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Expression of Estrogen Receptors in Placentas Originating from Premature Deliveries Induced by Arterial Hypertension

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1. Introduction

The role of sex steroids and their activity involve complex intracellular reactions and depend upon presence of a specific steroid receptor. Estrogens influence several processes in the human body, including tissues distant from genital organs. In the estrogen-dependent tissues the hormones control cell proliferation and influence cell differentiation.

Studies indicate that estrogens and estrogen receptors play important physiological roles in cardiovascular disease [1].

Estrogens act by controlling expression of specific genes in target cells [2,3]. Their transcriptional activity is mediated by two estrogen receptors, ER- α and ER- β , similar in structure and function.

Till the end of 1980s transmission of the message carried by the hormone was thought to be mediated by a single estrogen receptor only. In the mid 1990s studies were published which described the discovery of a new estrogen receptor in both animals and humans [4-7].

The new estrogen receptor, ER- β , proved to be highly homologous to the classical estrogen receptor, ER- α .

Functional differences at the molecular level between ER- α and ER- β are of principal importance for the body. Just as importantly, in the case of estrogen receptors the same ligand may play role of either an agonist or antagonist, depending on whether it binds to ER- α or ER- β . Therefore, following binding of the ligand ER- α and ER- β may induce distinct biological effects, linked to conformational changes of the receptor [8].

The transmission of estrogen-carried signal plays a significant role not only in normal but also in neoplastically altered tissues. The mediator in transmission of estrogen-carried message involves estrogen receptors, acting as transcription factors, activated by ligands [8-11] and by alternative pathways of growth factor intracellular signalling [12,13]. Their

activity is subjected to intracellular control and is regulated by several tissue-dependent co-modulators. Tissue distribution of the latter determines the final effect, i.e., activation or repression of the estrogen-dependent genes. Co-modulators are significant for activity of estrogen receptors and represent the functional link between the receptor and transcriptional apparatus [14,15].

Gestosis represents a disease developing with an elevated arterial blood pressure. It may be accompanied by proteinuria and/or oedemas. The disease poses a high risk both to the mother and the fetus. There are several subtypes of the disease and it seems that the pregnancy-induced hypertension is of a key significance. Gestosis develops in as many as 8-10% pregnancies after their 20th week [16-20].

Pregnancy is associated with vascular adaptations. These adaptations are critical in pregnancy because their dysfunctions are implicated in pathological pregnancies, such as preeclampsia and other disorders [21-23]. The vascular adaptations are mediated by estrogens.

Development of a normally functioning placenta requires an extreme coordination between various cellular structures, depending on specific growth factors and highly related to reciprocal signalling between the cells.

We evaluated the two estrogen receptors, which participate in control of several functions [8,24,25]. We hoped that the investigations might prove helpful in evaluation of pathology developing in placentas obtained from mothers with pre-term delivery. In order to achieve the goal we evaluated differences in expression of selected receptors in placentas originating from normal pregnancies as compared to those from pre-term deliveries, burdened in addition by arterial hypertension in the mother.

Thus, the principal aim of the studies involved characterization of changes in ER- α and ER- β expression in placentas obtained from healthy women and from women who demonstrated pregnancy-induced hypertension and who developed pre-term delivery. It was also planned to examine changes in quantitative distribution of the two receptors in central portions of the placentas as compared to their peripheral fragments.

2. Material and methods

2.1 Material

The control group included placentas obtained from 20 women, aging 21 to 34 years, originating from deliveries at term, in 37th week of pregnancy, with a normal blood pressure during the entire pregnancy.

The experimental group I included placentas from 20 patients aging 22 to 34 years, originating from pre-term deliveries between 26th and 32nd week of pregnancy, induced by hypertension, which developed between 20th and 25th week of pregnancy.

The experimental group II consisted of placentas obtained from 20 mothers, aging 24 to 34 years, following pre-term deliveries between 33rd and 37th week of pregnancy, induced by hypertension, which developed between 20th and 25th week of pregnancy.

The placentas were macroscopically examined, their weight, width and thickness were recorded and then, their samples were taken, comprising full cross-section of placenta with all its components, including amnion epithelium and basal decidua.

Before isolation of placenta samples the patients were informed on the aim of the studies. The planned investigative procedures were approved by the Medical Bioethical Commission.

2.2 Sampling of the material

Placenta samples, 0.5-1.0 cm in width, were isolated from the central zone, around the umbilical cord, and from the peripheral zone.

Samples targeted for immunohistochemical and morphological investigations were immersed in a buffered solution of paraformaldehyde. The tissue samples were fixed in 4% (w/v) paraformaldehyde solution buffered with phosphates of physiological saline (PBS) for 24 hours, at the temperature of 4^o C, and dehydrated in a row of alcohols of increasing concentration (50%, 70%, 95% and 100% - 3 times of 20 min each), clear in xylene (3x10 min), and left in 1:1 mixture of xylene and paraffin at room temperature overnight. Subsequently, the samples were transferred to paraffin of the temperature not higher than 60^o C for three hours, exchanging paraffin every full hour, and were embedded in paraffin blocks.

The paraffin blocks were sectioned at 5 μ m using a rotary microtome and the sections were placed on silanized microscope glasses. Before immunohistochemical tests the preparations were deparaffinized in an incubator (15 min, 56^o C), and xylene (3 \times 10 min) and rehydrated in a row of alcohols of a decreasing concentration, starting at the absolute alcohol and terminating at 30% alcohol, three minutes at every step. Finally, the preparations were washed in distilled water and, then, in 10 mM PBS, pH 7.5.

