RXRα is upregulated in first trimester endometrial glands of spontaneous abortions unlike LXR and PPARγ

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Abstract

Nuclear receptors are necessary for uterine invasion of the trophoblast and therefore important for maintaining a viable pregnancy. The aim of this study was to investigate the expression pattern and frequency of LXR, PPARγ and RXRα under physiological circumstances and in spontaneous abortions in endometrial glands and decidual tissue cells. A total of 28 (14 physiologic pregnancies/14 spontaneous abortion) human pregnancies in first trimester were analyzed for expression of the nuclear receptors LXR, RXRα and PPARγ. Expression changes were evaluated by immunohistochemistry in decidual tissue and endometrial glands of the decidua. RXRα expression was up-regulated in the endometrial glands of spontaneous abortion (P<0.015). Similar up regulation of RXRα was found in decidual tissue (P<0.05). LXR and PPARγ expression was unchanged in spontaneous abortion. By Correlation analysis we found a trend to positive correlation of LXR and PPARγ (Spearman correlation coefficient r=0.56, P=0.07) in endometrial glands. In decidual tissue, we found significant negative correlation in the control group, for the combination of RXRα and PPARγ (Spearman correlation coefficient r=0.913, P=0.03). Our data show that RXRα expression is increased in miscarriage in endometrial glands and correlation analysis showed that negative correlation between RXRα and PPARγ disappears in miscarriage. This shift is supposable responsible for the loss of regular function in trophoblast and embryonic tissue.

Introduction

Miscarriage is a common disorder in pregnancy, affecting 25-50% of all reproductive aged women.[1] Immunologic, endocrine and metabolic mechanisms are involved in the success of human pregnancy and disturbances in any of these processes can lead to fetal loss. Established risk factors are chromosomal or endocrine disorders, anatomical malformations or thrombophilia, but in nearly 50% of affected patients, the cause of miscarriage remains unknown.[1]

Nuclear receptors are key player in maintaining pregnancy. The nuclear retinoid X receptor (RXR), which is involved in cell proliferation, cell differentiation, and organogenesis,[2] is upregulated in extravillous trophoblast in recurrent miscarriages in humans.[3] RXR plays a pivotal role in the receptor family, due to its ability to form heterodimers with other nuclear receptors. Heterodimer partners are *e.g.*, peroxisome proliferator-activated receptor (PPAR), thyroid hormone receptor (TR), and liver X receptor (LXR).[4-6] Especially the expression of the isoform PPARγ is linked to trophoblast invasion[7-9] and downregulation of the isoform RXRα seems to protect against apoptosis in human trophoblasts.[3] LXR is a physiological regulator of lipid and cholesterol metabolism and inflammation,[10] of trophoblast invasion and maternal-fetal cholesterol transport.[11,12] These nuclear receptors are crucially involved in maintaining a viable pregnancy, their role had been clarified especially in human trophoblastic tissue: Toth *et al.* showed that extravillous trophoblast (EVT) in placentas of miscarriages show a significantly higher expression of RXRα in comparison to EVT in placentas of elective termination of healthy pregnancies.[13] Recent studies showed that LXR expression is decreased in miscarriage[14] and PPARγ is increased in EVT of abortive tissue.[15]

The endometrial glands (GE) of the uterus and the EVT form the decidua. The GE is known to be crucial for blastocyst implantation and decidualisation in pregnancy in mice,[16] it further provides a nutrient rich environment to support embryonic development until the placenta is functional in humans.[17]

Unfortunately, there is only limited knowledge about the role of nuclear receptors in miscarriage in endometrial glands and other parts of the decidua and therefore the aim of our study was to investigate the expression pattern of crucial nuclear receptors in different decidual parts, especially in the decidual glands, of regular and disturbed pregnancies.

