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Labour Induces Increased Concentrations of Biglycan and Hyaluronan in Human Fetal Membranes☆

M. Meinert [a,*], A. Malmström [d], E. Tufvesson [d], G. Westergren-Thorsson [d], A.C. Petersen [b], C. Laurent [c], N. Uldbjerg [a], G.V. Eriksen [a]

[a] *Department of Obstetrics and Gynecology, Research Laboratory, Skejby University Hospital, Brendstrupgerdsvej 1, 8200 Aarhus N, Denmark*
[b] *Department of Pathology, Aalborg University Hospital, 9100 Aalborg, Denmark*
[c] *Department of Clinical Science, University of Umeå, 901 87 Umeå, Sweden*
[d] *Department of Cell and Matrix Biology, Biomedical Center, C13, S-221 84 Lund, Sweden*

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Abstract

Objective: The proteoglycan decorin stabilizes collagen whereas biglycan and hyaluronan disrupt well-organized collagen. The aim was to compare hyaluronan and proteoglycans in human fetal membranes obtained before and after spontaneous labour at term.
Study design: Prelabour samples of fetal membranes ($N = 9$) were obtained from elective caesarean sections and regionally sampled from over the cervix (cervical membranes) and mid-zone samples between this area and the placental edge. Postlabour samples ($N = 11$) were obtained from spontaneous vaginal delivery and also regionally sampled. Amnion and chorio-decidua were analysed separately. The proteoglycans decorin and biglycan were analysed using alcian blue precipitation, SDS polyacrylamide gel electrophoresis and immunostaining. Hyaluronan was analysed using a radioimmunoassay and by histochemistry. Collagen was measured by estimating hydroxyproline content.
Results: In prelabour membranes the biglycan concentration (μg/mg wtw) in the cervical amnion was 40% lower than in the mid-zone amnion ($P < 0.05$). After delivery the cervical amnion showed a twofold increase in biglycan ($P < 0.05$), a 30% decrease in collagen ($P < 0.05$), and a 50% decrease in decorin concentration ($P < 0.05$). In mid-zone samples after delivery the concentrations of hyaluronan showed an increase form 1.0 to 4.9 μg/mg wtw ($P < 0.05$). Histology demonstrated a gelatinous substance, which separated amnion and chorio-decidua, in particular at the cervical site. This gelatinous substance contained hyaluronan at a concentration of 3.0 μg/mg wtw.
Conclusion: It is well established that prelabour fetal membranes are considerably stronger than postlabour fetal membranes. Two features may explain this; a weakening of the amnion combined with a separation of amnion and chorio-decidua. The biomechanical changes are consistent with the decrease in collagen and decorin, and the increase in hyaluronan and biglycan demonstrated in this study. The separation of the membranes is caused by the formation of a gelatinous substance, rich in hyaluronan. The results indicate that the biomechanical changes are not merely secondary to the stress of labour but that an active maturation process is involved.

Keywords: Decorin; Biglycan; Rupture of membranes; Collagen; Amnion; Chorio-decidua; Labour

1. Introduction

In most pregnancies at term the fetal membranes remain intact, until they rupture spontaneously, when labour is in full progress. Prelabour rupture of the membranes occurs in 10% of pregnancies at term and as many as 40% of preterm births and is therefore one of the main problems in perinatal medicine today [1].

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* Corresponding author. Tel.: +45 8949 6391; fax: +45 8949 6373.
E-mail address: mette.meinert@dadlnet.dk (M. Meinert).

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Fetal membranes from spontaneous vaginal delivery at term have reduced biomechanical strength compared with fetal membranes from elective caesarean section [2,3]. The rupture site has several histological and biochemical characteristics such as altered morphology, decreased biomechanical strength and increased concentration of proteinases [4–7]. Furthermore, the formation of a gelatinous substance separating the amnion and the chorio-decidua, may change the biomechanical strength, as the amnion and the chorio-decidua can no longer work in parallel [2,3].

