1 Nuclear Receptors in Pregnancy and Outcomes: Clinical Perspective

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Abstract

Pregnancy is characterised by profound hormonal and metabolic changes in the mother. Both oestrogen and progesterone, along with their respective nuclear receptors, have an important role in maintaining a healthy pregnancy. Equally, other nuclear receptors such as LXR, FXR and the PPARs play important roles in the gradual alterations in metabolism that ensure survival of mother and fetus. Disruptions in nuclear receptor signalling can result in pregnancy disorders such as gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, hypertensive disorders of pregnancy and preterm labour, all of which have both immediate and long-term implications for maternal and fetal health. By reviewing data from human studies and animal models, this chapter will describe the contribution of nuclear receptors to normal pregnancy, their role in gestational disorders and their potential as therapeutic targets.

Keywords

Pregnancy · Oestrogen · Progesterone · LXR · FXR · PPAR · Gestational diabetes · Hypertension · Cholestasis

1.1 Introduction

Pregnancy is a unique state in which the maternal organism must undergo a multitude of physiological adaptations to support the growth of a fetus, whilst also maintaining its own health. Numerous cardiovascular, renal, immune and metabolic changes occur in response to rising concentrations of reproductive hormones and the growing conceptus [1]. Not surprisingly, disruptions in the complex regulation of these maternal modifications can result in pregnancy disorders.

In humans, maternal preparations for pregnancy occur in every menstrual cycle regardless of the presence of a conceptus. The uterus and endometrium undergo changes that render them receptive to embryo implantation and placental development [2, 3]. The reproductive hormones oestrogen and progesterone play a key role in this process, along with their respective nuclear receptors (the ERs and PRs). Other nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs) also influence trophoblast development and placental formation. Comprehending

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M. J. Campbell, C. L. Bevan (eds.), *Nuclear Receptors in Human Health and Disease*, Advances in Experimental Medicine and Biology 1390, https://doi.org/10.1007/978-3-031-11836-4_1

the mechanisms underlying these early events is not only important for the understanding of early pregnancy pathologies such as recurrent miscarriage and implantation failure, but also later gestational complications. It is known that disruptions in decidualisation, implantation and trophoblast invasion can have a lasting effect on pregnancy, as they can constitute the pathophysiological basis for pre-eclampsia, intrauterine growth restriction and placental abruption [4].

After implantation, maternal metabolism adapts to cater for the increasing energetic demands of the fetus (Fig. 1.1). There are marked alterations in maternal metabolic pathways of uptake, storage and distribution of nutritional fuels to match different stages of fetal development [1]. Early pregnancy is characteristically an anabolic state that guarantees the storage of nutrients in preparation for later stages of gestation. This period is marked by increased insulin sensitivity, lipogenesis and lipid storage [5]. As pregnancy advances, insulin resistance progressively rises towards the third trimester, causing a shift to a catabolic state [5, 6]. Lipolysis is thus stimulated, leading to a state of physiological hyperlipidaemia in the mother [7]. Serum glucose concentrations rise, and glucose is prioritised to the fetus, whilst the mother relies on serum lipids for nutrition [5]. Although the mechanisms behind these changes are not fully under-

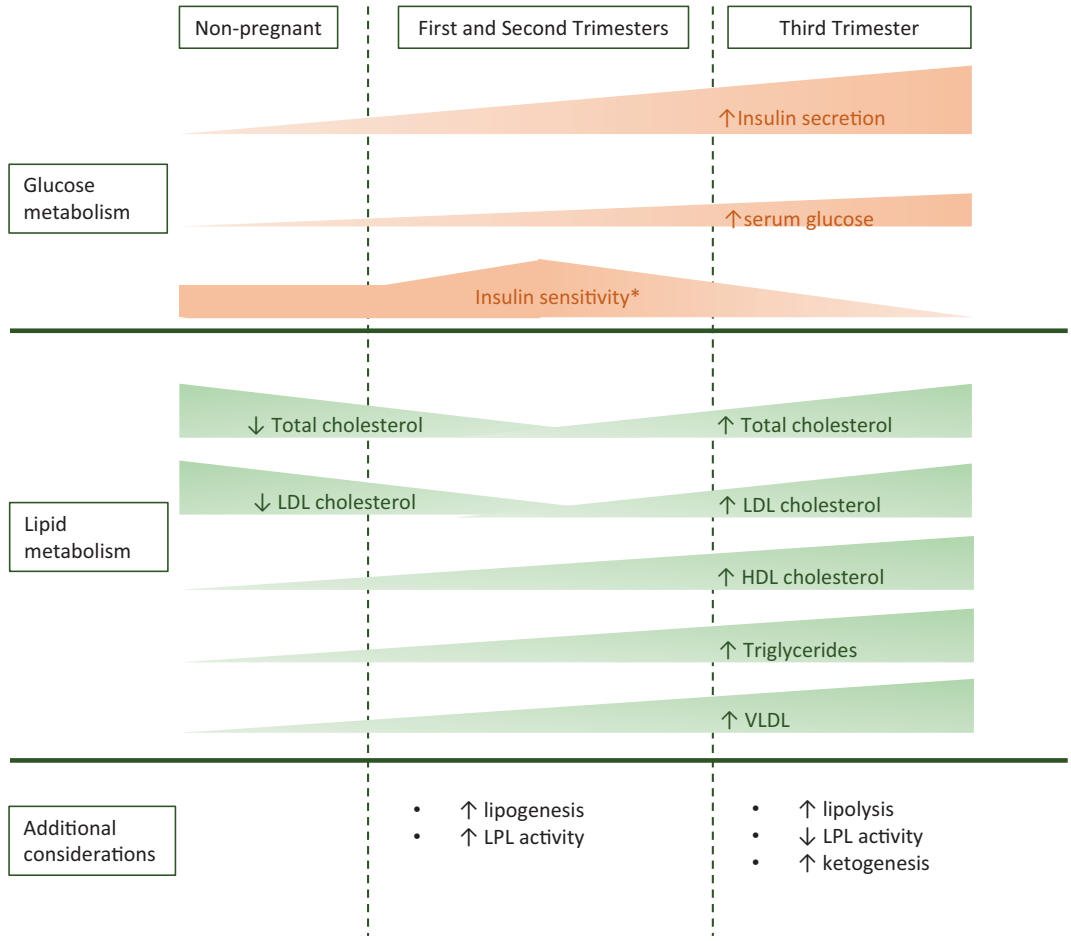

Fig. 1.1 Summary of changes in maternal metabolism during pregnancy. Arrows show direction of change. *: insulin sensitivity increases in the first trimester then progressively declines as the mother enters a catabolic state. *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *VLDL* very low-density lipoprotein, *LPL* lipoprotein lipase