In order to unmask antigens the preparations were boiled in a microwave oven (750 W) for 20 minutes in 10 mM citrate buffer, pH 6.0.

After cooling, they were washed in a buffer and activity of endogenous peroxidase was blocked by incubation with 1.5% (v/v) H₂O₂ in methanol for 10 minutes. Sites of non-specific binding were blocked using non-immunised, normal animal serum obtained from the animal in which later on secondary antibody was obtained, for 30 min at room temperature.

2.3 Antibodies

Monoclonal mouse anti-ER- α , directed against human estrogen receptor α , were purchased from Zymed Laboratories Inc., and used at the concentration of 1 μ g/ml. Polyclonal rabbit anti-ER- β , directed to human estrogen receptor β , were obtained from Affinity Bioreagents Inc., and used at the concentration of 5 μ g/ml.

2.4 Immunohistochemistry

After removal of serum, sections were overlaid with an appropriate primary antibody and left overnight at the temperature of 4^o C. Sites of primary antibody binding were visualized

using ABC technique. The sections were overlaid with appropriate secondary antibodies and, then, with avidin-biotinylated peroxidase complex (Vectastain ABC Kit, Vector Laboratories). The ABC complex was made visible using peroxidase substrate containing 3,3 diaminobenzidine (DAB) and hydrogen peroxide, in accordance with manufacturer's protocol (Vector Laboratories). The preparations were counterstained with Gill's hematoxylin, dehydrated and mounted. The negative control consisted of sections in which primary antibody was substituted by non-immunized serum of the animal in which subsequently primary antibody was obtained. In order to eliminate non-specific reactions the negative control was run in parallel on every slide.

An intra-organ and intra-cellular localization was evaluated under a light microscope (Nikon) at the magnification of 200x.

A quantitative analysis was conducted of ER- α and ER- β estrogen receptor contents. Using the KS100 computer software, optical density of microscope preparations was estimated in sites in which the colour immunohistochemical reaction developed. Absorption of the light wavelength pointed to optical density of cells in the cytoplasm, nucleus of which complexes of antibody with ER- α or ER- β were detected, reflecting the content of the reaction product.

The image analysis software of KS SA series was produced by Carl Zeiss Vision, Germany. The KS100/IBAS-C software was designed for measurements of interactively indicated geometric and densitometric parameters. At the stage of quantitative analysis autocalibration of the IBAS-C system takes place permitting calculations of surface area, mean lucidity, mean integrated lucidity, saturation coefficient, saturation coefficient in the scale of 1 to 255 and in % scale.

2.5 Statistical analysis

The results were collected in an Excel spread sheet (Microsoft, USA), and subsequently it was exported to STATISTICA software (Stat Soft, USA) to conduct statistical calculations.

For results of densitometric studies, estimation of significance of differences between placenta centre and periphery Student's *t* test for linked variables was used. On the other hand, Student's *t* test for unlinked variables was employed for inter-group differences. The differences were regarded significant at $p \leq 0.05$ level.

3. Results

3.1 Estrogen receptor ER- α

In the studies the placentas which were obtained from pre-term deliveries, were used in two groups: placentas from deliveries between 26th and 32nd week and those from deliveries between 33rd and 37th week. The control group consisted of placentas from at term deliveries.

Optical density of cells with expression of estrogen receptor reflects concentration of immunocytochemical reaction product in examined cells. Two types of the receptor, i.e., ER- α and ER- β were evaluated.

Appraisal of ER- α level in cytotrophoblast cells demonstrated a clearly decreasing optical density level of the product beginning at placentas from deliveries in the 26th-32nd week and ending at placentas from at term deliveries (Figures 1 and 2). The same analysis of peripheral parts of placentas showed that ER- α level was similar in the two experimental groups and in at term placentas (Figure 3).