Amnion is rich in collagen and the strength-bearing component of the fetal membranes [8]. It has not, however, been possible to establish an association between low levels of collagen in the amnion and preterm rupture of the membranes [9,10]. In the light of this we have found it important to study the two leucine-rich proteoglycans decorin and biglycan, which are essential for the function of the extracellular matrix. In a previous study we have described the amnion as containing a high amount of both collagen and decorin, whereas the chorion (=chorio-decidua) contained both decorin and biglycan [8]. Decorin increases tensile strength as it binds to collagen I, and III [11,12] in opposition to biglycan, which may weaken the interaction between decorin and collagen. Hyaluronan may further weaken the tissue, because it generates a great swelling pressure between the collagen fibrils, resulting in a further disorganisation of the extracellular matrix [13].

In this study we aimed to investigate whether regional differences in the concentration and distribution of proteoglycans, hyaluronan and collagen exist prior to labour, and whether they are involved in the final rapid remodelling of the membranes during labour.

2. Materials and methods

2.1. Materials

2.1.1. Patient details

Fetal membranes were obtained from 9 women undergoing elective caesarean deliveries performed in gestational week 39 (range 39 weeks 0 days' to 40 weeks 5 days') for breech presentation, former intrauterine death, or repeat caesarean deliveries (prelabour samples). 11 fetal membranes from vaginal delivery with spontaneous rupture of the membranes (postlabour samples) after the onset of labour (defined as painful contractions) were also obtained in gestational week 39 (range 39 weeks 0 days' to 40 weeks 3 days'). The gestational age of the prelabor and postlabor samples was determined by ultrasound examination and did not differ statistically ($P = 0.36$).

Informed consent was obtained from all patients. The ethics committee of Aarhus County, Denmark approved the study.

2.1.2. Tissue sampling

The fetal membranes were collected upon delivery, and biopsies were frozen at −80 °C immediately after samples were taken, using a cutting instrument of razor blades in parallel [8]. Light microscopy was used to exclude infected membranes after polymorphonuclear infiltration had been identified.

After delivery of the babies by caesarean section, fetal membranes overlying the cervix (cervical membrane) were located and marked by the application of a Babcock clip according to McLaren et al. [14]. Biopsies from this area were termed cervical membranes. The area within the jaws was not used. Mid-zone biopsies were obtained from halfway between the cervical area and the placental edge, approximately 10 cm from the cervical area.

Fetal membranes from spontaneous vaginal delivery at term were sampled from the rupture site after spontaneous rupture (=postlabour cervical membranes) and from the mid-zone area (see above).

Samples of amnion obtained from the cervical area weighed 30% more per cm^2 than mid-zone samples ($P < 0.05$). The water concentration was approximately 80%, highest at the postlabour cervical amnion and lowest value in the prelabour mid-zone amnion. However, no significant regional differences were found in the water concentration.

2.1.3. Preparation of biopsies

Samples of separated amniotic and chorio-decidual membranes were prepared from each placenta. Specimens of 1, 4 and 8 cm^2 were punched out from the regions mentioned above, using a cutting instrument of razor blades in parallel [5]. The samples were then briefly rinsed in phosphate-buffered saline (pH 7.4), and stored at −80 °C.

2.2. Analytical procedures

2.2.1. Collagen determination

Biopsies were extracted in 0.5 M HAc with 0.02 mg pepsin/ml buffer (Sigma P7012) 75 μl/mg tissue, and extracts as well as the unextractable fraction were hydrolysed and finally analysed for hydroxyproline according to Stegemann and Stalder [15]. Due to the presence of hydroxyproline in pepsin ([16] and Ida Vogel unpublished data), we measured the content in the batch of pepsin we used, and found it contained 2.8% hydroxyproline (1 mg pepsin ~28 μg hydroxyproline) and corrected our data with this value.