stood, nuclear receptors have been identified as plausible candidates for their regulation [8].

Close to term, changes in the uterine environment occur to facilitate parturition. The myometrium, previously quiescent, becomes responsive to labour stimuli and undergoes changes that facilitate its contractions. This is a process highly regulated by progesterone and its nuclear receptors.

In this chapter we will explore the contribution of nuclear receptors to the development of a normal pregnancy, focusing on early pregnancy events, maternal metabolic changes and mechanisms behind parturition. We will then describe how nuclear receptors are implicated in disorders such as gestational diabetes, hypertensive disorders of pregnancy, intrahepatic cholestasis of pregnancy and preterm labour.

1.2 The Role of Nuclear Receptors in Maintaining a Healthy Pregnancy

1.2.1 Progesterone Receptors and PPARS in Early Pregnancy

The development of a healthy materno-fetal interface is essential for pregnancy success. A key organ at this interface is the placenta. While maternal uterine receptivity is achieved through the process of endometrial decidualisation, the conceptus is responsible for the development of different trophoblastic lineages that will execute the placental functions of hormonal synthesis, materno-fetal exchange of nutrients and adequate supply to fetal tissues.

The process of decidualisation occurs in the second phase of the endometrial cycle, when progesterone concentrations rise following ovulation. It transforms the oestrogen-primed endometrial stromal cells into specialised secretory cells that facilitate implantation and trophoblast development [3]. Progesterone is a master regulator of this process via stimulation of its nuclear progesterone receptor (PR). Three forms of PRs have been identified in mice and humans: PR-A, PR-B and PR-C, with the first two recognised as the main isoforms present in the uterus [9]. PR can be activated by direct binding of progesterone, as well as through ligand-independent activation [10], illustrating the complexity of its function. Whilst the presence of both PR-A and PR-B is critical for the development of adequate decidual responses in mice, PR-B seems to have a less crucial role. Knockout studies in mice have shown that the absence of PR-B does not induce a markedly abnormal uterine phenotype [11, 12]. A temporal change in the expression of each isoform, as well as their relative expression, is also essential for adequate endometrial proliferation [13].

After fertilisation, the conceptus implants into the decidualised endometrium. Its extraembryonic tissues undergo differentiation into distinct lineages, followed by migration and invasion of maternal tissues to form the placenta. The lineage termed villous trophoblast (VT) forms the chorionic villi, the main materno-fetal exchange surface of the placenta. The extravillous trophoblast (EVT) is the lineage responsible for anchoring the placenta into maternal tissues and remodelling uterine spiral arteries to optimise placental perfusion (Fig. 1.2) [14, 15].

The nuclear peroxisome proliferator-activated receptor (PPAR) has been implicated in this early process of trophoblast differentiation and invasion. All three known PPAR isoforms, PPARα, PPARβ and PPARγ, are expressed in human and rodent placentas [16]. PPARγ and its heterodimer partner RXRα have the most widely reported role in this process. They are expressed in both VT and EVT [17]. Their essential role is illustrated by the fact that PPARγ-null mutations in mice result in early embryo demise secondary to inappropriate placental vascular formation and trophoblast differentiation [18]. *In vitro* experiments with PPARγ agonists showed that PPARγ activation abrogates maternal tissue invasion by the EVT, whilst PPARγ antagonists have the opposite effect [19–22]. There also seems to be an effect of PPARγ agonists on trophoblast differentiation. *In vitro* studies of PPARγ-null trophoblast stem cells showed defects in differentiation of all trophoblast layers [23],

