *et al.*, 2013). Defective endovascular trophoblast invasion may also be secondary to absence of natural killer cells in the thickened myometrial JZ that usually regulate the depth of trophoblast invasion (Robson *et al.*, 2012; Wallace *et al.*, 2012; Moffett and Colucci, 2014).

The rate and the extent of endovascular trophoblast invasion (proportion between areas immunoreactive to cytokeratin 7 and to CD34) are significantly reduced also in pregnant women with PCOS (Palomba *et al.*, 2012). Placenta in PCOS patients had a reduced weight, thickness, density and volume and a more irregular shape. The macroscopic findings of placentae could be interpreted as an epiphenomenon of the microscopic placental changes detected such as utero-placental vascular lesions, chronic villitis and intervillositis, abnormal villus maturity and absence of physiological change of the spiral vessels (Palomba *et al.*, 2013). Transferrin, fibrinogen variants, kininogen-1, annexin 2 and peroxiredoxin 2 are hyperexpressed in women with PE and in women with PCOS and are suggested to be the link between these diseases (Khan *et al.*, 2015).

Impaired utero-placental growth and vascular development in pregnancies following ART have been suggested from research involving animal models. ART and the transfer of embryos decreases vascular cell proliferation, the density of blood vessels and angiogenic factors, resulting in reduced placental vascular development, poor placental function and compromised fetal growth and development (Grazul-Bilska *et al.*, 2014). Gene expression is significantly altered in the placenta of mice models (>6% of the transcripts), with excessive gene repression of the complete transcriptome (Fauque *et al.*, 2010a; Zhang *et al.*, 2010). ART triggers the induction of placental genes involved in metabolism, immune response, transmembrane signaling and cellular proliferation and an alteration of genes involved in apoptosis pathways (Fauque *et al.*, 2010b; Zhang *et al.*, 2010; Nelissen *et al.*, 2014). An epigenetic disruption of DNA methylation may also contribute to inhibiting human trophoblastic invasion *in vitro* by disturbing expression of epigenetically regulated genes such as E-Cadherin (Rahnama *et al.*, 2006; Chelbi and Vaiman, 2008; Fig. 3).

The increased rate of PIH and PE suggests that there may be immunological maladaptation with oocyte donation. In fact, in pregnancies achieved after egg donation, the fetus may be viewed as a total allogeneic graft for the gravid woman and no longer a semi-allogeneic graft (Martínez-Varea *et al.*, 2014). These findings support the 'immunologic theory' suggesting that immunological intolerance between mother and fetus may affect placental function (Levron *et al.*, 2014).

Sex steroids and receptors

The steroidogenic function of placenta in PCOS women is altered, with a higher 3β-hydroxysteroid dehydrogenase type 1 and lower P450 aromatase activity, contributing to the high androgen concentrations observed in maternal blood of PCOS patients (Maliqueo *et al.*, 2013; Patel *et al.*, 2015). Interestingly, in the rat model the excess of maternal, fetal and placental androgens is associated with decreased placental size, affecting the ability of placenta to deliver nutrients to the fetus (Sun *et al.*, 2012). Despite the protective mechanisms of increased circulating maternal sex hormone-binding globulin and progesterone levels, maternal hyperandrogenemia may contribute to the development of PE or PTB by

affecting endovascular trophoblast invasion and induce placental alterations (Makieva *et al.*, 2014; Fig. 1).