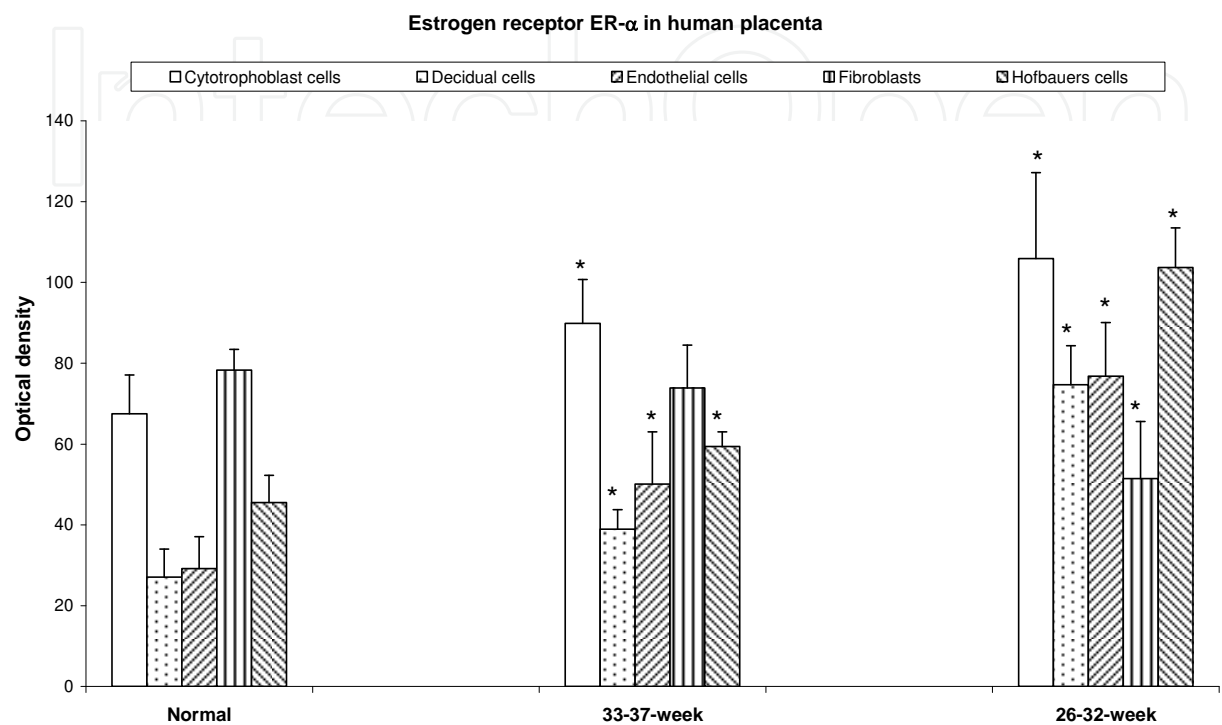


Fig. 1. Optical density of estrogen receptor ER- α in some cells originating from central part of human placentas originating from various periods of delivery. The data represent mean values \pm SD. * - statistically significant ($p<0.05$) in comparison with normal group

No significant differences were detected between placenta centre and placenta periphery in cytotrophoblast cell optical density tested for expression of estrogen receptor ER- α .

Analysis of ER- α distribution in decidua cells documented an abrupt, almost 100% decrease in concentration of the receptor between the group of placentas from 26th-32nd week and the group from 33rd-37th week in the central portion of placenta (Figures 1 and 2). Even lower expression of the receptor was detected the control group, in which ER- α level was three fold lower than in the experimental group I. Peripheral portions of the placentas manifested no more pronounced differences in ER- α concentrations in decidua cells between the studied groups (Figure 3).

Comparisons of product content in decidua cells following reaction for estrogen receptor ER- α manifested significant differences between central and peripheral part of placentas from pre-term deliveries (33rd and 37th week) and placentas originating from at term deliveries.

In the central portion of placentas originating from pre-term deliveries in 26th-32nd week optical density of endothelial cells with expression of estrogen receptor ER- α reached the highest value. In the subsequent group of placentas, originating from deliveries between 33rd and 37th week, the documented value amounted to around 70% of the level typical for

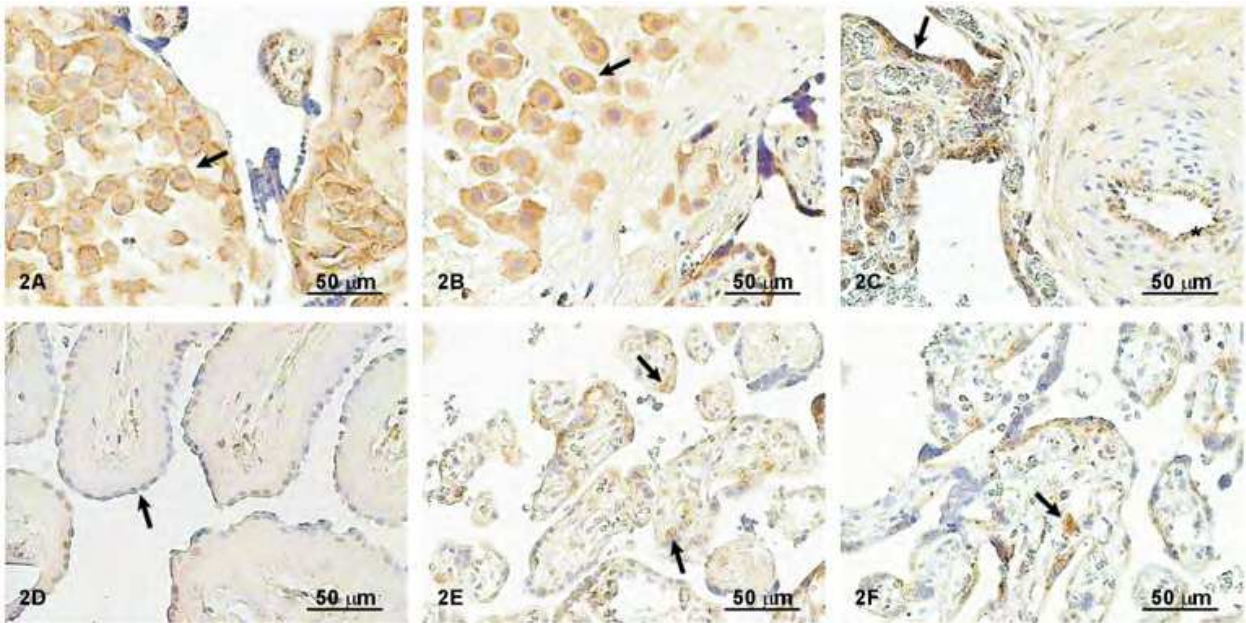


Fig. 2. Expression of estrogen receptor ER- α in decidual cells indicated by arrow (A,B), syncytiotrophoblasts (arrow) and endothelial cells (asterix) (C), cytotrophoblast cells (arrows) (E), Hofbauer’s cells (arrow) (F), and no expression in amnion epithelium (arrow) (D) originating from peripheral parts of normal-term placentas (E,F) and central parts of placentas delivered between 26th and 32nd week of pregnancy (A,C) and 33rd and 37th week of pregnancy (B,D).