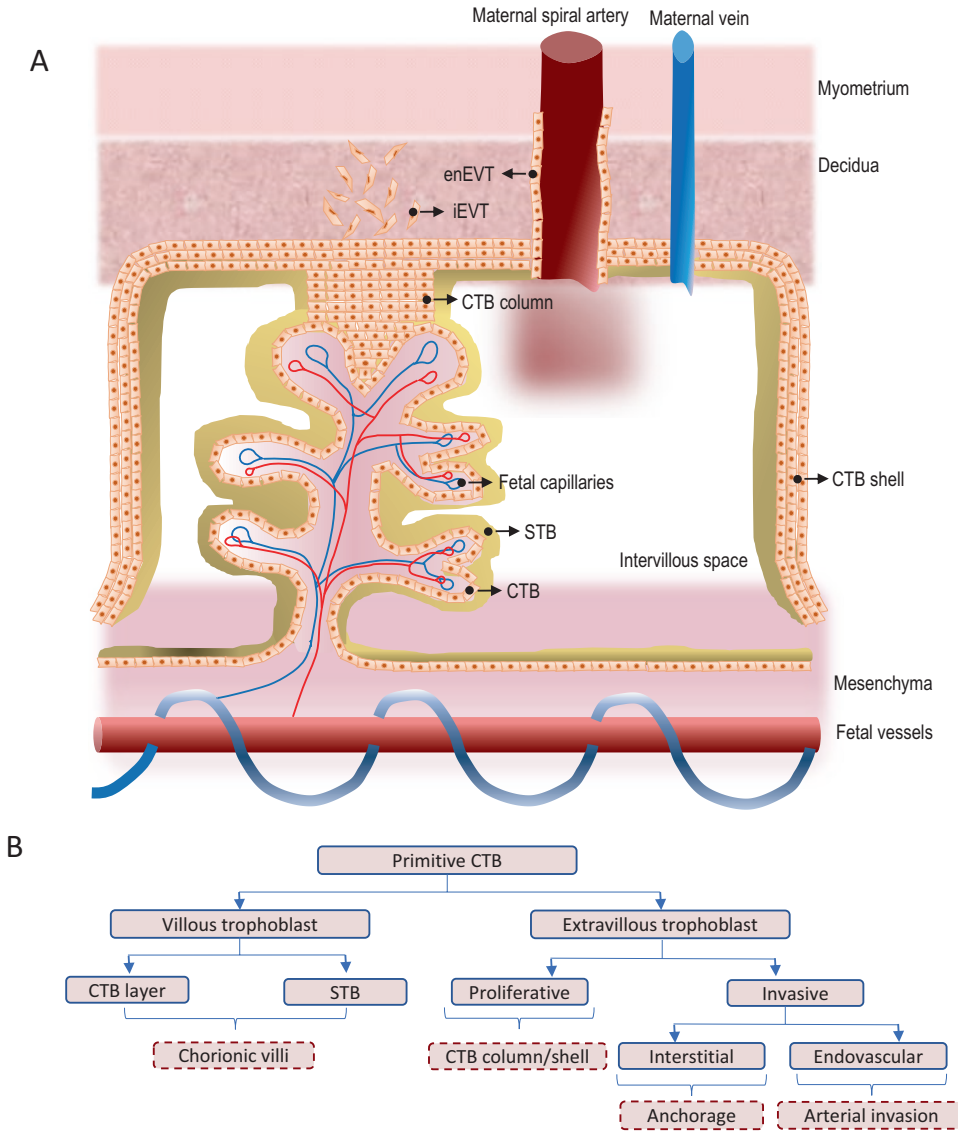

Fig. 1.2 Simplified representation of placental structure (a) and lineages (b). After implantation, the extraembryonic tissues of the blastocyst differentiate into distinct lineages to form the placenta. It first differentiates into the cytotrophoblast (CTB), a single layer of epithelial cells that gives origin to the chorionic villi, the functional units that facilitate feto-maternal exchange. The cytotrophoblast acts as a stem cell layer that generates all other lineages. The fusion of cells creates the multinucleated layer of the syncytiotrophoblast (STB), which is responsible for placental hormone synthesis. Each chorionic villus is made of a mesenchymal chore, fetal capillaries, a layer of cytotrophoblast and a layer of syncytiotrophoblast. The CTB proliferates into columns above the chorionic villi, giving rise to the (EVT), which is responsible for anchoring the placenta into maternal tissues. These columns merge to form a CTB shell, which is a continuous structure only breached by maternal vessels that provide blood to the intervillous space. The EVT then differentiates into the interstitial EVT (iEVT), which invades the maternal decidua, and the endovascular EVT (enEVT), which invades the spiral arteries and replace their smooth muscle to increase placental perfusion. Both LXRs and PPARs are involved in trophoblast differentiation and invasion

although one study showed that this effect might be ligand-dependent [24].

Similarly, liver X receptors (LXR) have been shown to affect trophoblast function. Two subtypes of LXR, LXRα and LXRβ, have been recognised to date. LXRα is highly expressed in tissues with high metabolic activity such as liver and adipose tissue, whereas LXRβ is ubiquitously expressed [25, 26]. Both are expressed in the placenta [27]. LXR is a master regulator of cholesterol metabolism and is activated by endogenous oxysterols [28]. A study in an *in vitro* model of invasive human trophoblast showed that activation of LXRβ by synthetic or endogenous ligands can inhibit trophoblast invasion [29]. LXR activation, by both oxysterols and a synthetic LXR agonist, can also impair trophoblast differentiation [30, 31].

1.2.2 Liver-X-Receptors, Clock Genes and Maternal Metabolic Adaptations in Mid-to-Late Pregnancy

Two groups of nuclear receptors, LXRs and the clock-regulating REV-ERBs, have been shown to influence maternal metabolic adaptations to pregnancy. LXR acts as a cholesterol sensor that prevents cholesterol accumulation in tissues. It is a strong promoter of reverse cholesterol transport, stimulating the transport of cholesterol from the periphery to the liver, whereby it is excreted through the biliary system [25]. In the event of high serum concentrations of cholesterol, LXR induces the expression of transporters ABCA1 and ABCG1, both of which facilitate the transfer of intracellular cholesterol onto apolipoproteins and HDL, and subsequent return of cholesterol to the liver [32, 33]. Despite preventing cholesterol accumulation, LXR has also a seemingly paradoxical role in *de novo* lipogenesis. It upregulates SREBP-1c, ACC, SCD1 and FAS, all of which participate in fatty acid (FA) and triglyceride (TG) synthesis pathways [34]. Thus, LXR stimulation can increase serum concentrations of TG and FAs. By promoting this effect, LXR facilitates cholesterol esterification by FAs, a process that decreases its toxic potential to cells [25]. A summary of the metabolic effects of LXR and its target genes can be found in Fig. 1.3a.

The role of LXR in promoting the marked lipogenic state of early pregnancy has been confirmed in a mouse model [35]. However, LXR did not seem to influence accompanying changes in cholesterol concentrations. The study showed that mouse pregnancy presents the expected findings of increased hepatic concentrations of TG in early stages. A simultaneous upregulation of the LXR targets Fas, Scd-1 and Srebp-1c was also observed. These changes then resolved later in pregnancy, when increased serum concentrations of TG were observed. The same alterations in lipid metabolism were reproduced in non-pregnant females fed LXR agonists, and were disrupted in LXR knockout mice, confirming the role of LXRs in the process.

