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Gestational Tissue Inflammatory Biomarkers at Term Labor: A Systematic Review of Literature

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Abstract

Parturition at term is characterized by inflammatory overload in both feto-maternal tissues. Despite the large number of individual studies on changes in inflammatory biomarkers linked to labor, a comprehensive profile of them in each of the uterine compartments is not available to better understand their mechanistic contributions to labor. This systematic review investigated the pro- and anti-inflammatory biomarkers reported in intrauterine tissues (amnion, chorion, decidua, placenta and myometrium) at term labor. We conducted a systematic review of studies on pro and antiinflammatory biomarkers (mRNA and/or protein) reported in feto-maternal tissues during normal human term labor, published in English (1980–2016), in three electronic data bases. From a total of 3,712 citations, 172 were included for final review. Each tissue expresses a unique set of biomarkers at the time of term labor, but there is significant overlap between tissues. All tissues had IL-6, IL-8, IL-1 β , COX-2, PGE-2, TNF- α , and hCAP18 in common at term labor. Common and unique inflammatory biomarkers are expressed in various feto-maternal compartments at term labor. Increase in proinflammatory markers in all gestational tissue signifies their harmonious functional role in promoting labor. Antiinflammatory markers at term labor are hardly reported.

Keywords

inflammation; term birth; pregnancy; myometrium; placenta; fetal membranes; decidua; systematic review

Introduction

Normal term parturition in human is initiated when fetal organ systems reach maturity around 37 – 40 weeks' gestation. Conventional theories of initiation signaling of parturition are primarily linked to feto-maternal endocrine and immune changes in the intra uterine cavity correlating with fetal growth and development.¹ Recently, we have reported fetal tissue senescence, correlated with fetal growth generating sterile inflammatory markers that

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can be propagated as paracrine fetal signals associated with parturition.² Homeostatic imbalances produced by both endocrine and paracrine factors produce an inflammatory overload that disrupts the maintenance of pregnancy. These signals transition a quiescent myometrium into an active status. Nonetheless, the profile of these signals, whether fetal or maternal derived, and their precise mechanism in initiating parturition are still unclear.

Understanding these signals and their mechanisms in normal term pregnancies can provide insights into pathologic activation of signals that can induce spontaneous preterm labor. Inflammatory overload of various uterine tissues has been associated with preterm labor.³ This inflammation is either infectious due to microbial invasion or sterile in the absence of microbes.⁴ Infection is well-documented to be involved in preterm labor, but the majority of preterm labor is associated with sterile inflammation.⁵ Both infectious and sterile inflammation share similar biochemical profile and are associated with an increased pro-inflammatory load though the amount and type of cytokines present differ.³ Similarly, term parturition is also linked to sterile inflammation with similar biomarkers seen in various fetal and maternal biologic fluids.² Although differences may exist in the initiators of term and preterm parturition, similarities in the biomarkers suggest inflammation still drives the final effector pathway resulting in labor and delivery. Inflammation is contributed by both fetal and maternal tissues but the precise contributions of any of the uterine tissue is still unclear.^{6,7} The lack of reliable biomarkers to predict eminent labor either at term or preterm also suggests the need for a better understanding of inflammatory profile reported so far. Understanding the differences in the inflammatory biomarkers produced by each uterine tissue is expected to help us to better understand tissue specific contributions to the overall load of inflammation as well as their unique inflammatory status during labor.

Our primary objective was to review the literature to identify biomarkers reported to be different at the time of normal term labor compared to term not in labor status in different gestational compartments, specifically, fetal membranes (amnion and chorion), placenta, decidua and myometrium.

Methods

The systematic review was conducted according to the recommendations of the MOOSE group and reported in accordance with the PRISMA Statement.^{8,9} This systematic review was registered in PROSPERO (registration number CRD42015029470).

Search methods for identification of studies

We performed a search for studies published from 1980-December 2016, in English, indexed in the following electronic databases: Medline, Embase (via Ovid), Web of Science, and Cumulative Index to Nursing and Allied Health Literature (CINAHL)

The search strategy was developed with the assistance of a librarian team experienced in systematic reviews. The search strived to identify studies that provided information on inflammatory biomarker signature of intrauterine compartments (fetal membranes, decidua, placenta and myometrium) in healthy women at term, in labor and not in labor. The main key words, adapted to each search were: inflammation, term birth, term parturition,

pregnancy, myometrium, placenta, fetal membranes, and decidua (See Appendix 1 for full details of the search).

Selection criteria

Types of studies—We included original studies on inflammatory biomarkers in human tissues of pregnancies at term (gestational age ≥ 37 weeks), of women in labor or not in labor. Studies using other models, including animal models and infectious models, of pregnancy were excluded. Studies were excluded if they focused exclusively on amniotic fluid samples, preterm labor, women with clinical signs of inflammation (fever, elevated C-reactive protein, foul smelling vaginal discharge, uterine tenderness) or with histologic signs of chorioamnionitis (presence of >3 –4 polymorphonuclear leukocytes in the membranes). We excluded studies that did not provide adequate descriptions of biochemical measurements, review articles, and those that were published only as abstracts (e.g. congress presentations).

Types of participants—We included studies that collected samples from healthy women of any age, parity or ethnicity, at full term gestation (≥ 37 weeks) who were either in labor or not in labor at the time of specimen collection for assay and analysis. We excluded studies that enrolled only women with preterm labor and delivery (both spontaneous and induced) or with chorioamnionitis. Studies that utilized cell lines from the gestational tissues of interest were also included.