Hormonal changes associated with ovulation induction in ART persist during the peri-implantation and early placentation periods, by affecting trophoblast differentiation and changing the distribution of cell types in the placenta (Mainigi *et al.*, 2014). Placentas from ART pregnancies were overrepresented in the highest quartile of weight, and the placental weight/birthweight ratio was commonly higher, even after adjusting for confounding factors (Haavaldsen *et al.*, 2012). Even though normal phenotypes and no microscopic alterations were observed, ultra-structural modifications, such as degenerative alterations of terminal villi, mainly in syncytiotrophoblasts, including a thicker placental barrier, decreased apical microvilli and increased multiple vacuoles in human term ART-derived placentas than in control placentae were observed (Zhang *et al.*, 2011). It was proposed that increased placental weight after IVF could be a compensatory process to ensure normal fetal growth. Similarly, in a mouse model, down-regulation of nutrient transport pathways, such as system A amino acid transporter and GLUT3 protein, have been demonstrated in blastocysts developed *in vitro* (Rinaudo and Schultz, 2004). Mouse placental weight correlated inversely with amino acid transport during late pregnancy, and the least efficient placenta (per unit of weight), had the greatest degree of enlargement (Bloise *et al.*, 2012). In most cases, successful compensation leads to the normal progress of pregnancy and the development of healthy offspring. If compensatory mechanisms are overwhelmed, improper maternal–fetal exchanges occur, potentially leading to abortion or adverse pregnancy outcomes such as growth restriction (Bloise *et al.*, 2014). Recent evidence in a mouse model confirmed that ART placentae exhibit down-regulation of a majority of placental nutrient transporters, including not only amino acid and glucose transporter but also the genes for the calcium, iron, thiamine and taurine transporters (Chen *et al.*, 2015). Moreover, ART placentae have histomorphological alterations with defects in placental layer segregation and glycogen cell migration, with a significantly greater glycogen-positive area rate. Thus, the disrupted expression of a majority of imprinted genes important for placental development and function results in structural abnormalities of the placenta (Chen *et al.*, 2015). Indeed, a murine model showed that placentas from ART had lower estriol levels and significantly higher activities of the steroid metabolizing enzymes UDP-glucuronosyltransferase and sulfotransferase. Thus, the ART placenta has a higher metabolism and clearance of steroids, affecting the passage of essential hormones for fetal growth (Collier *et al.*, 2009; Fig. 3).

Metabolic pathways

Metabolic mechanisms also mediate PCOS-related placental vascular dysfunction via increased sensitivity to vasoconstrictor substances (TX and endothelin (ET)) and blunting vasodilatory influences (PGs and NO). Gestational hyperinsulinemia induces vasoconstriction, resulting in shallower implantation and altered placental expression of the three isoforms of nitric oxide synthase (NOS) (neuronal-nNOS, inducible-iNOS and endothelial-eNOS) (Skarzinski *et al.*, 2009). Furthermore, placentae exposed to hyperinsulinemia have increased expression of endothelin converting enzyme 1 and the ET-A receptors, thus potentially contributing to the pathogenesis of FGR (Khamaisi *et al.*, 2012). Metabolic inflammation represents a newer concept, combining chronic metabolic disturbances with low-grade inflammatory responses, which engage in the release of pro-inflammatory cytokines by several organs (Hotamisligil, 2006). An activator of transcription 3 (STAT3) modulates placental nutrient transport and its signaling is increased in placentae of women with PCOS, independent of pregnancy-related complications and is activated by inflammatory and metabolic factors related to obesity (Maliqueo *et al.*, 2015; Fig. 1).

Inflammatory mechanisms

As shown in endometrium, myometrium and cervix, altered inflammatory mechanisms are found in placentas of women with reproductive disorders. Syncytiotrophoblast apoptosis and shedding of products that extensively damage endothelial integrity can decrease utero-placental flow and activate a cascade of molecular effects leading to hypoxia, thrombosis, and endothelial cell dysfunction and adverse pregnancy outcomes. Excessive oxidative stress and complement activation can lead to placental damage, abnormal placental development, generalized endothelial activation and release of antiangiogenic factors (Menon *et al.*, 2014). Thrombin significantly up-regulates proinflammatory chemokines, resulting in endothelial dysfunction or inappropriate endothelial cell activation, enhanced endothelial cell permeability and platelet aggregation which are common clinical manifestations in PE (Lockwood *et al.*, 2011).

