

# ROLE OF NUCLEAR RECEPTORS IN SPONTANEOUS AND RECURRENT MISCARRIAGE

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## ABSTRACT

Although early pregnancy loss is a common complication of human reproduction, a significant proportion of miscarriages still happen for unknown reasons. Nuclear receptors are key players in trophoblast invasion and metabolism; therefore, their agonists and ligands are a promising target for the prevention of miscarriage. This review gives an overview of the existing data and literature concerning the involvement of nuclear receptors in maintaining a viable pregnancy.

**Keywords:** Miscarriage, recurrent miscarriage, nuclear receptor, peroxisome proliferator-activated receptor (PPAR), retinoid X receptor (RXR), liver X receptor (LXR), thyroid hormone receptor (THR).

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## INTRODUCTION

Spontaneous miscarriage occurs in 12-15% of known pregnancies, whereas 30% of all conceptions are lost between implantation and the sixth week. The risk of subsequent miscarriage increases with maternal age and with the number of previous miscarriages.<sup>1</sup> Recurrent miscarriage (RM) is defined as three or more consecutive miscarriages. The risk of recurrent spontaneous miscarriage is much higher in patients with previous losses: the risk of miscarriage after two consecutive losses is 17-25% and the risk of miscarrying a fourth pregnancy after three consecutive losses is 25-46%. Yet there remains an unsolved problem: up to 50% of cases of recurrent losses do not have a clearly defined aetiology.<sup>2</sup>

## ROLE OF ESTABLISHED UNDERLYING CAUSES

Chromosomal abnormalities linked to maternal age are common risk factors for miscarriage.<sup>3</sup> Approximately 50-60% of early spontaneous miscarriages are associated with a chromosomal anomaly of the conceptus. The most common abnormality is aneuploidy, with autosomal trisomy

accounting for >50% of chromosomally abnormal abortuses.<sup>4</sup> In the case of RM, multiple underlying causes have been identified besides karyotype changes: uterine pathologies such as uterus arcuatus, which is a uterus with a fundal impression and which accounts for 15% of all women with RM;<sup>5</sup> endocrine dysfunctions, e.g. thyroid disorders; and autoimmune diseases, e.g. acquired or inherited thrombophilic disorders.<sup>6</sup> Investigations have shown that some RM patients remain in a permanent prothrombotic state outside pregnancy.<sup>7</sup>

Apart from the reasons mentioned above, the cause of RM remains unknown in up to 50% of cases.<sup>8</sup> Therefore, identification of possible risk factors is a focus of current research. This article summarises evidence for the known implications of nuclear receptors in spontaneous miscarriage and in RM. For readers with further interest in the physiological roles of nuclear receptors in pregnancy, we recommend the following reviews: McCarthy et al., 2013 (role of peroxisome proliferator-activated receptor [PPAR]);<sup>9</sup> Beltowski and Semczuk, 2010 (role of liver X receptor [LXR]);<sup>10</sup> and Mark et al., 2009 (role of retinoid X receptor [RXR]).<sup>11</sup>

## ROLE OF NUCLEAR RECEPTORS IN RECURRENT MISCARRIAGE

The large ligand-activated nuclear receptor superfamily includes PPAR, the retinoic acid receptors (RARs), RXR, the thyroid hormone receptors (THR), LXR, the vitamin D3 receptors, and the steroid receptors. These receptors all function as transcription factors and, after ligand activation, they bind DNA as homo or heterodimers and regulate gene expression.<sup>12</sup> A recent investigation showed that some of these receptors are crucially involved in the process of spontaneous and recurrent miscarriage.

## ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTORS IN MISCARRIAGE

This group of nuclear receptors is named for their ability to induce hepatic peroxisome proliferation in mice. Three PPAR isoforms ( $\alpha$ ,  $\beta/\delta$ , and  $\gamma$ ) have been identified to date and are encoded by different genes. PPARs are a key regulator of cell differentiation, the cell cycle, and the induction of apoptosis.<sup>13,14</sup> PPAR $\gamma$  is the isoform with the greatest influence on metabolism and is a strong regulator of the immune system and a key player in carcinogenesis. PPAR $\gamma$  binds to a specific DNA response element as a heterodimer with the RXR.<sup>14</sup>

PPAR $\gamma$  is of great interest in the field of miscarriage research for many reasons, such as its role in the regulation of fatty acid storage, glucose metabolism, and insulin sensitivity. In addition, PPAR $\gamma$  is involved in trophoblast differentiation and invasion,<sup>15</sup> as well as being a key player in anti-inflammatory processes,<sup>16</sup> and so this receptor can make an impact on the process of miscarriage in multiple ways. PPAR $\gamma$  disposes of a wide range of natural and synthetic ligands, such as 15-deoxy- $\Delta^{12,14}$ -prostaglandin J<sub>2</sub>, fatty acids including oxidised lipids, monounsaturated fatty acids such as oleic acid, and polyunsaturated fatty acids like linoleic acid and arachidonic acid.<sup>17-19</sup> In addition to their importance in miscarriage research, the clinical relevance of these receptors can be seen by the fact that synthetic PPAR $\gamma$  agonists, such as thiazolidinediones (TZDs), are already in widespread use in diabetes therapy in order to improve insulin sensitivity.<sup>12</sup>

PPAR is not only a key player in metabolism, however, as studies on PPAR-null mutant

mice revealed the central role of PPAR in fetal development and placentation. PPAR enhances the invasion of the placental trophoblast and therefore plays a major role in maintaining a viable pregnancy.<sup>15-20</sup> In a human *in vitro* model, cytotrophoblast invasion was abrogated in a dose-dependent manner by PPAR $\gamma$  stimulation, with its blockade leading to increased extravillous trophoblast (EVT) invasion.<sup>21,22</sup> Furthermore, PPAR $\gamma$  stimulation altered the differentiation of syncytiotrophoblast (ST),<sup>20</sup> and PPAR $\gamma$  ligands induced human chorionic gonadotropin (hCG) production in human trophoblasts.<sup>23</sup>

Further studies in miscarriage research have revealed that PPAR activation is connected with leptin: PPAR and leptin are two important adipose tissue factors involved in the regulation of energy metabolism.<sup>24</sup> Leptin is a regulator of satiety and energy homeostasis. It is synthesised in adipose tissue and also in the placenta, especially in the ST and EVT.<sup>25</sup> Proinflammatory cytokines, such as tumour necrosis factor alpha (TNF $\alpha$ ) and interleukin 1 (IL-1), may also directly induce leptin gene expression. Toth et al.<sup>26</sup> demonstrated that in normal and disturbed pregnancy there seems to be regulation of leptin triggered by nuclear hormone receptors such as PPARs and their coactivators. Enhanced expression of PPAR/RXR was identified in EVTs and STs of miscarriage. Leptin expression in the ST was lowest in miscarriages and highest in mole pregnancies.

Leptin induces hCG production in trophoblast cells.<sup>27</sup> Leptin production is upregulated during normal pregnancy, and leptin gene expression is regulated by a variety of hormones including oestrogen, which is responsible for the upregulation during pregnancy. Decreased leptin levels are associated with miscarriage.<sup>28</sup> The leptin-mediated secretion of proinflammatory cytokines such as IL-1, IL-6, TNF $\alpha$ , and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is inhibited through PPAR activation.<sup>29,30</sup> With regard to the dynamic interaction between PPAR $\gamma$  and leptin, there may be a potential strategy for intervening in the process of miscarriage: activation of PPAR $\gamma$  by natural ligands or TZDs inhibits leptin gene expression and leptin release both *in vivo* and *in vitro*.<sup>31,32</sup> PPAR $\gamma$  agonists positively regulate hCG, leptin, and human placental lactogen.<sup>20</sup> If these mechanisms are of any benefit in the prevention of miscarriage then they should be evaluated in future studies.