Materials and Methods

Patient data

We analyzed tissue samples from spontaneous abortions (n=14) and legal termination of pregnancy (n=14) at gestational weeks 7 to 12 were analyzed (Table 1). Tissue samples were obtained by dilatation and evacuation without any prior pharmaceutical induction. In cases of spontaneous abortion, surgery was performed within the first 24 h after diagnosis. All women included in the study had a null medical and family history. History taking was systematic. The aim was to exclude, apart from common disorders, possible impact of clotting disorders and autoimmune diseases, already known as aggravating factors for increased risk for miscarriages. Karyotype analysis excluded chromosomal abnormalities in all cases used for the study. In addition, we ruled out *via* microbiology analysis possible intrauterine infection (Bacteria and Chlamydia trachomatis). All women had a regular first trimester vaginal swab.

All patients gave signed informed consent allowing analysis of all clinical and laboratory data mentioned in this paper. The Human Investigation Review Board of the Ludwig-Maximilians-University Munich approved the study (Number of approval: 337-06).

Double-immunofluorescence staining

We undertook double-immunofluorescence staining in order to localize the nuclear receptors LXR, RXRα and to identify LXR and RXRα expressing cells in the same placental site. Double-immunofluorescence staining was performed on placentas of physiologic pregnancies and spontaneous miscarriages, both

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Key words: Spontaneous abortion; nuclear receptors; LXR; RXRα; PPARγ; endometrial glands.

Contributions: AP, RH experiments performing; JK, UJ, study design, manuscript writing; MK, SH, manuscript critical revision for important intellectual content. All authors have read and approved the final manuscript.

Conflict of interest: the authors declare no conflict of interest.

Acknowledgments: The authors wish to thank Christina Kuhn and Simone Hofmann for excellent technical support.

Received for publication: 15 April 2016.
Accepted for publication: 15 September 2016.

European Journal of Histochemistry 2016; 60:2665
doi:10.4081/ejh.2016.2665

groups from the first trimester. Slides were fixed with 5 % formalin in PBS, pH 7.4, for 5 min. Then the slides were blocked with ultra V blocking solution (Lab Vision™, Thermo Fisher Scientific Inc., Waltham, MA, USA) for 15 min. After that, incubation was performed with the primary antibodies anti-LXRα/β rabbit IgG, diluted 1:200 and anti-RXRα mouse IgG (AbD Serotec, Oxford, UK), diluted 1:50, and overnight at 4°C. The secondary antibodies, the Cy-3-labelled goat-anti-rabbit IgG (Dianova GmbH, Hamburg, Germany), diluted 1:500, and the Cy-2-labelled goat-anti-mouse IgG antibody, diluted 1:100, were applied on the slides. Finally, the slides were embedded in DAPI containing mounting buffer (Vector Laboratories, Burlingame, CA, USA). For identification of LXR/RXRα expressing cells, each section was additionally incubated with HLA-G mouse IgG1 (clone MEM-6/9) (AbD Serotec) which was diluted 1:50. For all slides, incubation took place for 1h. Sections were then incubated with the secondary antibodies. Afterwards, the slides were analyzed with a fluorescent Axioskop photomicroscope (Zeiss, Oberkochen, Germany). We took photos with a digital Axiocam camera system (Zeiss).

Immunohistochemistry

Placental tissue was fixed with 5% formalin in PBS, pH 7.4, for 24 h. Afterwards, the samples were embedded in paraffin wax. Next, the tissue slides were put in xylol for 20 min and then incubated in methanol/H_2O_2 for 20 min. Rehydration of the slides was performed using an alcohol gradient to distilled water. The slides were placed in a pressure cooker which contained sodium citrate (pH=6.0), afterwards we washed the slides in PBS. As blocking solution, slides were incubated with power block (BioGenex, Fremont, CA, USA) for 3 min which was diluted 1:10 in distilled water.