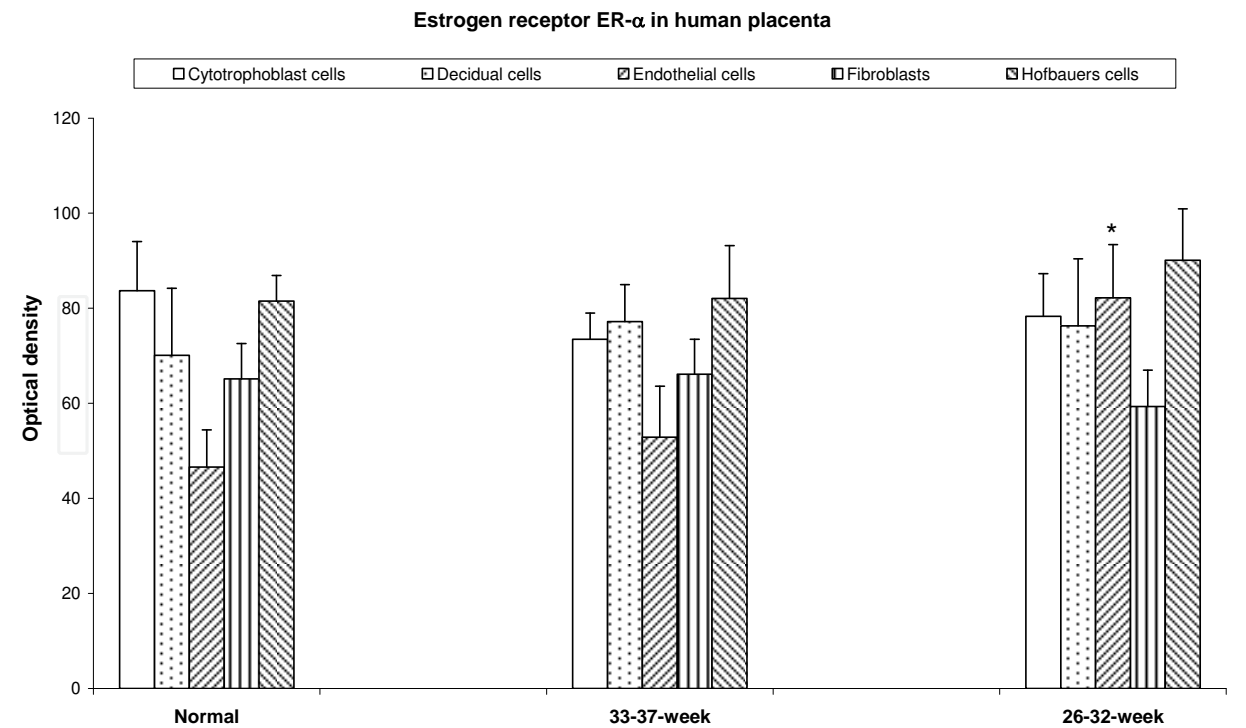


Fig. 3. Optical density of estrogen receptor ER- α in some cells originating from peripheral part of human placentas originating from various periods of delivery. The data represent mean values \pm SD. * - statistically significant ($p<0.05$) in comparison with normal group

group I and in the control group it was even lower (Figure 1). All the detected differences between reaction product content following the reaction detecting estrogen receptor ER- α in endothelial cells of studied groups proved significant.

A similar tendency was disclosed in peripheral portions of placentas. Also in this case the highest optical density in endothelial cells with expression of estrogen receptor ER- α was detected in placentas from the pre-term deliveries between 26th and 32nd week of pregnancy. In the experimental group II, the content of reaction product following the reaction detecting estrogen receptor ER- α clearly decreased (Figure 3) and resembled the values noted in placentas from at term deliveries.

In the analyzed time periods of pregnancy no significant differences were disclosed in the content of reaction product following reaction for estrogen receptor ER- α between the centre and the periphery of placenta.

In fibroblasts of central placenta portions, originating from group I of pre-term deliveries optical density of cells with expression of estrogen receptor ER- α reached the lowest value (Figures 1 and 2). In the subsequent group a rising tendency was noted and in the placentas at term the detected level corresponded to 150% of the values observed in group I.

In peripheral portions of placentas originating from pre-term deliveries between 26th and 32nd week of pregnancy optical density of fibroblasts with expression of estrogen receptor ER- α was comparable to values obtained in the remaining two groups.

No significant differences were disclosed in the product content following the reaction for estrogen receptor ER- α between fibroblasts situated in the centre as compared to those at the periphery of placentas.

In central portions of placentas originating from pre-term deliveries between 26th and 32nd week of pregnancy optical density of Hofbauer's cells with expression of estrogen receptor ER- α reached the highest value. In the subsequent analyzed experimental groups a rapid decrease was noted in the content of reaction product following the test for estrogen receptor ER- α , and in the group of placentas originating from deliveries between 33rd and 37th week of pregnancy the level amounted to 60% of the group I level and in placentas from at term deliveries it was even lower (Figure 1).

