Placental expression of heparan sulfate 3-O-sulfotransferase-3A1 in normotensive and pre-eclamptic pregnancies

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**ABSTRACT**

**Introduction:** The endothelial glycocalyx, consisting of membrane-bound proteoglycans and attached glycosaminoglycans plays an important role in vascular homeostasis. We aimed to assess whether glycocalyx mRNA transcripts are differentially expressed in placental tissue of pre-eclamptic and normotensive women.

**Methods:** We evaluated the expression of transcripts encoding for proteins involved in glycocalyx synthesis and degradation using a microarray analysis of placental mRNA obtained from pre-eclamptic and normotensive women. Participants were recruited from the department of obstetrics at a university hospital in Amsterdam, The Netherlands. The most prominent differentially expressed transcript was validated by qPCR on 112 additional placenta samples.

**Results:** Of 78 preselected genes involved in glycocalyx synthesis and degradation, only HS3ST3A1 mRNA was differentially expressed in placental tissue obtained from pre-eclamptic women (N=12) compared to normotensive women (N=12, fold change=0.61, \( p=0.02 \)). Validation with qPCR in additional placental samples of 64 normotensive and 48 pre-eclamptic women confirmed that normalized mRNA expression of HS3ST3A1 was decreased by 27% (95% CI 14% to 41%) in placental tissue obtained from pre-eclamptic compared to normotensive women \( (p<0.001) \). HS3ST3A1 expression was positively correlated with neonatal birth weight in normotensive women \( (r=0.35, p<0.01) \) and inversely correlated with mean arterial pressure of women with pre-eclampsia \( (r=0.32, p=0.02) \).

**Conclusions:** The mRNA expression of HS3ST3A1, which encodes for a 3-O sulfating enzyme of heparan sulfate (3-OST-3A1), is decreased in pre-eclamptic placental tissue. Expression of this glycocalyx synthesis transcript is correlated with maternal blood pressure and neonatal birth weight, suggesting a possible role in pre-eclampsia-associated placental dysfunction.
INTRODUCTION

Pre-eclampsia is a hypertensive emergency characterized by new onset hypertension and proteinuria in the second half of pregnancy and is a leading cause of maternal and fetal mortality and morbidity worldwide.[1] Placental dysfunction is critical in the pathophysiology of pre-eclampsia and its fetal sequelae including growth retardation and preterm birth.[2] Inadequate placental perfusion is currently considered a critical step in the pathophysiology of pre-eclampsia.[3] Incomplete spiral artery remodelling and cytotrophoblast differentiation from an epithelial origin to an endothelium-like anticoagulant phenotype may compromise placental blood flow.[2;4] This process of pseudo-vasculogenesis appears to be disturbed in pre-eclampsia and may contribute to local thrombosis and attenuation of placental perfusion.[5;6] The endothelial glycocalyx is a layer of complex sugars consisting of membrane-bound proteoglycans and attached glycosaminoglycan chains lining the intraluminal vessel wall. The endothelial glycocalyx is essential for endothelial function and thus organ perfusion by regulating its anticoagulant and anti-inflammatory properties.[7;8] Heparan sulfate is the major constituent within the glycocalyx and essential for the interaction between vascular endothelial growth factor (VEGF) and VEGFR1, the membrane bound FLT-1 surface receptor.[9;10] Scavenging of VEGF by the soluble form of FLT-1 has been shown to play a critical role in pre-eclampsia.[11] We hypothesize that analogous to the protective role of the glycocalyx in the systemic circulation, perturbation of the placental glycocalyx may jeopardize placental perfusion in pre-eclampsia. In the present study, we compared mRNA expression of enzymes involved in glycocalyx synthesis and degradation in placental tissue obtained from pre-eclamptic and normotensive pregnant women.