The slides were incubated with each primary antibody. The primary antibodies were anti-LXR rabbit IgG polyclonal antibody, which detects both isoforms LXRα and LXRβ (Lifespan Biosciences, Seattle, USA), anti-human RXRα mouse monoclonal IgG2a antibody (1 mg/mL) (clone No. K8508; PPMX, Perseus Proteomics) and anti-PPARγ rabbit polyclonal antibody (Abcam, Cambridge, UK). Anti-LXR (1 mg/mL), diluted 1:200 in power block, which was previously diluted in 1:100 in PBS. Anti-RXRα (1 mg/mL), diluted 1:200 in PBS and anti-PPARγ (0.2 mg/mL), diluted 1:1000 in Dako diluting medium (Dako

Table 1. Clinical characteristics of the study population.

Characteristic*	Normal pregnancy (n=14)	Spontaneous abortion (n=14)	P value°
Maternal age	33.0±6.7 (22-41)	31.5±8.8 (19-43)	0.25
Gestational age	9.0±2.0 (7-12)	9.84±1.4 (7-12)	0.95
Gravidity	3.1±2.0 (1-7)	2.2±2.6 (1-9)	0.61
Parity	1.2±1.2 (0-4)	1.2±2.6 (0-8)	0.36

*Mean, standard deviation, range; °Mann-Whitney-U test

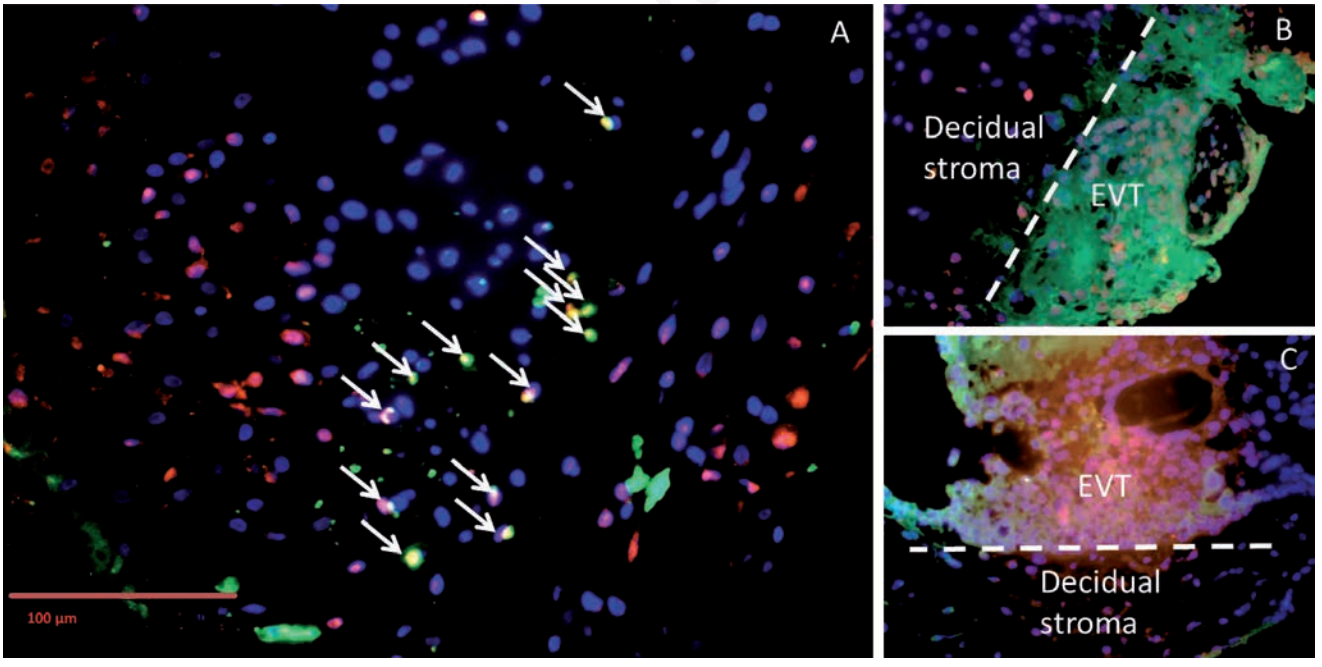

Figure 1. A) Analysis of LXR and RXRα co-expression in decidua; LXR expression is shown in red, RXRα expression is visualized in green, synchronized expression of both nuclear receptors is shown (yellow, marked by arrows); in addition, to cells showing co-expression, we also found singular expression of LXR (red) and RXRα (green); some nuclei are negative for both receptors (blue); the identification of cell type positive for either LXR or RXRα in the decidua was achieved with HLA-G double staining; HLA-G is a marker exclusively expressed by extravillous trophoblast cells (EVT). B), HLA-G expression in green and LXR expression in red are shown; the border between decidual stroma cells and the EVT is shown as a discontinuous line; both decidual stroma cells and EVT express LXR. C) HLA-G expression in green and RXRα expression in red are shown; the border between decidual stroma cells and the EVT is shown as a discontinuous line; both decidual stroma cells and EVT express RXRα.