## ROLE OF RETINOID X RECEPTOR IN MISCARRIAGE

The RXR consists of three isotypes that are referred to as RXR $\alpha$ , RXR $\beta\delta$ , and RXR $\gamma$ .<sup>33</sup> All three RXR isotypes are potentially important in maintaining a viable pregnancy, as they are all involved in cell proliferation, cell differentiation, embryonic patterning, and organogenesis,<sup>34</sup> but it is especially RXR $\alpha$  that is a key regulator during embryogenesis and morphogenesis.<sup>35</sup> The heterodimer of PPAR $\gamma$  and RXR $\alpha$  regulates the uptake of fatty acids in trophoblasts, which is essential for embryonic development and production of placental steroid hormones.<sup>16,36</sup> Furthermore, both partners promote trophoblast differentiation, possibly because they induce the secretion of important hormones such as hCG, leptin, and lactogen.<sup>20</sup> Homozygous RXR $\alpha$ -null mice die between embryonic days (E)13.5 and E16.5,<sup>37,38</sup> which highlights the role of RXR $\alpha$  during embryonic development.

Potentially, RXR $\alpha$  represents a potent target in the treatment of RM: invasion of cytotrophoblasts is indirectly correlated with the concentration of RXR $\alpha$  and PPAR $\gamma$ .<sup>16</sup> Enhanced expression of RXR $\alpha$  in EVT $s$  and villous trophoblasts of miscarried placentas was recently identified, and an increased number of apoptotic EVT is present in miscarried placentas.<sup>35</sup> RXR and its heterodimeric partner RAR can be activated by vitamin A derivatives termed 'retinoids'.<sup>39</sup> A likely conclusion is that RXR $\alpha$  plays an important role in the induction of apoptosis. Downregulation of RXR $\alpha$ , as observed in choriocarcinoma cells and trophoblasts, may serve as a protection against apoptosis and miscarriage.<sup>35</sup> In addition, increased retinoic acid, which is the main agonist of RXR, has an inhibitory effect on genes essential for implantation in the glandular epithelium (GE).<sup>40</sup> These results are in line with our findings of RXR upregulation in GE of miscarriage: the nuclear receptors PPAR $\gamma$  and RXR $\alpha$  are negatively correlated in the decidual tissue cells of physiological pregnancy, whereas this correlation is lost in miscarriage. Because expression of PPAR $\gamma$  is unchanged in abortive tissue compared with normal controls, we assume that upregulation of RXR $\alpha$  in abortive tissue is responsible for the loss of negatively correlated PPAR $\gamma$ /RXR $\alpha$  expression.

Combination of PPAR $\gamma$  with RXR $\alpha$  is essential for trophoblast differentiation, with the receptor complex inducing the secretion of gestational

hormones such as hCG, leptin, and lactogen.<sup>20,41</sup> The heterodimer further regulates the uptake of fatty acids in trophoblasts, which is crucial for the production of placental steroid hormones and fetal growth.<sup>16,36</sup> Because invasion of cytotrophoblasts is indirectly correlated with the concentration of RXR $\alpha$  and PPAR $\gamma$ ,<sup>16</sup> and the latter plays a specific role in trophoblast differentiation, function,<sup>15,42</sup> and fetal development,<sup>18</sup> the replacement by RXR $\alpha$  is likely to disturb physiological development during pregnancy. Furthermore, the isotype of RXR $\alpha$  plays an essential role during embryogenesis and morphogenesis,<sup>43</sup> and protects against apoptosis in trophoblasts, and so the enhanced expression of RXR $\alpha$  in miscarriage is twice as disruptive in early pregnancy. Expression of RXR $\alpha$  is increased in GE and trophoblasts during miscarriage and correlation analysis shows that increased LXR and RXR expression takes place during miscarriage, whereas LXR and PPAR $\gamma$  are upregulated simultaneously in regular GE. The loss of physiological correlation in nuclear receptors is supposedly responsible for the deficit in the regular function of trophoblasts and embryonic tissue.