2.2.2. Proteoglycan determination

The biopsies were cut into pieces of 4 mm^2 and homogenised using a manual mortar and extracted in 4 M guanidinium chloride, containing 0.05 M acetate and proteinase inhibitors [8]. The proteoglycans were precipitated by alcian blue (WiesLab AB, Lund, Sweden). The pellet was resolved in guanidinium chloride-propanol and the concentration of proteoglycans estimated by the absorbance of alcian blue at 600 nm [17,18]. Electrophoresis and analysis of the gels were carried out according to our previous protocol [8].

2.2.3. Hyaluronan determination

An aliquot of the guanidinium extract was diluted 20 times in buffered urea (6 M urea, 0.05 M HAc, pH 5.8, complemented with 0.01 M EDTA, 0.005 M *N*-ethylmalemide and 5 μg/ml Ovalbumin). The fraction containing hyaluronan was eluted with 0.6 M acetic acetate in urea, pH 5.8 (complemented with 0.005 M NEM, 0.01 M EDTA and 5 μg/ml ovalbumin), on columns of DEAE-52 (0.5 × 0.7 cm). Hyaluronan was then quantitated using a radioimmunoassay (Amersham Pharmacia Biotech, Bucks, UK) [19].

2.3. Immunohistochemistry (decorin and biglycan)

Tissue preparation was performed according to our previous protocol [8]. In short, the tissue sections were digested with chondroitinase ABC (EC 4.2.2.4; Seikagaku Kogyo Co, Tokyo, Japan). The slides were then treated with 5% swine-serum before this was removed and replaced with a 1:200 dilution of rabbit polyclonal antibodies against human decorin (LF 51) and biglycan (LF 150) antibody (gifts from Dr. Larry Fisher, National Institute of Dental and Craniophacial Research, Bethesda, USA). The secondary antibody, swine-anti-rabbit (DAKO A/S, Glostrup, Denmark) was then added for 30 min. Reactivity was detected with avidin-biotin-vector red complex technique (Vector, Burlingame, CA). Negative control slides were incubated with BSA and no primary antibody.

2.4. Histochemistry (hyaluronan)

The fixation was done in 3% glutaraldehyde with 5% sucrose added [8]. The isolation and biotin labelling of the hyaluronan-binding protein (HABP) has been described in detail elsewhere [20]. Histostaining was performed using the avidin-biotin-peroxidase complex technique (VectaStain ABC kit, Vector,