Scientific, Glostrup, Denmark). Incubation of the sections with the primary antibodies lasted for 16 h at 4°C. The Vectastain Elite Rabbit/Mouse IgG ABC-Kit (Vector Laboratories) was used for visualization. The sections were stained with DAB and counter-stained with hemalaun. At the end, sections were dehydrated and cover-slipped with Shandon Consul Mount Medium (Thermo Fisher Scientific). Examination of the slides was performed by two independent observers (RH and AV) using a Leitz Diaplan microscope (Leitz, Wetzlar, Germany). Per slide, ten fields were analyzed with the semiquantitative immunoreactive score (IRS). The IRS score examines the intensity and distribution of antigen expression: It is calculated by multiplying the percentage of positively stained cells (0, no staining, <10% of the cells; 2, 11-50%; 3, 51-80%, 4, >80%) with the cells staining intensity (0, none; 1, weak; 2, moderate; 3, strong).

As positive controls we used breast cancer tissue for PPARγ and RXRα detection and colon tissue for detection of LXR. Negative controls were conducted by replacement of anti-LXR antibody, anti-RXRα antibody or anti-PPARγ antibody and alternative incubation of the slides with mouse respectively rabbit IgG control antibodies (Dako).

Statistics

Data collection and processing as well as analysis of statistical data were performed with SPSS/PC software package, ver. 20 (SPSS GmbH, Munich, Germany). The Mann-Whitney-U test for evaluation of two independent groups. This test is a one-way analysis of variance and analyses two parameters that are independent from each other. Correlation analysis was performed with the non-parametric Spearman's rank correlation coefficient, which analyses the statistical dependence between two monotonic, non-linear variables. Values with $P<0.05$ were considered statistically significant.

Results

Double-immuno-fluorescence staining

In this study, decidual tissue in placentas from miscarriages expressed LXR, stained in red and cells expressing RXRα stained in green. Cells expressing neither LXR nor RXRα stained in blue. Triple filter excitation showed expression of LXR and RXRα in the same decidual cells, indicated by yellow staining, identifying cells in the decidua expressing LXR and RXRα together. Therefore, co-expression of LXR and RXRα was demonstrated in decidua of spontaneous miscarriages (Figure 1A) HLA-G was used as antigen that is expressed exclusively in extravillous trophoblast cells. We showed that LXR (Figure 1B) and RXRα (Figure 1C) is expressed in EVT, as well as in decidual stromal cells. These cells are characterized by a red dot in the nucleus and do not show any positive green staining as EVT do.