In cases of peripheral placenta portions the content of reaction product in Hofbauer's cells following the test for estrogen receptor ER- α was comparable in all the three investigated groups of placentas (Figure 3).

Upon comparison of the reaction product content in Hofbauer's cells following the test for estrogen receptor ER- α between central and peripheral portions of the placentas significant inter-zone differences were disclosed in placentas originating from at term deliveries and pre-term deliveries of group II.

3.2 Estrogen receptor ER- β

Following evaluation of ER- β levels in decidua cells the central portions of placentas originating from deliveries from 26th – 32nd week and 33rd – 37th week contained a similar optical density of the reaction product and an evidently higher optical density than that noted in placenta following at term deliveries (Figures 4 and 5). The same analysis

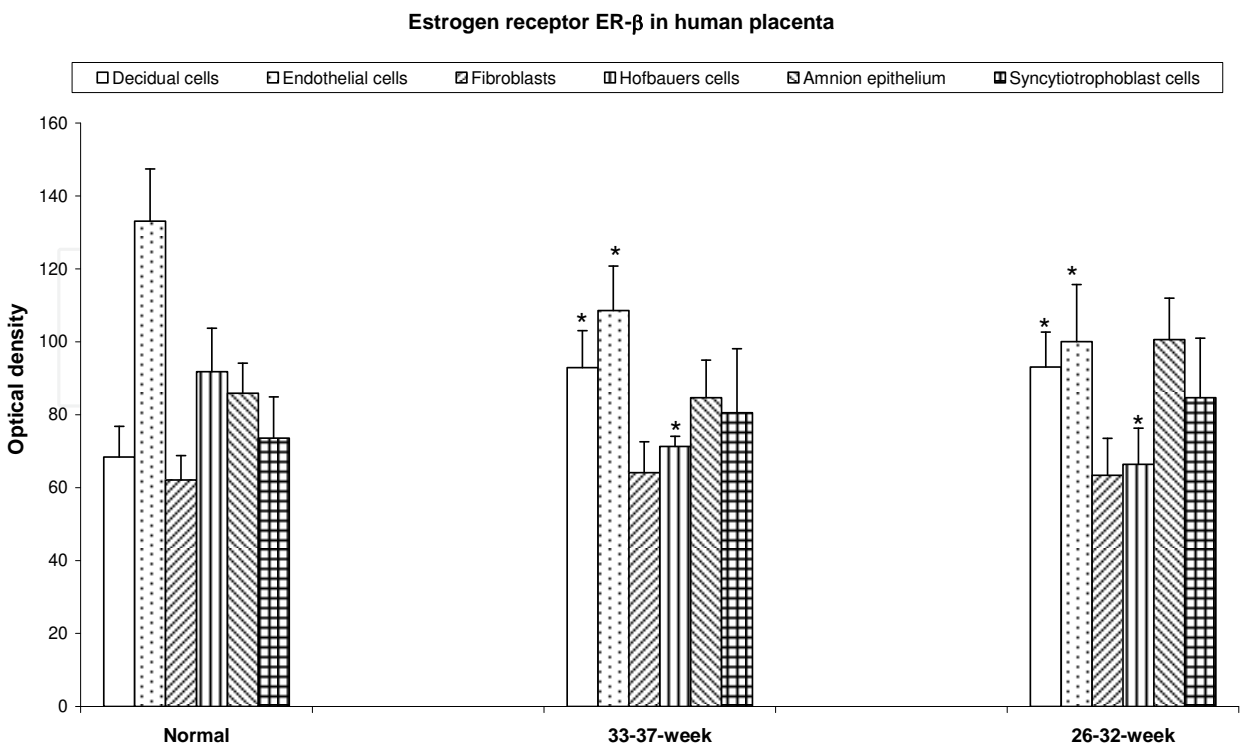


Fig. 4. Optical density of estrogen receptor ER-β in some cells originating from central part of human placentas originating from various periods of delivery. The data represent mean values ± SD. * - statistically significant ($p<0.05$) in comparison with normal group