METHODS

Study population
For this study, clinical data and biosamples were obtained from participants in the Pre-eclampsia And Non eclampsia DAtabase (PANDA) program of the department of obstetrics of the Academic Medical Center in Amsterdam, The Netherlands. Definitions and clinical criteria used in the biobank program have been published previously.[12;13] Briefly, pre-eclampsia was defined by systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg recorded on two occasions at least 4 hours apart, after 20 weeks’ gestation in a previously normotensive woman combined with new-onset proteinuria with urinary protein excretion ≥ 300 mg/24-hour or >1+ on protein dipstick. BP was measured manually in the sitting position at the right upper arm using an aneroid sphygmomanometer. Diastolic BP was determined at Korotkoff sound V. Birth weight percentiles were assessed according to the
local Dutch birth weight percentiles. The appropriate chart was chosen based on parity and
gender of the baby. (http://www.perinatreg.nl/). HELLP syndrome was defined by lactate
dehydrogenase ≥ 600 U/L or haptoglobin < 0.2 g/L, aspartate or alanine aminotransferase
≥70 U/L, and platelet count < 100 *10^9/L. Experiments were carried out in accordance with
the declaration of Helsinki after informed consent from the participants was obtained.
Experiments were approved by an independent ethics committee.

**Microarray analysis, Tissue preparation and Quantitative Real-Time PCR**

Genes involved in glycocalyx synthesis and degradation were selected from the human
GLYCOv4 oligonucleotide array, a custom AffymetrixGeneChip designed for the Consortium
for Functional Glycomics which is freely available online (see http://glycomics.scripps.
edu/coreE/glycogenelistsv4Human.xls). Differential expression of this subset of genes was
assessed in 12 normotensive and 12 pre-eclamptic placenta samples using previously
obtained RNA microarray data from (NCBI Gene Expression Omnibus GSE54618).[12]

For quantitative real-time PCR (qPCR), placental biopsies from a macroscopically viable
(non-infarcted) central cotyledon from the maternal side were obtained immediately after
delivery and stored in RNAlater (Ambion) at −80°C until use. Isolation of mRNA was carried
out using the Magna Pure LC mRNA HS Kit (Roche) and reverse transcription was performed
with random hexamers using AMV First Strand cDNA Synthesis Kit (Roche). Q-PCR was
performed on a LightCycler 480 system (Roche) according to the manufacturer’s protocol,
with cDNA reaction mixtures containing 0.4 μmol/L of each primer (Invitrogen), 100 nmol/L
UPL probe (Roche) and 5 μl Absolute qPCR mix (Thermo Scientific) in a total volume of
10 μl. Primers/probes were designed using the Roche Universal ProbeLibrary Assay Design
Center: HS3ST3A1, AGGCCATCATCATCGGAGT/CTGCGGTCGAAGAAGTGG, UPL probe# 67;
PSMD4, GGCAAGATCACCTTCTGCAC/CTTCCCACAAAGGCAATGAT, UPL probe# 21. Data were
analyzed and quantified, using the second derivative maximum for Cp determination, with
the LightCycler 480 software 1.5.0 (Roche). HS3ST3A1 copy numbers were normalized to
PSMD4 (proteasome 26S subunit, non-ATPase 4) mRNA copy numbers.

To determine tissue specificity of HS3ST3A1 expression, 10 μg total RNA from 20 normal
human tissues (thymus, stomach, trachea, uterus, spinal cord, skeletal muscle, spleen, testis,
liver, lung, placenta, prostate, fetal brain, fetal liver, heart, kidney, colon, small intestine,
brain (whole), mammary gland) were reverse transcribed and investigated by the real-time
qPCR method described above. The Human Total RNA Master Panel was purchased from
Clontech (Mountain View, CA, USA).

Total RNA was pooled from Caucasian males and females with a wide age range. The number
of sources for the RNA pool was variable and ranged from 1 (stomach) to 64 (thyroid) per
tissue and is provided in the product description by Clontech (catalog No: 636643).
In situ hybridisation
In situ hybridisation was performed as described previously.[14] Briefly, placental tissue was fixed in 4% paraformaldehyde, dehydrated in a graded alcohol series, and embedded in paraplast. Sections with a thickness of 10 μm were mounted onto aminoalkylsilane-coated slides. Probe binding was observed using NBT/BCIP, according to the manufacturer’s protocol (Roche). After colour development, sections were rinsed in double-distilled water, dehydrated in a graded alcohol series, treated by xylene and embedded in Entellan (Merck, Darmstadt, Germany). Probes correspond to nucleotides 232 to 926 of HS3ST3A1 mRNA, (Genbank NM_006042.2).