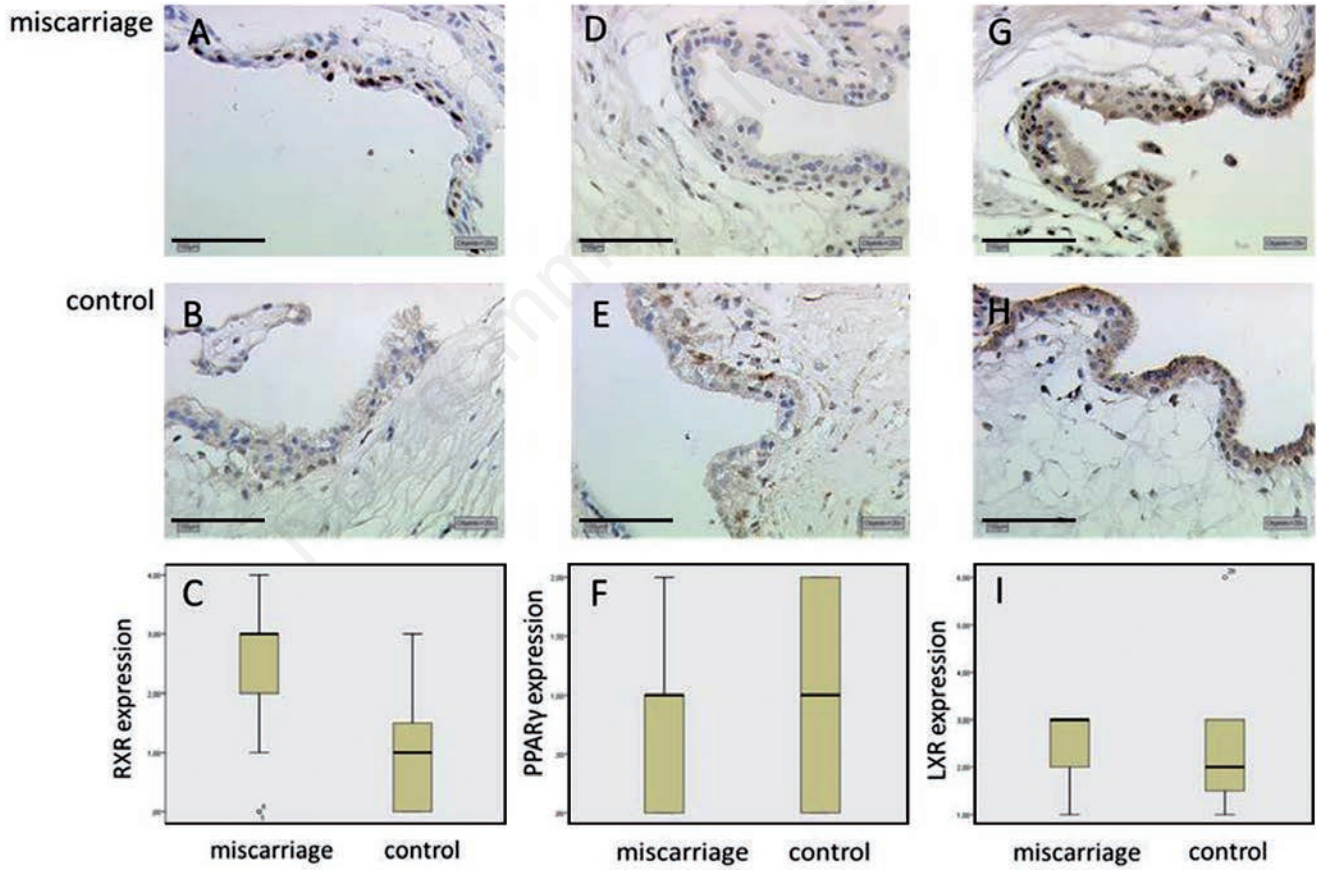

Figure 2. Immunohistochemical pictures of nuclear expression in endometrial glands: RXRα expression of spontaneous abortion (A) is significantly increased in comparison to RXR expression of control placentas (B). The expression of PPARγ (D,E) and LXR (G,H) was unchanged in spontaneous miscarriage in endometrial glands. Box plots representing the semiquantitative analysis of the expression of different nuclear receptors (C, RXRα; F, PPARγ; I, LXR) in endometrial glands of spontaneous abortion and control placentas derived immunohistochemically. The boxes display the range between the 25th and 75th percentile and the black horizontal line indicates the median. The bars represent the 5th and 95th percentiles. Circles indicate values, which are more than 1.5 times the box length. The y-axis represents the IRS score.