## ROLE OF LIVER X RECEPTOR IN MISCARRIAGE

LXR is a physiological regulator of lipid and cholesterol metabolism that also acts in an anti-inflammatory capacity. Because LXRs control diverse pathways in development, reproduction, metabolism, and inflammation, they have potential as therapeutic targets.<sup>44</sup> LXRs are expressed in human and mouse trophoblasts and the placenta from early gestation,<sup>45</sup> and are regulators of trophoblast invasion<sup>46</sup> and maternal-fetal cholesterol transport,<sup>10,47</sup> which makes them key players for successful placentation and embryonic development.<sup>48</sup>

LXR expression is downregulated in the ST of the placenta of a spontaneous abortion. However, the difference is greatest in the decidua of miscarriage; in the decidua of RMs there is no expression of LXR at all. Therefore, the downregulation of LXR could be a signal of excessive oxidative stress in the ST of spontaneous abortions. In RM, however, there is a strong immune modulation component and additional mechanisms, which, together with oxidative stress, can cause abortion.<sup>49</sup> Strong downregulation of LXR in the EVT and no significantly altered

expression in the ST occurs in RM. Therefore, pregnancy loss occurs in RM before oxidative damage reaches the ST layer of the placenta.

In addition, double-immunofluorescence staining showed that LXR, as well as RXR $\alpha$  and PPAR $\gamma$ , is expressed by the EVT, and RXR $\alpha$  and LXR showed co-expression in the same EVT cells. In the ST, a positive correlation for the combination of LXR/PPAR $\gamma$  occurs in abortions and there is a negative correlation for LXR/RXR $\alpha$ .<sup>48</sup> LXR activation with synthetic or natural ligands inhibits trophoblast invasion *in vitro*,<sup>42</sup> therefore correlation of LXR and RXR $\alpha$  might be a sign of increased maternal-fetal cholesterol transport. Plösch et al.<sup>47</sup> showed that LXR upregulation leads to increased expression of the LXR target genes *ABCG1* and *ABCA1*. This mechanism is believed to increase the cholesterol flux from mother to fetus.<sup>47</sup> This may be indicative of pronounced demand during embryogenesis, as cholesterol is crucially involved in neural pattern formation via hedgehog proteins and in brain development.<sup>50-52</sup>

The GE of the uterus and the EVT form the decidua. The GE is known to be crucial for blastocyst implantation and decidualisation in pregnancy,<sup>53</sup> and it further provides a nutrient-rich environment to support embryonic development until the placenta is functional.<sup>54</sup> Expression of PPAR $\gamma$  and LXR is unchanged in the GE of miscarriage: expression changes in these receptors are restricted to trophoblasts. In the GE of physiological pregnancy, a positive correlation between LXR and PPAR $\gamma$  was demonstrated (Knabl et al., unpublished data): here we can speculate that LXR and PPAR $\gamma$  are upregulated simultaneously in regular GE. As this correlation was not found in abortive tissue, increased LXR and RXR expression can be seen in miscarriage. Proper function of the GE plays a key role in implantation of the conceptus and decidualisation of the uterine stroma.<sup>53,55</sup> As increased LXR signalling reduces synthesis and secretion of hCG from trophoblast cells,<sup>56</sup> and decreases trophoblast invasiveness by matrix metalloproteinase 9,<sup>57</sup> these effects may be a consequence of a disturbed function in GE.