Data on the contribution of LXR to adaptations in later pregnancy are scarce. LXR expression, along with the expression of other nuclear receptors, was shown to be reduced in the liver of mice in late pregnancy [36]. In a different study, changes in lipid metabolism in late pregnancy occurred in the presence of normal protein levels of both LXRα and LXRβ [35]. However, administration of LXR agonists had little effect on the downstream LXR gene expression profile. It is therefore possible that although LXR expression and protein availability remains constant throughout pregnancy, gestational signals in later stages interfere with its function.

Changes in lipid metabolism in early pregnancy also seem to be associated with disruptions in the body's clock function. Circadian signals are known to influence metabolic pathways [37]. The nuclear receptors REV-ERB-α and REV-ERB-β have been shown to regulate a feedback loop between the body's master clock at the suprachiasmatic nucleus and peripheral organs [38, 39]. A study in mice showed that the expression of the lipogenic genes *Fas, Scd2 and Hmgcr* are increased in early pregnancy in comparison to late pregnancy. This increase seems to be uncoupled from the normal circadian oscillations in *Rev-erb-α* and *Rev-erb-β* expression. In late pregnancy, this synchronicity is restored and becomes similar to that

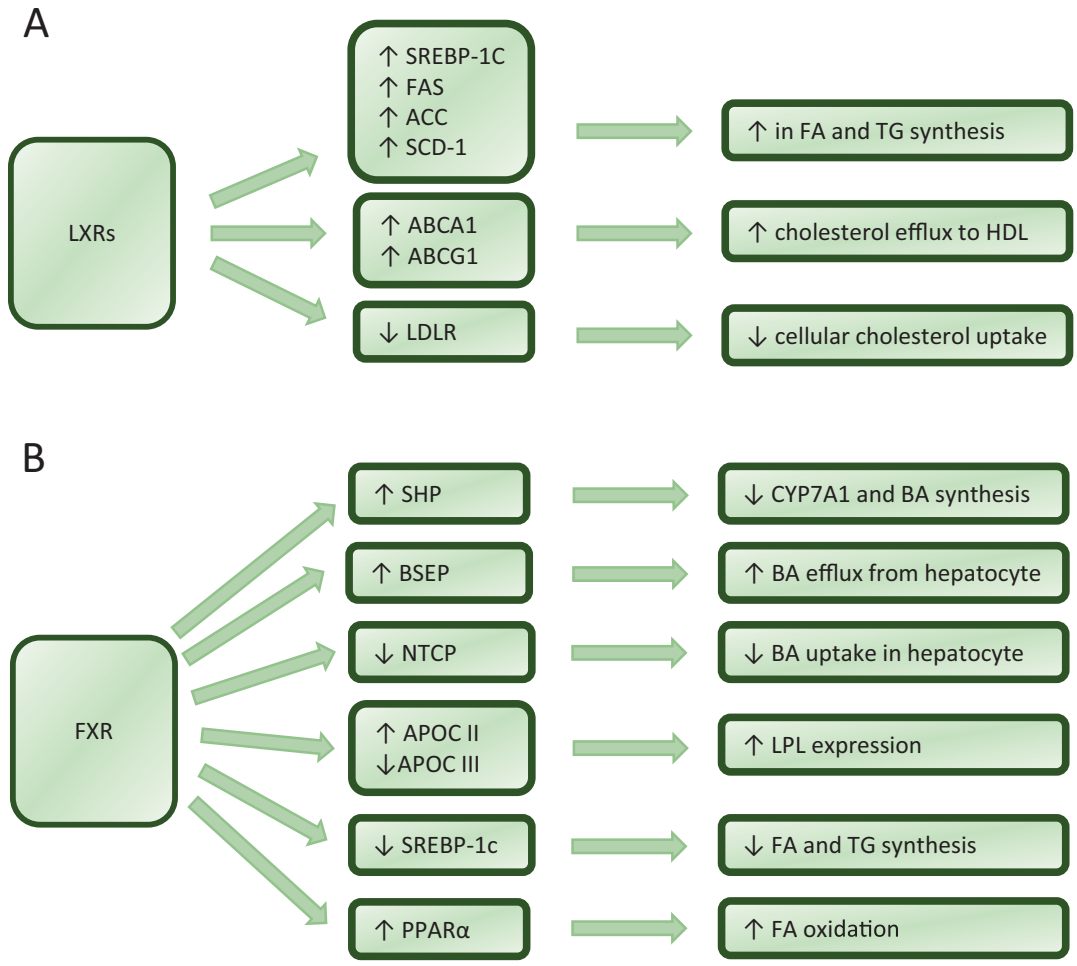

Fig. 1.3 Simplified representation of the metabolic effects of nuclear receptors LXR and FXR. Arrows show the direction of effect on gene targets and physiological processes of (**a**) LXR and (**b**) FXR. *LXR* Liver-X-receptor, *SREBP-1C* Sterol regulatory element-binding protein 1, *FAS* Fatty acid synthase, *ACC* Acetyl-CoA carboxylase, *SCD-1* Stearoyl-CoA desaturase 1, *ABCA1* ATP-binding cassette transporter A1, *ABCG1* ATP-binding cassette transporter G1, *LDLR* Low-density lipoprotein receptor, *FA* fatty acid, *TG* triglyceride, *HDL* high-density lipoprotein, *FXR* farnesoid-Xreceptor, *SHP* small heterodimer partner, *BSEP* bile salt export pump, *NTCP* Sodium-taurocholate co-transporting polypeptide, *APOCII* Apolipoprotein C-II, *APOCIII* apolipoprotein C-III, *PPARα* Peroxisome proliferator-activated receptor alpha, *CYP7A1* 7α-hydroxylase, *BA* bile acid, *LPL* lipoprotein lipase

of non-pregnant females. This shows that, for the anabolic state of early pregnancy to occur, hepatic gene expression becomes independent of the usual hepatic clock system [40].