Evaluation of nuclear receptor staining in glandular epithelial tissue

We identified the expression of PPARγ, LXR and RXRα in nuclei/cytoplasma of cells in endometrial glands in regular pregnancy and miscarriage (Figure 2). RXR expression was significantly higher in the endometrial glands of spontaneous abortion (Figure 2A) compared to normal pregnancy (Figure 2B, IRS 3 *versus* 1, P<0.015). Expression of PPARγ was unchanged in spontaneous miscarriage (Figure 2D) compared to normal control glandular epithelial tissue (Figure 2E; PPARγ IRS 1 *versus* 1, P=0.69). The expression of LXR was significantly not changed in spontaneous miscarriage (Figure 2G) compared to normal control glandular tissue (Figure 2H; LXR IRS 3 *versus* 2, P=0.56). A summary of the staining results in Box Plots is given in Figure 2 C,F,I for RXRα, PPARγ LXR respectively.

Evaluation of nuclear receptor staining in decidual tissue

We identified the expression of PPARγ, LXR and RXRα in nuclei/cytoplasma of cells in decidual tissue of normal pregnancy and miscarriage (Figure 3). The number of RXR expressing cells was significantly higher in the decidual tissue of spontaneous abortion (Figure 3A) compared to normal pregnancy (Figure 3B, IRS 3 *versus* 2, P<0.05). Expression of PPARγ was unchanged in spontaneous miscarriage (Figure 3D) compared to normal control decidual tissue (Figure 3E; PPAR IRS 1 *versus* 1, P=0.85). The expression of LXR was not significantly changed in spontaneous miscarriage (Figure 3G) compared to normal control decidual tissue (Figure 3H; LXR IRS 2 *versus* 2, P=0.56). A summary of the staining results in Box Plots is given in Figure 3 C,F,I for RXR , PPAR , LXR respectively. A summary of all staining results is presented in Table 2.

Correlation analysis

To evaluate the co-expression of nuclear receptor in different parts of the decidua, we performed correlation analysis. In the endometrial glands of physiologic pregnancy, we found a trend to positive correlation for LXR and PPARγ (Spearman correlation coefficient r=0.56; P=0.07). In miscarriage, we did not detect any correlation of nuclear receptors identified in endometrial glands.

We further evaluated the correlation of nuclear receptor changes comparing decidual cells in miscarriage and normal pregnancy. In decidual cells, we found significant negative correlation in the control group, for the combination of RXRα and PPARγ (Spearman correlation coefficient r = –0.913, P=0.03). This correlation disappeared in spontaneous miscarriage.