Statistical analysis
Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) for variables with a skewed distribution. Categorical data are expressed as number and percentages. Between group differences were assessed by t-test for parametric and Mann–Whitney U test for non-parametric distributions. One-way ANOVA was used to assess differences in three groups. Chi-square statistics were used for categorical variables. Linear regression analysis was used to assess the correlation of HS3ST3A1 mRNA expression with neonatal birth and maternal blood pressure. For statistical analyses, SPSS software was used (Statistical Package for the Social Sciences, version 19.0, Inc. Chicago, Illinois, USA). P-values were considered to indicate a significant difference if \( p<0.05 \).

RESULTS
Microarray analysis
All of the 78 preselected transcripts relating to glyocalyx synthesis and degradation present on the Functional Glycomics AffymetrixGeneChip were also present on the Illumina HumanHT-12v.4 Expression BeadChips. Of this subset, only expression of HS3ST3A1 was significantly different in placental tissue of pre-eclamptic women compared to placental tissue of normotensive women (fold change 0.61, \( p=0.02 \), Supplemental Table). Expression of HEXB tended to be higher in pre-eclamptic placentas, but this was not significant (fold change 1.84, \( p=0.06 \)). Expression of other 3-O sulfation isoforms including HS3ST1 and HS3ST3B1 were comparable in normotensive and pre-eclamptic placental tissue. Expression of EXT1 and EXT2, involved in heparan sulfate chain initiation and elongation was also similar in both groups. Micro-array expression of HS3ST3A1 correlated negatively with that of PAI-1 (r=0.65, \( p<0.001 \)). There was no correlation of HS3ST3A1 expression with that of FGF-10 or FGF-R2. The decrease in HS3ST3A1 mRNA expression in pre-eclamptic placentas was further validated in another population by real-time qPCR. The 24 subjects included in the microarray analysis, were excluded from participation in the subsequent qPCR analysis.
Clinical characteristics of pre-eclamptic and normotensive women

In total, placental tissues of 112 pregnant women (48 with a pre-eclamptic pregnancy and 64 with a normotensive pregnancy) were included in the qPCR analysis. Baseline characteristics and comparisons of patients with and without pre-eclampsia are summarized in Table 1. HELLP syndrome was present in 19 (40%) women with pre-eclampsia. Antihypertensive treatment was started in 36 (75%) women with preeclampsia, of whom 25 (66%) received a calcium-antagonist (nifedipine OROS), while 26 (68%) were treated with a central α1 agonist (methyldopa), 12 (32%) received a combined α1 and β-blocking agent (labetalol) and 1 (3%) received a selective serotonin 5-HT2-antagonist (Ketanserin). MgSO4 was administered to 20 (42%) pre-eclamptic women. Ten (21%) women with pre-eclampsia were not treated with any type of antihypertensive medication. Of these women, one received MgSO4 prior to delivery. Three pre-eclamptic women used anticoagulant therapy patients during pregnancy, 2 received low-molecular-weight heparin, a vitamin K antagonist and aspirin at a certain period during their pregnancy, while one patient was treated with low-molecular-weight heparin only. Of all normotensive women, 11 (17%) received a calcium antagonist (nifedipine OROS) as a tocolytic agent to delay preterm labour. None of the normotensive patients received anticoagulant therapy.