1.2.3 Parturition

Human labour is a complex event resulting from cervical ripening and myometrial contractions that culminate in the expulsion of the fetus and the placenta. In order to prevent early delivery of the fetus, the uterus remains quiescent throughout gestation until endocrine, pro-inflammatory and mechanical changes occur to trigger myometrial activation [41]. Inflammation is a central feature of human labour (Fig. 1.4), and development of a pro-inflammatory state within the uterus is one of the initial triggers for parturition.

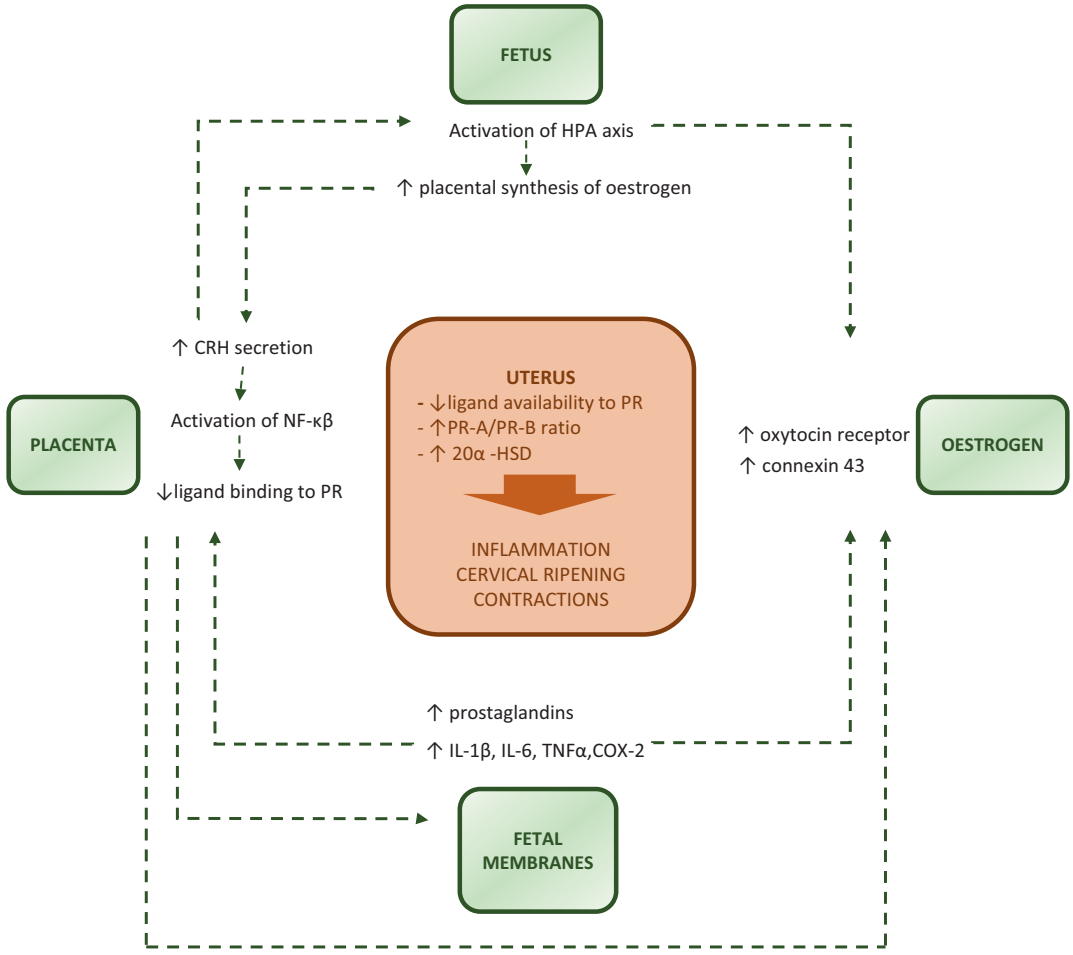

Fig. 1.4 Simplified representation of the mechanisms underlying labour. Dashed arrows represent a positive effect. *PR* progesterone receptor, *HPA axis* hypothalamic-pituitary-adrenal axis, *CRH* corticotropin-releasing hormone

Progesterone is a major regulator of uterine quiescence. It provides anti-inflammatory and anti-contractile signals to the myometrium. PR blocks the activation of nuclear factor κβ (NF-κβ), an important initiator of the labour cascade of events, and its downstream inflammatory targets [42, 43]. At the same time, PR upregulates the expression of NF-κβ inhibitor [44]. In the myometrium, activation of PR inhibits the synthesis of connexin 43 (cx43), thus blocking the formation of gap junctions that are responsible for uterine contractions [45]. In addition, by upregulating zinc finger E-box binding homeobox proteins ZEB1 and ZEB2, the PR inhibits the expression of contractile genes, including the oxytocin receptor [46].

In most mammals, the onset of labour is marked by increased inflammatory stimuli in uterine tissues accompanied by a progressive decrease in circulating progesterone concentrations. In human pregnancy, however, serum concentrations of progesterone remain stable throughout gestation. It is thought that labour onset is secondary to a "functional withdrawal" of progesterone, triggered by a change in the relative expression and function of progesterone receptor isoforms [47]. There is substantive evidence to suggest that PR-B is the principal driver of uterine quiescence, whereas PR-A, when not bound to progesterone, has the ability to act as an endogenous repressor of PR-B [48]. A recent study in genetically modified mice has confirmed the distinct roles of PR-A and PR-B in

myometrial contractility. Mice that overexpressed the PR-B isoform had an increased length of gestation and poor uterine contractions. Mice overexpressing the PR-A isoform, on the other hand, showed increased uterine contractility. Downstream target genes of both isoforms were also analysed, confirming a stronger anti-contractile role of PR-B [49].