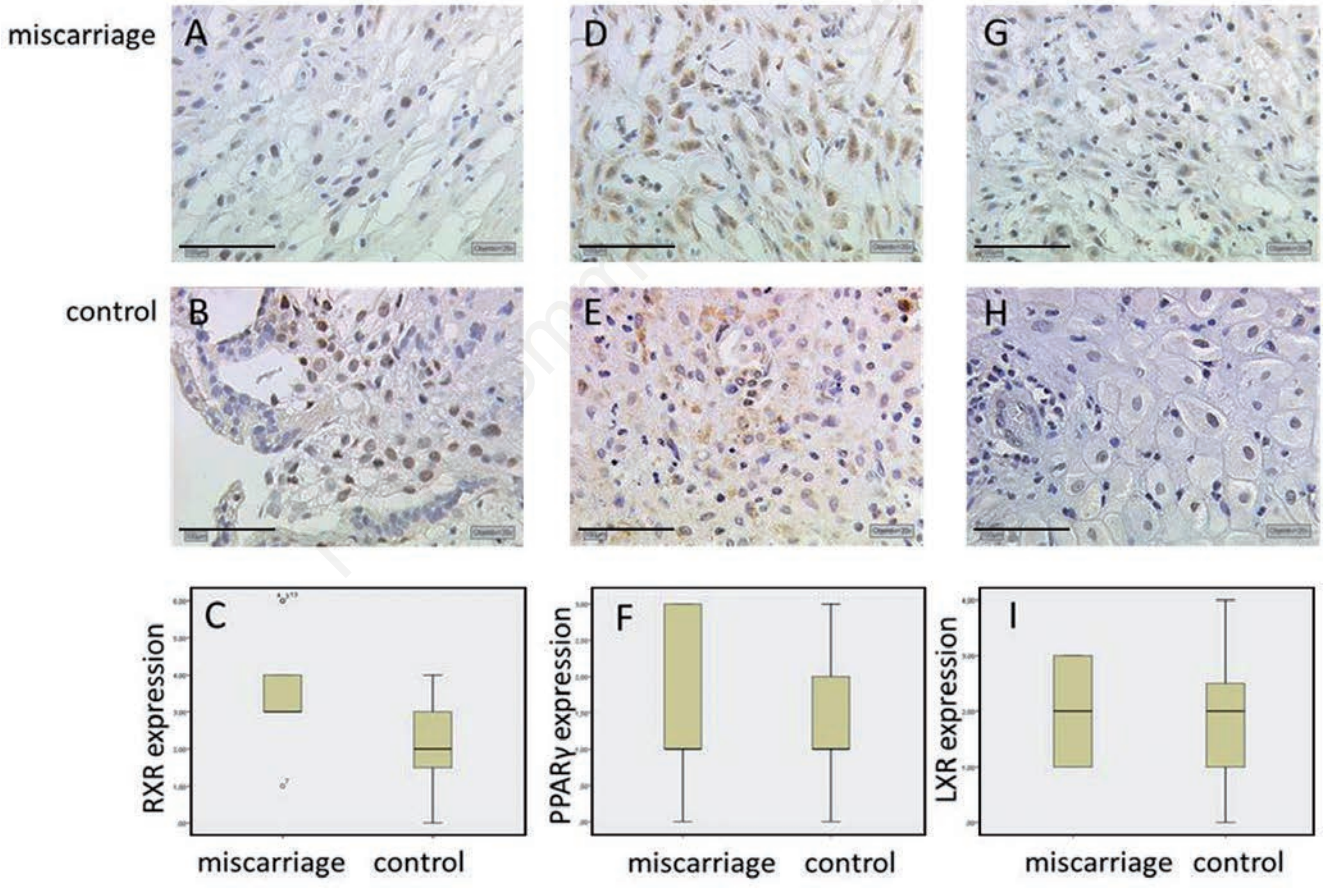

Figure 3. Immunohistochemical pictures of nuclear expression in decidual tissue: the number of RXRα expressing decidual stromal cells of spontaneous abortion (A) is significantly increased in comparison to the number of RXRα expressing cells in the decidua of control placentas (B). The expression of PPARγ (D,E) and LXR (G,H) remained unchanged in spontaneous miscarriage Box plots representing the semiquantitative analysis of expression of the different nuclear receptors (C, RXRα; F, PPARγ; I, LXR) in decidual tissue of spontaneous abortion and control placentas derived immunohistochemically. The boxes display the range between the 25th and 75th percentile and the black horizontal line indicates the median. The bars represent the 5th and 95th percentiles. Circles indicate values, which are more than 1.5 times the box length. The y-axis represents the IRS score.

Table 2. Summary of staining results.