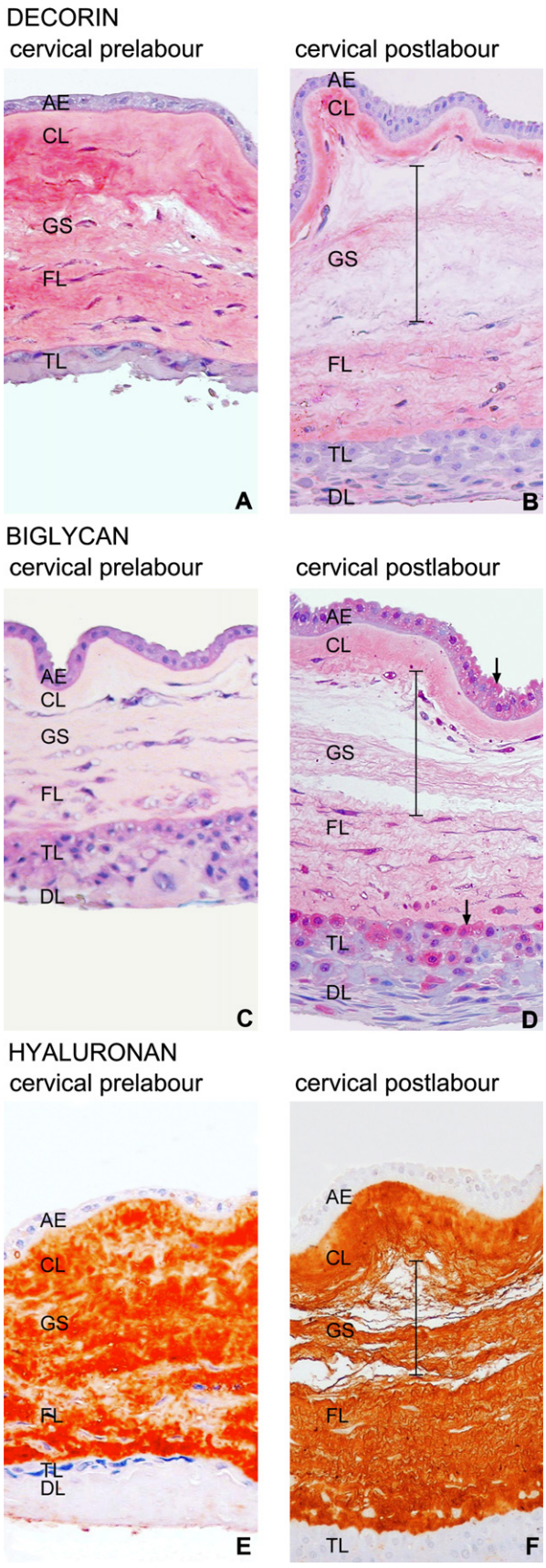

Fig. 1. Histostaining for hyaluronan and immunostaining for decorin and biglycan in prelabour and postlabor fetal membranes. A + B. Before delivery immunostaining for decorin (red) is intense in the collagen rich compact layer (CL) and fibroblastic chorion (FL). After delivery this staining is less intense. Staining of the gelatinous (GS) substance is weak C + D. Immunostaining for biglycan (red) is distinct in the vicinity of cells in the postlabour cervical membrane. E + F. Staining (brown) for hyaluronan is intense in the collagen rich compact layer (CL) and fibroblastic chorion (FL). The amniotic epithelium (AE) and the trophoblastic layer (TL) revealed no staining.

Burlingame, CA). Negative control slides were incubated with 50 units/ml Streptomyces hyaluronidase.

2.5. Statistical analysis

Wilcoxon signed rank tests were used in the comparisons between samples within the same patient groups. Comparisons between different patients groups were determined by Mann–Whitney Rank Sum Tests. Data are expressed as median (25 and 75 percentiles). The level of significance used was $P < 0.05$.

3. Results

3.1. Histology

Photomicrographs demonstrating the immunolocalization of decorin, hyaluronan, and biglycan are shown in Fig. 1. In all parts of the membranes decorin and hyaluronan co-localised with collagen (Fig. 1A,B,E,F), whereas biglycan appeared primarily in the vicinity of epithelial cells, trophoblasts and fibroblasts (Fig. 1C,D). Postlabour membranes exhibited decreased immunostaining for decorin (Fig. 1E,F).

3.2. Amnion, biochemical analysis

The main proteoglycan in the prelabour amnion was decorin. In the cervical amnion the concentration of biglycan was less than half the concentration of mid-zone amnion. (1.0 vs. 0.4 μg/mg, $P < 0.05$) (Table 1). There were no other regional differences in the prelabour membranes concerning hydroxyproline, decorin or hyaluronan.

3.3. Chorio-decidua, biochemical analysis

The main proteoglycan in the prelabour chorio-decidua was biglycan in the mid-zone area, whereas the cervical chorio-decidua tended to be richer in decorin (1.3 vs. 0.7 μg/mg) (Fig. 2 and Table 1) [8].

3.4. Postlabour membranes, biochemical analysis

Several significant changes in proteoglycans were observed; Biglycan was increased in mid-zone chorio-decidua samples (1.3 vs. 1.8 μg/mg, $P < 0.05$) and in cervical amnion (0.4 vs. 0.8 μg/mg, $P < 0.05$) (Table 1). In the cervical amnion, delivery induced a significant decrease in both decorin (Figs. 1 and 2) as well as hydroxyproline concentrations (Table 1).