Studies in human myometrium have shown a marked increase in PR-A expression close to term, increasing the PR-A to PR-B ratio [50, 51]. In addition, in the period leading up to labour onset, a change in progesterone metabolism within the myometrium takes place. The expression of the enzyme 20α-hydroxysteroid dehydrogenase (20α-HSD), that converts progesterone into an inactive metabolite, markedly increases, decreasing the ability of progesterone to bind to PR-A [52, 53]. The unliganded PR-A, in addition to repressing PR-B, acts as a transcriptional activator of cx43 [48, 54]. The anti-inflammatory properties of PR-B are then overcome, and unrestrained tissue inflammation perpetuates labour signals [55]. In particular, an increase in IL-1β within the uterus increases NF-κβ activity, whilst at the same time repressing PR-B activity and further perpetuating the cycle of myometrial activation [56].

1.3 Nuclear Receptors and Gestational Disorders

1.3.1 Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) is defined by the presence of glucose intolerance that develops, or is first recognised, in pregnancy [57]. The global prevalence of GDM is on the rise, with an estimated 16% of pregnancies affected by some form of hyperglycaemia [58]. This increase is thought to be linked to the equally rising prevalence of obesity amongst reproductive age women, and increase in maternal age [58, 59]. Pregnancies affected by GDM have an increased risk of poor outcomes, with the most prevalent complication being fetal macrosomia and its related birth injuries [57]. Fetal death, preterm birth and neonatal unit admission are also recognised outcomes [60]. Mothers affected by GDM are also more likely to develop pre-eclampsia, adding to the existing maternal and fetal morbidity [60]. The implications of GDM for future health are a much wider public health issue; affected women have an approximately 26% increased risk of developing type 2 diabetes mellitus 15 years after their GDM diagnosis, and are at higher risk of developing cardiovascular disease in later life [61, 62]. Meanwhile, children exposed to GDM in the intrauterine environment can have suboptimal neurodevelopmental outcomes and also increased risk of developing metabolic disease later in life [59, 63, 64].

Oestrogen can influence glucose homeostasis [65], and oestrogen receptors have been investigated in the pathophysiology of diabetes mellitus. An association between the rs1256031 polymorphism in the oestrogen receptor β (Erβ) gene and the development of type 2 diabetes mellitus has been found in a Mexican study [66]. A similar study in a Chinese population did not confirm this association in GDM-affected women [67]. GDM development has, however, been associated with the PVuII single nucleotide polymorphisms in oestrogen receptor α (Erα) [68].

Outside of pregnancy, the development of insulin resistance and diabetes is closely related to disorders in lipid metabolism. Abnormal serum and tissue concentrations of lipids can be both cause and consequence of impaired glucose homeostasis [69–71]. Nuclear receptors involved in lipid regulation have thus been investigated in the context of type 2 diabetes mellitus. LXR agonists have been shown to influence glucose metabolism both *in vitro* and in mice, and are thought to be potent serum glucose-lowering agents [72–74]. However, a concomitant rise in serum triglyceride concentrations with the use of these agents has so far hindered their development as anti-diabetic drugs [74]. The contribution of LXR to GDM pathogenesis and its role in treatment of GDM have not been explored to the same extent. An analysis of gene expression in the adipose tissue of women affected by GDM showed an overall reduced expression of LXR and evidence of abnormal adipose tissue metabo-

lism [75]. Although it is plausible that these changes might contribute to the development of GDM, substantive data are lacking.

Farnesoid X receptors (FXR) are also seen as promising targets for the treatment of glucose disorders [74]. Whilst LXR acts primarily as a cholesterol sensor, FXR is a sensor of the end products of cholesterol metabolism – bile acids (BA). When serum BA concentrations are raised, FXR inhibits further BA synthesis, whilst at the same time promoting BA excretion from the hepatocyte to the biliary system (Fig. 1.5). This is an important step in cholesterol metabolism, as it is excreted in the bile in the form of BAs. Therefore, FXR is also implicated in the control of lipid metabolism (Fig. 1.3b). In addition to modulating cholesterol concentrations, it induces the expression of LPL and downregulates SREBP-1c, generating an overall effect of lowering serum triglyceride concentrations. There also seems to be an impact of FXR on glucose metabolism both directly, via repression of gluconeogenic genes, and indirectly by controlling serum concentrations of TG and free fatty acids (FFAs). Indeed, FXR-null mice show a dyslipidaemic and hyperglycaemic profile with hypertriglyceridemia, high concentrations of circulating FFAs, impaired glucose tolerance and decreased insulin sensitivity [76]. A study in pregnant FXR-null mice also demonstrated new onset of impaired glucose tolerance and insulin resistance in comparison to controls [77]. A randomised controlled trial investigating the effects of the natural FXR agonist obeticholic acid (OCA) showed that it increases insulin sensitivity and improves liver inflammation in adults affected by type 2 diabe-