PPARγ		LXR		RXRα		
Decidua	Glandular	Decidua	Glandular	Decidua	Glandular	
1.27	1.00	1.80	2.36	2.17	0.91	Mean (control)
0.90	0.89	1.10	2.43	1.11	0.94	SD (control)
1.43	0.85	2.07	2.31	3.71	2.31	Mean (miscarriage)
1.16	0.80	0.92	0.85	1.44	1.24	SD (miscarriage)

Discussion

Irrespective of increasing knowledge for early pregnancy loss, a significant proportion of miscarriages still happen for unknown reasons.[18] Changes in nuclear receptors of abortive EVT had been recently identified as underlying causes. In the present work we evaluated expression changes of nuclear receptors in endometrial glands of spontaneous abortion. We found a strong up-regulation of RXRα in endometrial glands of spontaneous miscarriage, similarly as it is already known in trophoblastic tissue of abortions. A likewise trend was identified for decidual tissue cells. Expression of PPARγ and LXR was unchanged in endometrial glands of miscarriage: Expression changes of these receptors are restricted to trophoblasts. Furthermore, we demonstrated interesting new insights in receptor expression correlation in different parts of the decidua; in endometrial glands of physiologic pregnancy, we found a trend to positive correlation for LXR and PPARγ.

Here we can speculate that LXR and PPARγ are upregulated simultaneously in regular GE. As this correlation was not found in abortive tissue, increased LXR and RXRα expression can be seen in miscarriage. Proper function of the endometrial glands plays a key role in implantation of the conceptus and decidualisation of the uterine stroma.[16,19] Increased LXR signaling reduces synthesis and secretion of hCG from trophoblasts cells[20] and decreases trophoblast invasiveness by matrix metalloproteinase 9;[21] these effects may be a consequence of a disturbed function in endometrial glands. To detect LXR expression we used a non-selective polyclonal antibody, therefore we only can speculate about the contribution of the single receptor. We know that LXRα is expressed in a tissue-specific manner, primarily in endocrine active tissues, whereas LXRβ is more ubiquitously. The expression patterns suggest regulation of different physiological functions by the two receptors.[22,23] Both LXR isoform are expressed in the placenta - LXRα is mainly localized in the villous trophoblast and in endothelial vessels.[24] LXRα regulates the intrauterine cholesterol metabolism.[12] In contrast, the isoform LXRββ was found primarily in decidual tissue, and activation of LXRβ with natural ligands inhibits trophoblast invasion *in vitro*. Therefore, LXRβ plays a pivotal role in the control of human trophoblast invasion. Both isoforms seem crucial for regular maintenance of pregnancy. We can speculate that alterations in endometrial glands as a part of the decidua mainly relate to LXRβ, which is crucial for invasion. Additionally, increased retinoic acid (the main agonist of RXRβ) has an inhibitory effect on genes essential for implantation in endometrial glands.[25] These findings go in line with our results of RXR upregulation in endometrial glands of miscarriage.

In decidual tissue cells of physiologic pregnancy, we found a negative correlation of nuclear receptors PPARγ and RXRα, but this correlation was lost in miscarriages. Since expression of PPARγ is unchanged in abortive tissue compared to normal controls, we assume that upregulation of RXRα in abortive tissue is responsible for the loss of negatively correlated PPARγ/RXRα expression. Combination of PPARγ with RXRα is essential for trophoblast differentiation, the receptor complex induces the secretion of gestational hormones like human chorionic gonadotropin, leptin and lactogen.[8,26] The heterodimer further regulates the uptake of fatty acids in trophoblasts, which is crucial for the production of placental steroid hormones and fetal growth.[7,27] As invasion of cytotrophoblasts is indirectly correlated to the activity of RXRα and PPARγ[7] and the latter plays a specific role in trophoblast differentiation, function,[28,29] and fetal development,[30] the replacement by RXRα is likely to disturb physiologic development in pregnancy. Furthermore, the isotype RXRα plays an essential role during embryogenesis and morphogenesis,[31]and protects against apoptosis in trophoblasts, so the enhanced expression of RXRα in miscarriage is twice disruptive in early pregnancy. To conclude, our data show that RXRα expression is increased in miscarriage in endometrial glands and correlation analysis showed that increased LXR and RXRα expression takes place in miscarriage, whereas LXR and PPARγ are upregulated simultaneously in regular GE. The loss of physiologically nuclear receptors correlation is supposable responsible for the deficit in regular function in trophoblast and embryonic tissue.

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