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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...
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; Kjerulf 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 (Touilis et al., 2009; Palomba et al., 2010; De Fréne et al., 2014).

Women with PCOS and glucose intolerance may develop GDM (5–40% risk; Touilis 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., 2011).
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).
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 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
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 hyper-androgenism, 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 chemotraction 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 Flkbp52−/− 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 (Cruijeras 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 glycodeolin that significantly correlate with reduced trophoblast invasion (Palomba et al., 2012). Moreover, lower glycodeolin 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 (PG2 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 (Broens 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 PGF2α 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 (Cruijeras 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 (Cavittini et al., 2013), potentially predisposing women with uterine fibroids to PTB and pPROM, especially if multiple fibroids are present or if placenta occurs adjacent to or overlying a fibroid. In addition, dysfunctional uterine contractility, anatomical distortion of the uterine cavity and subsequent poor placentaent 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 (Hirotâ 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 (Makiieva 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 (Makiieva 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 pROM 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 epitome 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-Bliska 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 (Martinez-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 steriodogenic 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 alter-
tations (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 phe-
notypes 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 (Rинаudo and Schultz, 2004).
Mouse placental weight correlated inversely with amino acid transport
during late pregnancy, and the least efficient placentae (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 off-
spring. If compensatory mechanisms are overwhelmed, improper materi-
—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 dis-
rupted expression of a majority of imprinted genes important for placen-
tal development and function results in structural abnormalities of the
placenta (Chen et al., 2015). Indeed, a murine model showed that placentae 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
clarity 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 hyperinsulinaemia induces vasoconstriction, resulting
in shallower implantation and altered placentan expression of the three
isoforms of nitric oxide synthase (NOS) (neuronal-nNOS, inducible-
NOS and endothelial-eNOS) (Skarzinski et al., 2009). Furthermore, placentae exposed to hyperinsulinaemia 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). Metabol-
ic inflammation represents a newer concept, combining chronic meta-
bolic 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 inflamma-
tory mechanisms are found in placentae of women with reproductive dis-
orders. Syncytiotrophoblast apoptosis and shedding of products that
tensively damage endothelial integrity can decrease utero-placental
flow and activate a cascade of molecular effects leading to hypoxia, throm-
bosis, and endothelial cell dysfunction and adverse pregnancy outcomes.
Excessive oxidative stress and complement activation can lead to placen-
tal damage, abnormal placental development, generalized endothelial
activation and release of antiangiogenic factors (Menon et al., 2014).
Thrombin significantly up-regulates proinflammatory chemokines, result-
ing 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 proinflamma-
tory macrophages, which express high levels of IL-1, TNF-α and IL-6,
associated with increased expression of chemotactic cytokines and neu-
rophils in the maternal interstitial space and in muscularity of placental
vesicles (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 endomet-
riosis and adenomyosis and PTB, as suggested by chorioamniotic or sys-
temic 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,
neangiogenesis and autoimmune disease in membranes. CpG methyla-
tion analysis revealed 5999 differentially methylated regions. These data
support the hypothesis that maternal endometriosis persists during preg-
nancy and affects the decidua 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). Inter-
estingly, amion mesenchymal cells from pregnancies with PTB show ac-
tivation 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 placen-
tal lipid loading, increased placental cell death (apoptosis) and com-
prised intracellular nucleotides (lower RNA levels and integrity, higher DNA damage) (Raunig et al., 2011). Furthermore, ART manipu-
lation resulted in increased inflammation through the IL-6 pathway and
greater oxidative stress in placentas, both of which were particularly ap-
parent 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 placentatal 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.

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