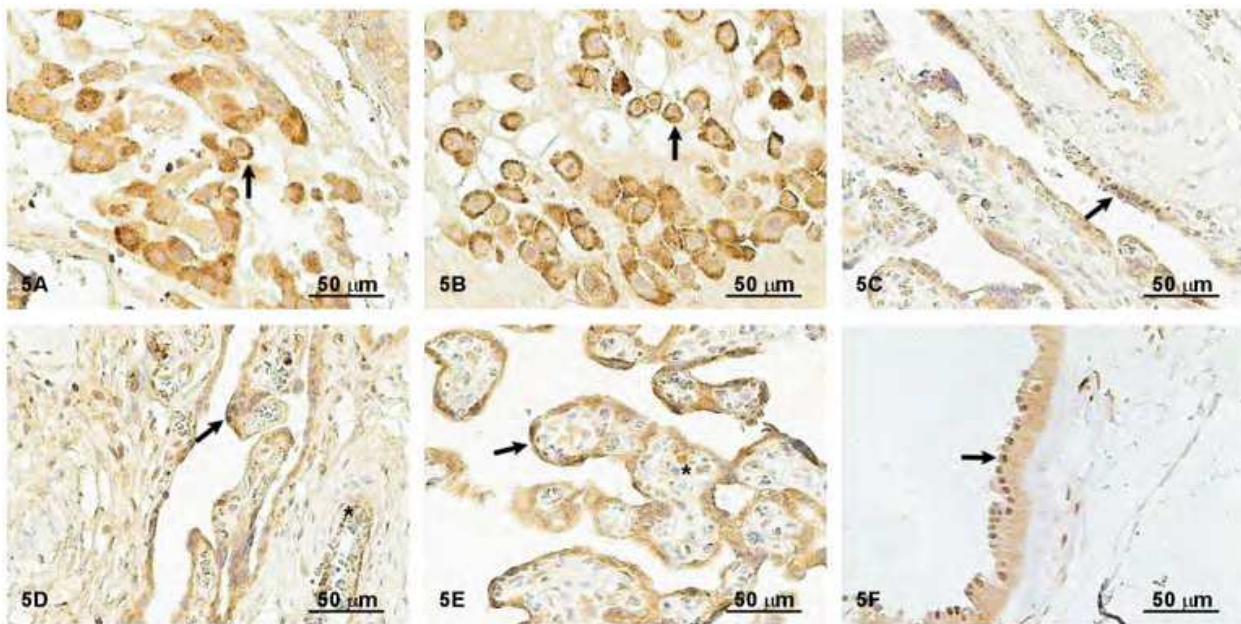


Fig. 5. Expression of estrogen receptor ER-β in decidual cells indicated by arrow (A,B), syncytiotrophoblasts (arrow) (C,D,E), endothelial cells (asterix) (C,D), and Hofbauer’s cells (asterix) (E) and amnion epithelium (arrow) (F) originating from peripheral parts of normal-term placentas (B,D), central parts of placentas delivered between 26th and 32nd week of pregnancy (A,C) and 33rd and 37th week of pregnancy (E,F).

performed in peripheral portions of the placentas detected in all cases the same levels of ER- β expression (Figure 6).

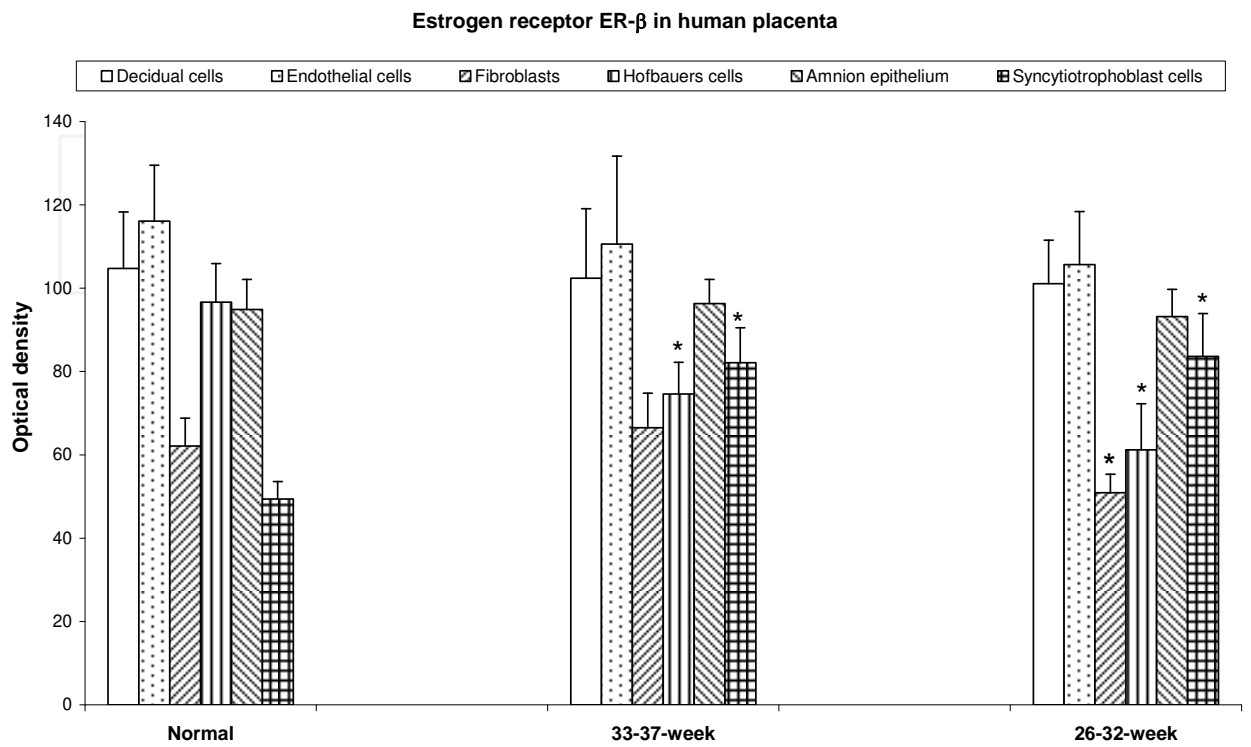


Fig. 6. Optical density of estrogen receptor ER- β in some cells originating from peripheral part of human placentas originating from various periods of delivery. The data represent mean values \pm SD. * - statistically significant ($p < 0.05$) in comparison with normal group

Upon comparison of the reaction product content following the test for estrogen receptor ER- β in decidua cells originating from either central or peripheral placenta portions significant differences were detected exclusively in the placenta originating from at term deliveries.