3.5. Hyaluronan

The most striking effect of labour was a huge increase in hyaluronan (Table 1). This was observed in both mid-zone amniotic (1.0 vs. 4.9 μg/mg, $P < 0.05$) and chorio-decidual (0.7

Table 1
The concentration of decorin, biglycan and hyaluronan (μg/mg wet weight) and hydroxyproline (μg/mg dry weight) in amnion and chorion. Values are given as median (25 and 75 percentiles)

	Prelabour ($N = 9$)		Postlabour ($N = 11$)	
	Mid-zone membrane	Cervical membrane	Mid-zone membrane	Cervical membrane
Amnion				
Decorin	1.7 (1.6–2.1)	1.5 (1.3–1.8)	1.9 (1.5–2.3)	1.0 (0.9–1.3)†*
Biglycan	1.0 (0.7–1.4)	0.4 (0.3–0.5)†	0.8 (0.6–1.1)	0.8 (0.5–1.2)*
Hyaluronan	1.0 (0.8–5.8)	1.2 (1.1–3.1)	4.9 (3.8–7.1)*	2.9 (2.0–3.8)†
Hydroxyproline	47 (39–61)	52 (40–58)	61 (52–70)	42 (37–45)†
Chorio-decidua				
Decorin	1.0 (0.8–1.5)	1.3 (1.0–1.6)	0.8 (0.7–1.4)	1.2 (0.9–1.5)
Biglycan	1.3 (0.6–1.6)	0.7 (0.6–1.0)	1.8 (1.4–2.9)*	1.2 (0.9–1.5)
Hyaluronan	0.7 (0–1.8)	1.3 (0.8–1.6)	2.3 (1.9–3.2)*	2.0 (1.6–2.3)
Hydroxyproline	17 (14–24)	15 (5–16)	20 (14–22)	14 (8–19)†

*$P < 0.05$ (prelabour vs. postlabour).
†$P < 0.05$ (mid-zone vs. cervical membrane).

vs. 2.3 μg/mg, $P < 0.05$) samples. Macroscopically a ''gelatinous substance'' occurred between the amnion and the chorio-decidua. This gelatinous substance stained positively for hyaluronan (Fig. 1B,F, indicated by the line) and was not present in prelabour samples (Fig. 1A). Gelatinous substance isolated from 3 membranes after separation of amnion and chorio-decidua contained water (96%), hyaluronan (3 μg/mg wet weight), decorin (0.3 μg/mg wet weight), biglycan (0.1 μg/mg wet weight), and collagen (0.4 μg/mg wet weight) (Fig. 2, lane 9).

4. Comment

We show for the first time, that the initiation of labour induces biochemical changes at three levels within the fetal membranes. Primarily, an extraordinary increase in hyaluronan was observed in postlabour membranes. In the mid-zone membranes this increase was three-fold ($P < 0.05$). Hyaluronan increases the swelling pressure of the tissue thereby pressing the collagen fibres apart and decreasing the tensile strength [13]. The increased hyaluronan concentration may very well contribute to the decreased biomechanical strength in the amnion and the increased extensibility of both the amnion and chorio-decidua [2,3]. Most probably, the 38% increase in biglycan in chorio-decidua is also important, as biglycan interferes with the decorin-collagen interaction and disrupts the structural integrity of the tissue [21,22].

The second and most remarkable feature, however, is the formation of a hyaluronan-rich gelatinous substance between the amnion and the chorio-decidua. This induces a separation of chorio-decidua from amnion and as a result they are no longer able to work in parallel. Two publications on biomechanical properties of fetal membranes have demonstrated that such a separation of the two membranes results in significantly decreased biomechanical strength [2,3].

Lastly, at the cervical site a decrease in both decorin and collagen after delivery contributes to a further weakening of the membrane. This is of major importance as these components have strength bearing capacities. El Khwad et al. found vaginally delivered fetal membranes containing a weak zone overlying the cervix, which correlates well with our findings [5]. The thinning of the decidual layer at the cervical site supports our finding of low biglycan in this area both before and after labour, as biglycan appeared in the cellular layers [14,23].