Table 1: Comparison of baseline maternal and neonatal characteristics between women with and without pre-eclampsia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre-eclampsia</th>
<th>Normotensive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>48</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>32±5</td>
<td>29±6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>25 (53%)</td>
<td>30 (49%)</td>
<td>0.81</td>
</tr>
<tr>
<td>Body Mass Index, kg/m2, (mean ± SD)</td>
<td>26±5</td>
<td>24±6</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic BP, mmHg (mean ± SD)</td>
<td>170±19</td>
<td>121±16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP, mmHg (mean ± SD)</td>
<td>104±18</td>
<td>71±11</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Proteinuria, g/24hrs, (median, [IQR])</td>
<td>1.9 [0.7-4.8]</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td>Platelet count, x10^9/L (mean ± SD)</td>
<td>146±89</td>
<td>249±66</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lactate dehydrogenase,* U/L (median, [IQR])</td>
<td>299 [233-635]</td>
<td>180 [189-301]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nulliparous, N (%)</td>
<td>26 (54%)</td>
<td>31 (48%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Gestational age at delivery, days (mean ± SD)</td>
<td>240±27</td>
<td>245±34</td>
<td>0.40</td>
</tr>
<tr>
<td>Antenatal steroids,§ N (%)</td>
<td>22 (49%)</td>
<td>24 (39%)</td>
<td>0.23</td>
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<tr>
<td>Delivery by caesarean section</td>
<td>28 (58%)</td>
<td>24 (38%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Birth weight, grams (mean ± SD)</td>
<td>2026±966</td>
<td>2473±1093</td>
<td>0.03</td>
</tr>
<tr>
<td>Placental weight, grams,† (median, [IQR])</td>
<td>212 [191-280]</td>
<td>271 [208-295]</td>
<td>0.14</td>
</tr>
<tr>
<td>Blood loss at delivery, mL (median, [IQR])</td>
<td>475 [200-650]</td>
<td>250 [200-362]</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Data missing for 5 women with pre-eclampsia and 55 normotensive women. §Missing data for 3 normotensive pregnant women and 5 women with pre-eclampsia. † Data available for 17 normotensive women and 20 women with pre-eclampsia
Placental Expression of HS3ST3A1 is Decreased in Pre-eclampsia

Quantitative Real-Time PCR and In situ hybridisation

Normalized mRNA expression of HS3ST3A1 was decreased by 27% (95% CI 14% to 41%) in placental tissue obtained from pre-eclamptic women (0.05±0.02) compared to normotensive women (0.07±0.03, \( p < 0.001 \), Figure 1). To assess whether differential expression of HS3ST3A1 is influenced by differences in birth weight, HS3ST3A1 mRNA expression was stratified by neonatal birth weight category. HS3ST3A1 expression was significantly lower in pre-eclamptic placental tissue compared to normotensive placental tissue for neonates in the same birth weight category (20-80th percentile).

Expression was also lower in pre-eclamptic placental tissue of other birth weight categories, but this was not statistically significant (Figure 2). To determine placental specificity of HS3ST3A1 mRNA expression, we performed real-time qPCR on a RNA tissue panel. Compared to most tissues investigated, including brain, heart, kidney and liver, placental expression of HS3ST3A1 was relatively high. However, even higher expression was observed in spleen and trachea (Figure 3). In situ hybridization showed that HS3ST3A1 mRNA was most prominently expressed in the syncytiotrophoblast and the endothelium of villous blood vessels (Figure 4).

Figure 1: Comparison of HS3ST3A1 mRNA expression in placental tissue of women with and without pre-eclampsia

qPCR analysis showing significantly higher HS3ST3A1 mRNA expression in placental tissue of normotensive (NT) women, (N=64) compared to placenta from women with a pre-eclamptic (PE) pregnancy ( N=48). Data are expressed as mean±SD.* indicates \( p < 0.001 \).
Figure 2: Association of HS3ST3A1 mRNA expression and birth weight

* indicates p<0.05 using one-way-ANOVA, # indicates p<0.01 using students t-test.

Figure 3: Quantification of tissue specific HS3ST3A1 mRNA expression

Expression of HS3ST3A1 mRNA in various tissues. Bars represent the mean of duplicate qPCR reactions, error bars are left out due to standard deviations that were too small for depiction. Expression was normalized to mRNA copy numbers of the housekeeping gene PSMD4. Compared to most tissues investigated, placental expression of HS3ST3A1 is relatively high. The highest expression was observed in spleen and trachea.
Figure 4: In situ hybridisation

Localization of placental HS3ST3A1 mRNA expression in 10 μm thick sections of a 38+5 week placenta. In panel A and B an anti-sense probe for HS3ST3A1 has been used, while panel C shows the hybridization signal of the control sense probe. HS3ST3A1 mRNA expression (blue color) is localized throughout the placenta, but distinctively high expression is detected in the syncytiotrophoblast layer (arrows) and in some parts of the vascular endothelium (arrow head, panel B). Magnification 200x, scale bar represents 100 μm.
Correlation of HS3ST3A1 expression with birth weight and blood pressure

Birth weights of neonates from normotensive women were positively correlated with placental HS3ST3A1 mRNA expression (r=0.35, p<0.01), but this was not observed in women with pre-eclampsia (r=0.26, p=0.08). Normalized HS3ST3A1 mRNA expression was inversely correlated with mean arterial pressure of pre-eclamptic women (r=0.32, p=0.02, Figure 5A), but not of normotensive women (r=0.07, p=0.61). The amount of antihypertensive agents required for treatment of women with pre-eclampsia was also associated with HS3ST3A1 expression. Lower HS3ST3A1 expression coincided with more blood pressure lowering medication (Figure 5B).