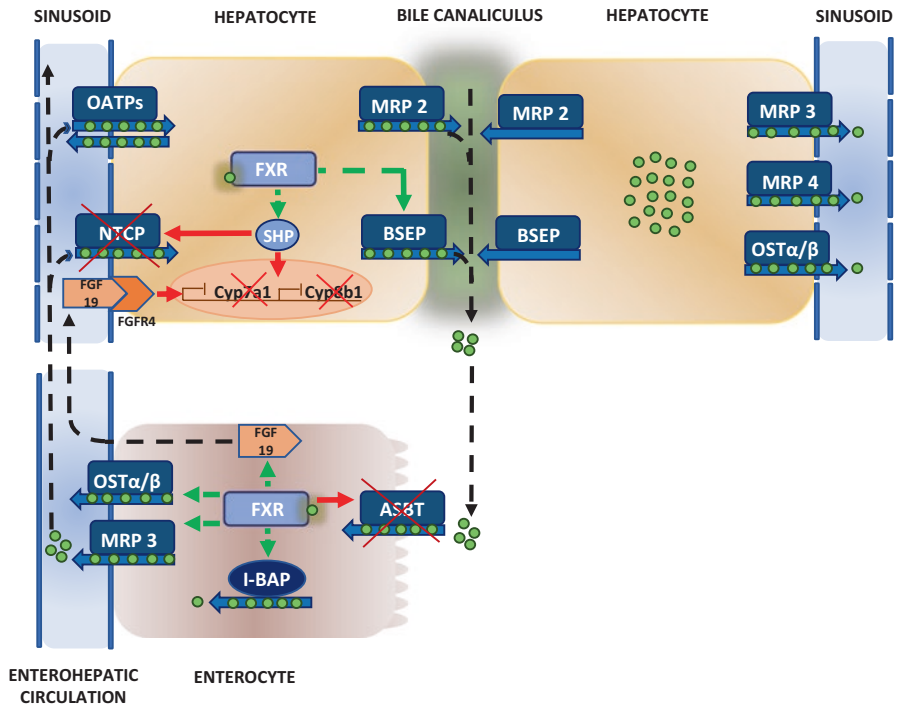

Fig. 1.5 Summary of the main BA transporters in the enterohepatic circulation and FXR effects in the hepatocyte and enterocyte. The hepatocyte on the left represents the effects of FXR activation by bile acids (circles). Dashed green arrows represent transcriptional activation and solid red arrows transcriptional repression. The hepatocyte on the right represents additional bile acid transporters upregulated in the event of cholestasis. Once bile acids reach the intestinal lumen they activate FXR in the enterocyte. FXR then induces the synthesis of FGF19, which reaches the hepatocyte to further repress Cyp7a1 and Cyp8b1 after binding to its receptor, FGFR4. *FXR* Farnesoid X Receptor, *SHP* small heterodimer partner

tes mellitus and non-alcoholic liver disease [78]. Based on these findings, the effects of OCA were also studied in a mouse model of diet-induced GDM [79]. Although a reduction in serum cholesterol concentrations was observed, no changes in glucose tolerance occurred.

1.3.2 Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a gestational liver disorder that presents with maternal pruritus and increased serum BAs. Its prevalence varies in different ethnicities and around the globe, ranging between 0.2% and 5.6% of pregnancies [80, 81]. Although maternal symptoms tend to resolve soon after delivery, ICP is associated with adverse pregnancy outcomes, which are directly related to serum BA concentrations. Preterm birth and neonatal unit admissions are more likely to occur when serum BAs are above 40 μmolL, whilst the stillbirth rate increases with BAs above 100 μmol/L [82, 83].

ICP has a multifactorial aetiology, with environmental and genetic components [84–87], but FXR and its target genes are a central aspect of the pathophysiology of the disease. FXR is a master controller of the enterohepatic circulation, a process that regulates synthesis and excretion of BAs in the hepatocyte, and their subsequent recycling through the bowel [88] (Fig. 1.5). Its natural ligands consist of both conjugated and unconjugated BAs [89, 90]. When high serum concentrations of BAs are detected, FXR suppresses the enzyme CYP7A1, the rate-limiting step in the synthesis of BAs from cholesterol, whilst at the same time inducing the expression of the transporter BSEP thus downregulating NTCP [89, 91–94]. The overall effect is a reduction in BA synthesis, increase in BA excretion into bile and reduction in BA uptake in the hepatocyte.

There is evidence to suggest that FXR function is blunted in normal murine pregnancy. In fact, both mouse and human pregnancy show increased serum BA concentrations when compared with non-pregnant controls [95]. Microarray followed by Ingenuity Pathway Analysis (IPA) have been performed in FXR-knockout and pregnant mice, showing that the attenuated response to rising BAs is similar in both groups i.e. reduced induction of FXR downstream targets *Shp*, *Bsep*, *Mrp3* and *Mdr1a* [95]. This effect is thought to be mediated by rising concentrations of maternal hormones, as a direct interaction between ERα, sulfated progesterone metabolites and FXR has been reported [86, 95–98]. The exact purpose of this physiological change in FXR function during pregnancy is unknown, but it might play a role in regulating some of the maternal metabolic changes.

In ICP, it is thought that the altered hormonal environment as a consequence of pregnancy unmasks the disease in genetically predisposed women. Sulfated progesterone metabolites are markedly increased in the serum of women affected by ICP when compared to controls [98], and this is thought to interfere with FXR function. Women with ICP also present with dyslipidaemia and are at increased risk of developing GDM [99–101]. Both changes are consistent with findings in FXR knockout mice, confirming the finding of an attenuated FXR response in the condition [76].

The goals of ICP treatment are maternal symptom control and reduction of fetal risks. Ursodeoxycholic acid (UDCA) is commonly prescribed to treat the disease. UDCA is a naturally occurring, relatively hydrophilic BA that makes up approximately 3% of the human BA pool [102]. Its effects occur by transformation of the BA pool into a less hydrophobic, hence less cytotoxic one, and by regulation of hepatic BA transporters both at a transcriptional and protein level [103]. A large 2019 randomised placebo-controlled trial showed that UDCA has some effect on maternal pruritus but in this study it was not effective in reducing adverse perinatal outcomes [104]. However, a more recent individual participant data meta-analysis that included data from a considerably higher number of ICP cases with serum BA concentrations ≥40 μmol/L than in the randomised placebo-controlled trial, showed that UDCA treatment reduces rates of stillbirth and preterm birth when maternal serum

BA concentrations are elevated above this threshold [105].

Similar to GDM, ICP is associated with long-term metabolic consequences for the fetus. A cohort study in affected babies showed that they were likely to develop features of the metabolic syndrome in adolescence. These findings were replicated in a mouse model of gestational cholestasis, and the mechanisms behind these changes are thought to be a disruption of lipid homeostasis in the fetoplacental unit [106]. In mice, UDCA treatment during pregnancy was able to reverse some of these features in the offspring [107].