Analysis of ER- β distribution in endothelial cells of the central portion of placenta manifested a slight tendency for rising concentration of the receptor beginning at placentas from deliveries in 26th-32nd week and ending at placentas following at term deliveries (Figures 4 and 5). Comparable changes in concentrations of the receptor were noted in peripheral portions of placentas (Figure 6).

In the analyzed time periods of pregnancies no significant differences were observed between the centre and periphery of placentas in the content of reaction product in endothelial cells following the test for estrogen receptor ER- β .

The levels of ER- β receptor in fibroblasts were comparable in all studied groups, both in the central and the peripheral portions (Figures 4 and 6).

Analysis of the content of reaction product in fibroblasts following the test for estrogen receptor ER- β disclosed no significant differences between placental central and peripheral portions.

In contrast, levels of ER- β in Hofbauer's cells in the experimental groups proved to be significantly lower than in the control, both in the central and in the peripheral portions (Figures 4 and 6).

Upon comparison of reaction product content in Hofbauer's cells following the test for estrogen receptor ER- β in the central vs the peripheral portions of placenta no significant inter-zone differences were noted in the studied groups of placentas.

In central portions of placentas originating from deliveries between 26th and 32nd week of pregnancy amnion epithelial cells with expression of estrogen receptor ER- β demonstrated the highest optical density. In the subsequent experimental group a decrease was noted in the content in the product of a reaction for estrogen receptor ER- β , to the level comparable to that noted in placentas following at term deliveries.

Cells of amnion epithelium in peripheral portions of placentas originating from deliveries between 26th to 32nd week of pregnancy demonstrated optical density observed in the remaining two investigated groups of placentas.

Analysis of optical density in amnion epithelial cells with expression of estrogen receptor ER- β demonstrated no significant differences between centre and periphery of placenta.

In central portions of placentas optical density of the reaction product in syncytiotrophoblast cells following the test for estrogen receptor ER- β was analogous in all the investigated groups (Figure 4).

In peripheral portions of placentas optical density in syncytiotrophoblast cells with expression of estrogen receptor ER- β demonstrated a similar level in the experimental groups and a clearly lower level in the control group (Figure 6).

Comparison of optical densities in syncytiotrophoblast cells with expression of estrogen receptor ER- β disclosed no significant differences between experimental groups but they differed significantly in this respect from the control group.

4. Discussion

The presence of estrogens receptors in human tissues used to be evaluated by several investigators using various techniques, including RT-PCR, *in situ* hybridization and immunohistochemistry. The studies demonstrated their presence both in estrogen-dependent tissues and in tissues not recognized as estrogen-dependent, situated beyond the genital organs. Detailed recognition of estrogen receptor significance in organs and tissues functionally distant from generative functions is important for diagnosis and therapy of several diseases in men and women.

Expression of ER- α and ER- β has been examined in normal placentas and pre-term delivered placentas of women with diabetes mellitus and arterial hypertension. Pre-term placentas have demonstrated a clearly higher than normal level of ER- α , in line with the report of Schiessl et al. [26]. However, our observation pertained the central portion of placenta. Akram et al. [27] suggest the possible roles of ER and PR expression in the pathogenesis of both fetal growth restriction and preeclampsia, with lower levels contributing to higher likelihoods of disease outcome. ER- α is known to play a significant role in proliferation processes. High levels of the

receptor may point to elevated requirements of estrogens. This may be linked to reconstruction of this portion of placenta. It should be kept in mind that in the third trimester of pregnancy and following the 32nd week of pregnancy in particular placenta may develop various abnormalities, frequently defined as senescence of placenta [28,29]. In general, the abnormalities are linked to degeneration of villi although they involve also interstitial fibrosis and swelling of sinusoids in the villi [30,31]. The more pronounced proliferation in this portion of placenta (unpublished data) may point to such alterations. However, we should remember that involvement of ER- β receptor is indispensable in terminal maturation of estrogen-dependent cells. In our studies expression of the receptor in placentas of experimental groups has been evidently higher than in normal placentas. Earlier a similar observation was published by Bukovsky et al. [32,33], who in addition documented the unique role of ER- β in the control of placental function. Since trophoblast represents the principal source of placental hormones, high expression of ER- α and ER- β in trophoblast cells may be linked to estrogen stimulation of placental hormone production.

The wide range of ER- β manifestation and its presence in organs which lack ER- α and in organs which till now have been thought to be untypical for effects of estrogens, such as lungs, intestines, urinary bladder, proves that ER- β does not just reproduce the classical receptor but that it carries its specific functions. A detailed recognition of significance of estrogen receptors in organs and tissues functionally distant from progenitor functions is important for diagnosis and therapy of multiple diseases both in women and men.

The observed augmented immunoreactivity of ER- β in our studies, e.g., decidual cells or in amnion epithelium should not be surprising. Taylor and Al-Azzawi [6] observed different distribution and expression of the receptor in resting and proliferating mammary gland. The same team demonstrated that in uterus ER- β was detected in cell nuclei of all stromal cells. This proves that ER- β may be of high significance in development of some organs.

According to our knowledge individual reports only pertained localization of estrogen receptors in human placenta and no data are available as to the cellular distribution of the receptors in vicinity of umbilical cord and, independently, at the periphery of placenta.