Figure 5: Association of HS3ST3A1 expression and blood pressure

Linear regression analysis shows that HS3ST3A1 expression is inversely correlated with mean arterial pressure in pre-eclamptic women (A). The number of antihypertensive drugs required for treatment of pre-eclampsia is associated with HS3ST3A1 expression. The with less antihypertensive agents required, the higher HS3ST3A1 expression (B). Data are expressed as mean±SD. * indicates p<0.05 using one-way-ANOVA.

DISCUSSION

Our data suggest a possible role for HS3ST3A1 in the pathophysiology of pre-eclampsia. We show that mRNA expression of HS3ST3A1 is decreased by approximately 30% in placental tissue of women with a pre-eclamptic pregnancy compared to placentas from women after a normotensive pregnancy. In addition, HS3ST3A1 mRNA levels were associated with neonatal birth weight and maternal blood pressure.
Placental Expression of HS3ST3A1 is Decreased in Pre-eclampsia

Differential expression of HS3ST3A1 has also been demonstrated by other RNA microarray studies in women with and without pre-eclampsia. From the NCBI Gene Expression Omnibus,[15] two microarray studies with a relatively large samples size (GSE25906 and GSE10588) showed significantly lower HS3ST3A1 mRNA levels in pre-eclamptic placentas compared to controls when analyzed by the NCBI GEO2R web tool using standard settings (fold change 0.70, \(p=0.001\) for GSE25906, and fold change 0.62, \(p=0.003\) for GSE10588). Four other studies with a relatively small sample size also showed decreased HS3ST3A1 mRNA levels in de pre-eclamptic placenta, but not at a statistically significant level. These data suggest that downregulation of HS3ST3A1 is common in the pre-eclamptic placenta and supports the external validity of our findings. In addition, we validated and quantified HS3ST3A1 mRNA expression by real-time qPCR and were able to link HS3ST3A1 expression with neonatal and maternal outcomes.

Heparan sulfates are composed of repeating disaccharide units attached to transmembrane anchoring proteins such as syndecans and may have a variety of physiological functions depending on their sulfation pattern.[16] HS3ST3A1 encodes for a heparan sulfate sulfotransferase (3-OST-3A1) that transfers a sulfo group from 3’-phosphoadenosine 5’-phosphosulfate (PAPS) to the 3-OH position of a glucosamine unit present in heparan sulfate chains.[17] 3-O sulfation is the least frequent modification of heparan sulfates and is carried out at the final stage of heparan sulfate biosynthesis in the Golgi apparatus by a family of seven 3-OST iso-enzymes, which possess distinctive substrate-specificities within the polysaccharide structure.[17;18]

HS3ST3A1 has been shown to stimulate epithelial cell proliferation via interaction with the Fibroblast growth factor 10 (FGF-10)/FGF receptor-2b complex.[19] Via a rapid feedback mechanism, FGF-10/FGF receptor-2b signaling directly augments HS3ST3A1 expression up to 7-fold within hours.