## ROLE OF THYROID HORMONE RECEPTORS IN MISCARRIAGE

Thyroid hormones are essential for the maintenance of pregnancy, and a deficiency of maternal thyroid hormones has been associated with early pregnancy loss.<sup>58</sup> The ligands of THR play a

major role in trophoblast differentiation and fetal neurodevelopment.<sup>59</sup> Thyroid hormones bind to specific nuclear receptors. Two genes, *THRA* (*NR1A1*) and *THRB* (*NR1A2*), encode the isoforms THR $\alpha$  and THR $\beta$  which code for the four ligand-binding thyroid receptors THR $\alpha$ 1, THR $\beta$ 1, THR $\beta$ 2, and THR $\beta$ 3, and the four non-ligand binding receptors.<sup>60,61</sup> While the isoforms THR $\alpha$ 1, THR $\alpha$ 2, and THR $\beta$ 3 are widely expressed, the expression of THR $\beta$ 2 is restricted to the hypothalamus and pituitary gland.<sup>62</sup> The hormone T<sub>3</sub> is the high-affinity ligand of THR and thereby regulates gene transcription.<sup>63</sup> After this hormone has bound to the ligand-binding site, the THR switches to its active form and recruits specific co-activators such as SRC1-3 and PGC-1.<sup>64</sup> A two-fold increase in miscarriage and stillbirth rates can result from untreated hypothyroidism.<sup>65</sup> Hyperthyroidism and autoimmunity can also have severe effects on pregnancy outcome. Therefore, the maintenance of a euthyroid state is crucial during pregnancy and necessary for the prevention of disturbed placentation syndromes such as pre-eclampsia and intrauterine growth restriction.<sup>65</sup> Results obtained by our group show that expression of the THRs: THR $\alpha$ 1, THR $\beta$ 2, THR $\beta$ 1, and THR $\beta$ 2 is downregulated in abortive placentas, which also leads to miscarriage. The THRs are predominantly expressed in decidual stromal cells.<sup>66</sup> Only THR $\beta$ 2 is also expressed in EVT cells. PPAR $\gamma$  expression was also investigated by our group and we identified an upregulation of PPAR $\gamma$  in miscarriage.<sup>16,35,66,67</sup> Interestingly, a recent study showed that activation of PPAR $\gamma$  signalling via rosiglitazone induced a strong downregulation of both THR $\alpha$  and THR $\beta$  in both brown adipose tissue and in rats *in vivo*.<sup>68</sup> Based on these results, we may speculate that the downregulation of THRs is also mediated by activated PPAR $\gamma$ , and probably the RXR system, in abortion.

## SUMMARY

Nuclear receptors are key players in maintaining a viable pregnancy and play an important role in spontaneous miscarriage and RMs:

- The expression of the nuclear receptors PPAR $\gamma$ , RXR $\alpha$ , LXR, and THRs is altered in miscarriage: this group of nuclear receptors is important for embryogenesis and trophoblast invasion.
- Enhanced expression of PPAR/RXR was identified in the EVTs and STs of miscarriage. Expression of PPAR $\gamma$  and LXR was unchanged

in the GE of miscarriage: expression changes of these receptors are restricted to trophoblasts.

- RXR $\alpha$  expression is increased in miscarriage in the GE and trophoblasts, and correlation analysis showed that increased LXR and RXR expression takes place in miscarriage, whereas LXR and PPAR $\gamma$  are upregulated simultaneously in regular GE. The loss of physiological correlation in nuclear receptors is supposedly responsible for the deficit in regular function in trophoblast and embryonic tissue.
- LXR expression is downregulated in ST and EVT in spontaneous miscarriage. A strong downregulation of LXR in the EVT and no

significantly altered expression in the ST occurs in RM. Therefore, pregnancy loss occurs in RM before oxidative damage reaches the ST layer of the placenta.

- Expression of the THR: THR $\alpha$ 1, THR $\alpha$ 2, THR $\beta$ 1, and THR $\beta$ 2 is downregulated in abortive placentas, which also leads to miscarriage. The THRs are predominantly expressed in decidual stromal cells.

Future research should focus on the investigation of existing agonists and antagonists in the prevention of miscarriage in order to bring experimental data towards achieving clinical improvement.

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