Both in central and peripheral placenta portions on its fetal side a nuclear and cytoplasmic localization of the receptors has been observed in variable intensities in various cells. Estrogen receptor ER- α has been noted in fibroblasts of amnion, in cell nuclei of cytotrophoblast cells of the chorionic plate. The cytoplasmic reaction has been detected in some stromal cells of chorionic trunks while nuclear and cytoplasmic reaction has been noted in endothelial cells of some large vessels. Within the villi a nuclear reaction has been documented in cytotrophoblast cells, nuclear and cytoplasmic reaction in vascular endothelium cells and a cytoplasmic reaction has been noted in Hofbauer's cells. Both nuclear and cytoplasmic reaction has been detected in decidua cells and fibroblasts while the nuclear reaction has characterized cytotrophoblast cells in basal membrane of the placenta. The observation has confirmed the earlier reports on the matter [6]. The data confirm that in certain tissues cells exhibit an exclusive expression of the nuclear receptor only while in other cells both the nuclear and the cytoplasmic forms of the receptor are produced.

In the analysed time periods of pregnancy no changes in localization of estrogen receptor ER- α have been disclosed in either central or peripheral portions of placenta but differences have been detected in the content of reaction product following the test for estrogen receptor

ER- α (Figures 1 and 3). Differences have also been noted in optical density of cells manifesting expression of estrogen receptor ER- α between centre and periphery of placentas in the analyzed groups.

On the fetal side, both in the central and peripheral portions of placenta, a nuclear reaction for estrogen receptor ER- β has been observed in epithelial cells of the amnion while both nuclear and cytoplasmic reaction has characterized fibroblasts of the amnion. In syncytiotrophoblast cells of chorionic plate a cytoplasmic reaction has been detected. In chorionic trunks and in villi nuclear reaction has been documented in endothelial cells and a cytoplasmic reaction in syncytiotrophoblast cells.

Within villi a cytoplasmic reaction has been seen also in Hofbauer's cells. Both nuclear and cytoplasmic reaction has been detected in decidua cells and in fibroblasts and a cytoplasmic reaction in syncytiotrophoblast cells in basal membrane of the placenta.

In analogy to the estrogen receptor ER- α , localization of estrogen receptor ER- β has shown no alterations in the studied periods on pregnancy. Even if in most tissues distribution of ER- β seems to be linked to expression of ER- α , expression of ER- β does not seem to be related to expression of ER- α . On the other hand, differences in optical density have been detected between cells with expression of estrogen receptor ER- β located in placenta centre as compared to placenta periphery and between groups of various duration of pregnancy (Figures 4 and 6). Moreover, differences have been documented in intensity of the reaction product following the test for estrogen receptor ER- β between central and peripheral portions of placentas in the analyzed groups.

Similarly to suggestions of Bukovsky et al. [32], our studies manifest that ER- α is sufficient for basic differentiation of estrogen-sensitive tissues. Lack of ER- β results in defects in morphology of terminally differentiated tissues and our results show that expression of ER- β is required for final differentiation of estrogen-dependent tissues. This applies to cytotrophoblast cells, decidua cells and Hofbauer's cells. If the placentas originating from pre-term deliveries contained degenerative lesions, the high level of ER- β expression in the above mentioned cells may indicate that highly advanced reparative processes develop in the placentas. Su et al. [33] hypothesize that endothelial ER- β appears to be a master regulator of prostanoid biosynthesis and contributes to high-resistance fetoplacental blood flow.

We were studied expression of estrogen receptors in term and pre-term delivered (induced by hypertension) placentas. Higher expression ER- α was observed in central zone of pre-term placentas than in term placentas. In peripheral there were no significant differences in ER- α content. ER- β expression was in pre-term placentas higher only in decidual cells and syncytiotrophoblast.

Its known that estrogen receptors play role in proliferation cells angiogenesis. Differences in ER contents in placentas from normal and pathological pregnancies may indicate on changes in estrogen synthesis or theirs placental transport, what may be reason of hypertension development.

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Recent Advances in Research on the Human Placenta

Edited by Dr. Jing Zheng

ISBN 978-953-51-0194-9

Hard cover, 428 pages

Publisher InTech

Published online 07, March, 2012

Published in print edition March, 2012

This book contains the total of 19 chapters, each of which is written by one or several experts in the corresponding field. The objective of this book is to provide a comprehensive and most updated overview of the human placenta, including current advances and future directions in the early detection, recognition, and management of placental abnormalities as well as the most common placental structure and functions, abnormalities, toxicology, infections, and pathologies. It also includes a highly controversial topic, therapeutic applications of the human placenta. A collection of articles presented by active investigators provides a clear update in the area of placental research for medical students, nurse practitioners, practicing clinicians, and biomedical researchers in the fields of obstetrics, pediatrics, family practice, genetics, and others who may be interested in human placentas.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Andrzej Plewka, Danuta Plewka and Grażyna Nowaczyk (2012). Expression of Estrogen Receptors in Placentas Originating from Premature Deliveries Induced by Arterial Hypertension, Recent Advances in Research on the Human Placenta, Dr. Jing Zheng (Ed.), ISBN: 978-953-51-0194-9, InTech, Available from: <http://www.intechopen.com/books/recent-advances-in-research-on-the-human-placenta/expression-of-estrogen-receptors-in-placentas-originating-from-premature-deliveries-induced-by-arter>

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