In 1962 Bourne marked the membranes overlaying the cervix, defined as the cervical membranes, with dye through the internal os long before spontaneous rupture. Bourne thereby established that this area corresponds to the site of rupture [24]. This observation justifies the definition of postlabour cervical membranes to be the rupture site used in this study.

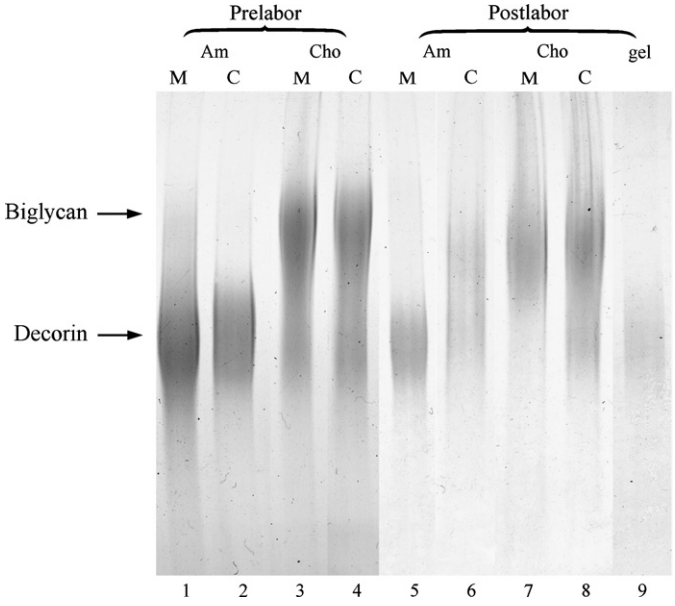

Fig. 2. Decorin and biglycan in two fetal membranes (one prelabour and one postlabour). The two proteoglycans were precipitated by alcian blue and separated on SDS-PAGE gradient gel (4–12%). Small proteoglycans (PGS) from bovine sclera were used as standard [5] (not shown). *Lane 1*, midway amnion, prelabour; *Lane 2*, cervical amnion, prelabour; *Lane 3*, midway chorio-decidua, prelabour; *Lane 4*, cervical chorio-decidua, prelabour; *Lane 5*, midway amnion, postlabour; *Lane 6*, cervical amnion, postlabour; *Lane 7*, midway chorio-decidua, postlabour; *Lane 8*, cervical chorio-decidua, postlabour; *Lane 9*, spongy layer with gelatinous substance, postlabour.

Our findings correspond well with increased concentrations of leukocyte elastase and MMP-9 found at the cervical site. These cytokines are known to degrade collagen and decorin [5,7,25].

TGF-β is secreted by trophoblasts in the chorio-decidua (Fig. 2) or by infiltrating leukocytes that are seen in the decidua [26]. TGF-β selectively stimulates hyaluronan and biglycan and may play a role in the remodelling [27,28]. Biglycan have binding sites for TGF-β, which may also be of interest in regulation of this cytokine.

The remodelling of the fetal membranes during labour is comparable with the well-described ripening process that takes place in the human cervix during labour. These tissues are closely related and may be involved in a common signalling pathway together with the fetus. The cervical ripening process is associated with increased collagenase, increased proteoglycan turnover, decrease in the synthesis of decorin and increased synthesis of the large proteoglycan versican [29,30]. The cervical ripening is an inflammatory process involving a tremendous increase in cytokines, IL-6, IL-8, GCS-F (granulocyte colony stimulating factor) and TGF-β [31]. The final rapid remodelling in the fetal membranes mimics the remodelling process in the cervix concerning the decrease in decorin, whereas no increases in large proteoglycans were found [29].

Greater knowledge of fetal membrane remodelling is important for our efforts to find out whether fetal membranes are involved in dynamic processes during pregnancy and parturition.

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