Placentae of obese women have increased infiltration of proinflammatory macrophages, which express high levels of IL-1, TNF-α and IL-6, associated with increased expression of chemotactic cytokines and neutrophils in the maternal interstitial space and in muscularity of placental vessels (Challier *et al.*, 2008). This pro-inflammatory maternal and fetal environment may play a role in mediating adverse pregnancy outcomes for both mother and fetus, such as GDM and PE (Roberts *et al.*, 2011).

Inflammation appears to be the most obvious link between endometriosis and adenomyosis and PTB, as suggested by chorioamniotic or systemic inflammations (Blank *et al.*, 2008). Recently, endometriotic-like lesions (glandular components in the choriodecidual layer surrounded by enlarged decidualized cells) have been described along the entire membrane surface within the decidual side of the chorion–decidua of the fetal membranes from women affected with severe endometriosis (Marcellin *et al.*, 2015). Significant alterations were observed for 2773 genes involved in glandular function, the endocrine and nervous systems, neoangiogenesis and autoimmune disease in membranes. CpG methylation analysis revealed 5999 differentially methylated regions. These data support the hypothesis that maternal endometriosis persists during pregnancy and affects the decidual side of the chorion–decidua, possibly involved in PTB (Marcellin *et al.*, 2015; Fig. 2).

In extravillous trophoblasts PAR-1 and PAR-2 are likely to play a role in the maintenance of the placental circulation (O'Brien *et al.*, 2003). Interestingly, amnion mesenchymal cells from pregnancies with PTB show activation of PAR-1 (Mogami *et al.*, 2014), an enzyme also involved in endometriosis pathogenesis.

Placental inflammation and oxidative stress are significantly raised in the mouse model of ART. Specific testing revealed significantly lower placental lipid loading, increased placental cell death (apoptosis) and compromised intracellular nucleotides (lower RNA levels and integrity, higher DNA damage) (Raunig *et al.*, 2011). Furthermore, ART manipulation resulted in increased inflammation through the IL-6 pathway and greater oxidative stress in placentas, both of which were particularly apparent in placentae from pregnancies achieved through ICSI. Excessive placental inflammation and oxidative stress may be a critical factor in the higher incidence of PTB, LBW and pediatric imprinting disorders reported following ART (Raunig *et al.*, 2011; Fig. 3).

Conclusions

From the present data, it is evident that patients with PCOS, endometriosis, adenomyosis, uterine fibroids and/or unexplained infertility show a series of endometrial, myometrial, cervical and placental alterations that underlie the poor obstetric outcomes observed in these patients. Pre-pregnancy hormonal dysfunction that includes hyperandrogenism, progesterone resistance and hyperinsulinism appears to impair uterine placentation mechanisms. Metabolic dysfunction prevails in PCOS, while inflammatory mechanisms are more relevant in endometriosis, adenomyosis and uterine fibroids, although endometrial inflammation also is present women with PCOS. When ART is utilized, an effect on placental adaptive function is shown. We therefore hypothesize that abnormal endometrial and myometrial hormonal/inflammatory mechanisms lead to a greater risk of PTB; whereas, hormonal/metabolic derangement lead to PE or GDM.

In clinical practice, many women of child-bearing age have more than one reproductive disorder, as these rarely occur in isolation (Holoch *et al.*, 2014). Therefore, concomitant reproductive disorders should be considered to increase the risk of poor pregnancy and neonatal outcomes once a pregnancy is achieved. Understanding the inflammatory, endocrine and metabolic mechanisms responsible for the increased incidence of obstetric complications associated with reproductive disorders may help in developing new therapies. Studies to date suggest that patients with reproductive disorders and/or undergoing ART belong to a 'high risk' category for pregnancy. It is thus important that evidence-based preconception and prenatal guidelines be developed to minimize pre-pregnancy abnormalities and risk factors, and for advising women, alerting the health care teams to the high risk status of the pregnancy for the mother and the neonate, and to optimize pregnancy outcomes overall.

Authors' roles

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