Decreased HS3ST3A1 expression might therefore be a cause as well as a consequence of FGF-10 induced epithelial cell proliferation. In addition to epithelial cell proliferation, FGF-10 factor signaling has been shown to stimulate activity of plasminogen activator inhibitor-1 (PAI-1) in trophoblast cells isolated from first trimester placentas.[20] In the current study we did not observe a relation between HS3ST3A1 and FGF-10 or FGFR2b expression. In contrast, HS3ST3A1 expression negatively correlated with PAI-1. PAI-1 contributes to a thrombophilic state by inhibiting fibrinolysis and has been implicated in the pathogenesis of pre-eclampsia.[21;22] Increased PAI-1 levels in pre-eclampsia are maintained into the third trimester,[23] and could contribute to increased coagulation in the placenta leading to hypoperfusion and placental insufficiency. Although merely speculative, decreased FGF-10 signaling due to decreased HS3ST3A1 expression might partly explain our observation that lower HS3ST3A1 expression coincides with lower neonatal birth weight via both decreased proliferation and increased coagulation.
HS3ST3B1, a 3-OST isoform, has also been linked to activation of inflammation, which is involved in the pathophysiology of pre-eclampsia. Within the family of 3-O sulfotransferases, HS3ST3A1 is highly homologous to HS3ST3B1, and they seem to act on identical substrates. [18] Sulfation of heparan sulfate by HS3ST3B1 has been implicated in the regulation of Natural Killer (NK) cell activation via interaction with their Killer Immunoglobulin-like Receptors (KIR). [24] Nearly half of all cells present at the maternal-fetal interface are immune cells, comprising of a vast majority of decidual NK cells. [25]

Within the decidua, these cell express up to three-fold higher levels of KIR compared to peripheral blood Natural Killer cells. [26] The combination of certain maternal KIR genotypes and Human Leucocyte Antigen (HLA) haplotypes is associated with a higher risk of pre-eclampsia, [27] possibly because of stronger inhibition of NK cell activation. Decidual NK cells have been shown to stimulate trophoblast invasion, decidual artery remodelling and are capable of producing vascular endothelial growth factor (VEGF) and placental growth factor (PLGF), suggesting that decidual NK activation may be involved in the pathogenesis of pre-eclampsia. [28] The ability of 3-O sulfated heparan sulfates to directly regulate NK cell activity, provides a possible explanation for the observed correlation of HS3ST3A1 expression with birth weight and maternal blood pressure.

This study has some limitations that need to be addressed. First, placental tissue was obtained from macroscopically viable (non-infarcted) central cotyledons. Data on HS3ST3A1 expression in less viable placental tissue might be informative with regard to the pathogenesis of pre-eclampsia, but is not available for the current study. Second, of in total 78 preselected glycocalyx genes only HS3ST3A1 was differentially expressed in our microarray analysis. However, a recent meta-analysis of pre-eclampsia RNA microarray data showed that additional glycocalyx genes from the preselected list of 78 genes were differentially expressed in normotensive and pre-eclamptic pregnancies. [29] The identification of more pre-eclampsia associated glycocalyx genes in the meta-analysis is most likely due to the much greater number of samples in that study (139 normotensive and 116 preeclamptic pregnancies). Third, we assessed the association of HS3ST3A1 mRNA expression with clinical characteristics, while actual 3-OST-3A1 enzyme activity might provide more insight into the functional relevance of decreased HS3ST3A1 expression. Fourth, because of preterm births of unknown cause, the birth weight of neonates in the control group was relatively low. As HS3ST3A1 mRNA expression positively correlated with birth weight, the actual difference in HS3ST3A1 expression between normotensive en pre-eclamptic women could therefore have been underestimated. Finally, this study points out that HS3ST3A1 is decreased in pre-eclampsia and correlated with birth weight and maternal blood pressure, but cannot discriminate between cause or consequence. With regard to the possible interaction between 3-OST-3A1 and FGF-10, both are possible at the same time.
In conclusion, this study shows that HS3ST3A1 mRNA expression is significantly decreased in placental tissue of a relatively large cohort of women with pre-eclampsia. Normalized HS3ST3A1 mRNA expression is related to neonatal birth weight and maternal blood pressure. The mechanism by which 3-OST-3A1 may be involved in the pathogenesis of pre-eclampsia remains to be studied.

Based on the scarce current knowledge on the functions of 3-O sulfated heparan chains, regulation of FGF-10 signaling and decidual NK cell activity by HS3ST3A1/3-OST-3A1 might be relevant in the pathophysiology of pre-eclampsia.
REFERENCES


Placental Expression of HS3ST3A1 is Decreased in Pre-eclampsia


[22] L. Zhao, M.B. Bracken, A.T. Dewan, S. Chen Association between the SERPINE1 (PAI-1) 4G/5G insertion/deletion promoter polymorphism (rs1799889) and pre-eclampsia: a systematic review and meta-analysis Mol Hum Reprod, 19 (3) (2013), pp.136-143