1.3.3 Pre-eclampsia

Pre-eclampsia is a multisystem disorder of pregnancy characterised by raised maternal blood pressure after 20 weeks of gestation and endothelial dysfunction, and it can result in multiorgan dysfunction [108]. It is one of the leading causes of maternal and fetal morbidity and mortality in low- and middle-income countries [109], causing approximately 14% of maternal deaths worldwide [110].

The placenta seems to be central in the pathophysiology of the disease. Placental dysfunction results in recurrent ischemia-reperfusion injury in the placental bed, triggering an angiogenic imbalance in the mother [111]. The origin of this placental dysfunction is a subject of debate: although conventionally it is thought to be the result of insufficient invasion of spiral arteries by the EVT, new lines of evidence propose that abnormal placental perfusion is secondary to underlying abnormalities in maternal cardiac function that preclude an adequate maternal cardiovascular adaptation to pregnancy [112]. Definitive treatment of pre-eclampsia consists of delivery of the fetus and the placenta; however, this causes a dilemma for clinicians and women when a fetus is preterm. The recommended practice is strict control of maternal blood pressure and planned delivery from 37 weeks of gestation, with the decision to deliver severe cases prior to this taken on a case by case basis [113–115].

Given the influence of PPARγ on trophoblast differentiation and development, there is an increasing interest in its role in the pathogenesis and treatment of pre-eclampsia. The expression of PPARγ in placentas of women affected by pre-eclampsia has been investigated, but no differences have been found in comparison to controls [116, 117]. No associations between polymorphisms of the PPARγ receptor gene and the development or severity of pre-eclampsia have been found either [118]. Administration of PPARγ antagonists in mice induces a phenotype of raised blood pressure, reduced pup weight and endothelial dysfunction, similar to a pre-eclamptic phenotype [119]. In addition, the balance between pro- and anti-angiogenic factors in maternal serum is disrupted in a way similar to the disease in humans, and the studied mice show evidence of impaired trophoblast differentiation. Administration of the PPARγ agonist rosiglitazone reverses the majority of these changes [120, 121]. One study has shown that women who develop pre-eclampsia have decreased serum concentrations of PPARγ activators, which are normally increased in unaffected pregnancies. These findings are present before the onset of disease [122].

LXRs have also been investigated in the context of pre-eclampsia. Their roles in trophoblast development and regulation of placental cholesterol metabolism have been postulated as contributing factors to its pathogenesis [123]. LXRα mRNA expression and LXRβ protein levels have been investigated in placentas from women affected by pre-eclampsia, with variable results [124, 125]. One study showed that expression of both LXRα and its target endoglin, a regulator of trophoblast invasiveness and endothelial function previously implicated in the pathogenesis of pre-eclampsia, were both increased in placentas from affected women [125].

1.3.4 Spontaneous Preterm Labour

Preterm labour (PTL) is defined as the onset of regular uterine contractions and cervical dilatation prior to 37 weeks of pregnancy. An estimated

15 million babies are born premature every year, and the complications of an early birth are the leading cause of mortality in children under 5 years of age [126, 127]. Considering that inflammation is central to the onset of labour, conditions that cause an increase in the inflammatory load of uterine tissues are potential triggers of early labour. Recognised causes are maternal or fetal infection, early activation of the fetal hypothalamic-pituitary-adrenal axis, chorion-decidual haemorrhage, over-distention of the myometrium (e.g. multifetal gestation), changes in the vaginal microbiome and maternal stress [128–130]. However, a significant number of cases of preterm labour do not have an identifiable cause.

So far, no effective treatment for PTL has been found. Pharmacological strategies consist of a reactive approach that aims to delay the onset of parturition for a few days, with the aim of allowing time for fetal lung maturation with exogenous corticosteroids. Progesterone supplementation has been extensively studied as a preventative strategy. The rationale for this approach remains questionable, as it is an established fact that the onset of human labour is not secondary to decreasing progesterone concentrations. Nevertheless, positive results have been found in women at high risk of PTL, such as those with a previous history of PTL, evidence of a short cervix or multifetal pregnancies. The most recent individual participant meta-analysis evaluating randomised clinical trials in this subject has shown that the administration of vaginal progesterone and intramuscular 17-hydroxyprogesterone caproate (17-OHPC) are successful in preventing birth before 34 weeks in high risk singleton pregnancies [131]. This effect seems to be stronger in women with a reduced cervical length.

The challenges in developing strategies for the prevention of preterm birth stem from the fact that it has multiple causative factors, with likely distinct molecular mechanisms. In addition, the background risk of different populations varies, hindering the assessment of interventions. The mechanisms through which progesterone supplementation can prevent PTL are still not fully understood. A study of progesterone supplementation in mice showed no changes in the expression of molecules related to uterine contractility, cervical remodelling or local inflammation [132]. A different study showed that vaginal progesterone, in contrast to intramuscular 17-OHPC, has an influence on the myometrial immune profile and molecules related to cervical ripening [133]. It is also possible that different preparations of progestogens exert distinct effects on PRs and labour mechanisms, or can evade the myometrial changes in progesterone metabolism in different ways [134]. Understanding these mechanisms would allow us to optimise the use of progesterone for prevention of PTL.

1.4 Conclusions

Nuclear receptors are remarkable integrators of hormonal, nutritional and transcriptional pathways that are increasingly recognised as important orchestrators of pregnancy adaptations. They are an essential part of early events of pregnancy, maternal metabolic adaptations and parturition. So far, the prospect of treating gestational disorders with modulators of nuclear receptors has been mainly considered with reference to treatment strategies applied to non-gestational pathologies. A better understanding of the role of nuclear receptors in normal gestation and its specific disorders is necessary to enable consideration of potential new therapeutic strategies.

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