Types of outcome measures—In this study, a biomarker is defined as physiologic or pathophysiologic biochemical or bio-molecular alterations at the organ, tissue, cell or sub-cellular level in response to an exposure that are measurable in biological samples and or in cell and tissue culture supernatants in an *in vitro* study that can become the signature of the onset of phenotypic outcome (i.e. term labor or term not in labor). We included studies that reported on the changes in biomarkers at the time of term labor as long as the outcome was related to term labor not complicated by chorioamnionitis. In addition, we also included studies reporting biomarker changes *in vitro*, in culture environment from normal term tissues collected at term (labor vs not in labor).

Types of biomarker assessment—Studies that assessed inflammation related (pro and anti-inflammatory) biomarker levels for protein or RNA were included in the review.

Data collection and analysis

Selection of studies—All citations retrieved through the search strategy were downloaded to a common file and duplicates were excluded. Two authors (E.H. and L.R.) independently screened the title and abstracts of all unique citations and selected those that were potentially relevant for full text reading. The studies that fulfilled the aforementioned selection criteria were included in the review.

Data extraction—A specific data extraction form was created for this study to collect the following information: study identification (author, year and journal of publication), biomarker(s), assay type, gestational tissue studied, and the findings and or phenotype. Two authors (E.H. and L.S.R.) independently extracted data from the studies, compared their

findings, resolved disagreements through discussion and produced a single final form for each included study.

Quality assessment—There were no well validated quality assessment tools available for basic science research at the time of this review. Therefore, we developed a quality assessment tool, which was adapted from another quality assessment tool¹⁰ to rate the quality as low, acceptable, or high (Table 1). We assessed each included study for the value of the hypothesis, the strength of study design (description of population studied, inclusion/exclusion criteria, definition of phenotype studied), description of samples (collection, processing, storage) and reagents used, the details of the methods section that will allow replication and reproducibility of data, number of repeat experiments, use of controls, appropriate use of statistical tests, sufficient explanation of results and if the results support the conclusions.

Data synthesis

We present data from each study in a descriptive format and created a table with all the inflammatory biomarker phenotypes of term labor in each gestational tissue compartment. We then identified the biomarkers that overlap between the compartments to produce a list of the biomarkers common and unique to each of the gestational tissue compartments at the time of term labor.

Results

The electronic search yielded 3807 citations, which were reduced to 3712 after the exclusion of duplicates. After title and abstract screening, 3535 citations were excluded and 177 were selected for full text reading. An additional 5 studies were excluded after a full text review (Table 2). A total of 172 studies fulfilled the selection criteria and were included in the review and data analysis (Figure 1).

Main characteristics of studies

The main characteristics and findings of the included studies are summarized in Appendix Table 2. Studies (N=172) were conducted by researchers from many different institutions around the globe but predominantly from North America (33%; N=57), Western Europe (31%; N=54), Australia/New Zealand (20%; N=35) and Asia (13%; N=22). Studies included investigated term labor or simulated *in vitro* term labor in either the amnion (62%; N=106), chorion (56%; N=96), decidua (47%; N=81), placenta (23%; N=40) or myometrium (31%; N=53) and various combinations of the gestational tissues (Table 3).

Methods used for biomarker determination

Biomarker measurements were undertaken by investigators using various techniques including but not limited to: western blot (36%; N=62), enzyme linked immunosorbent assay (ELISA) (34%; N=58), radioimmunoassay (RIA) (26%; N=37), reverse transcriptase polymerase chain reaction (PCR) (47%; N=80), immunostaining (histochemistry or cytochemistry) (41%; N=70), in situ hybridization (8%; N=13), Northern blot (10%; N=17), gel zymography (6%; N=11), and electrophoretic mobility shift assay (EMSA) (2%; N=5).

Main findings

The number of participants (number of samples or subjects) per study ranged from 1–88; most studies included >10 healthy women at term. The number of women studied in term labor ranged from 1–44, with an average of 10; the number of women at term not in labor ranged from 3–44, with an average of 10.

The majority of included studies reported on more than one tissue, biomarker and assay types. As shown in Table 3, we found 106 studies that reported on amnion, 96 on chorion, 81 on decidua, 40 on placenta, and 53 on myometrium. Clinical specimens (specimens collected and processed right after delivery and assayed for markers) constituted 280 of our data points whereas 175 were based on *in vitro* culture based analysis. In the latter group, tissues were collected after normal term in labor and/or term not in labor deliveries, and biomarkers produced were assayed (for protein or mRNA) after culturing them *in vitro*.

Table 4 shows a comprehensive list of the biomarkers reported by each tissues type. The combination of biomarkers is unique to each tissue type but there is significant overlap between various tissues, which is further depicted in a VENN diagram (Figure 2). Seven biomarkers were found to be common to all tissues at the time of term labor and they include interleukin (IL)-6, IL-8, IL-1 β , cyclooxygenase-2 (COX-2), prostaglandin E₂ (PGE₂), tumor necrosis factor (TNF)- α , and human cathelicidin 18 (hCAP18).

Quality Assessment

Based on the quality assessment tool that we developed (Table 1), 121 articles (70%) were graded as being of high quality, 46 (27%) of acceptable quality and 5 (3%) of low quality (Figure 3). The domains with the lowest quality scores were having an appropriate sample size for internal validity and replicability of study. The domains with the highest quality scores were in sufficiently describing the question/objective and having results, which support the conclusion.

In summary, we identified a unique set of biomarker in each individual compartment as well as biomarkers that are common to all compartments at the time of term labor.

Discussion

Increased inflammatory load in gestational tissues is a major contributor to events culminating in human parturition.^{3,5} Although, several reports have identified various inflammatory biomarkers associated with normal term parturition, the contribution of biomarkers by each uterine tissue is not completely clear. A comprehensive profile is expected to provide a better understanding of tissue specific biomarkers as well as biomarkers that are commonly produced by each tissue. Understanding the functional role of biomarkers producing parturition-associated changes in each tissue will help to understand their mechanistic contributions.

After an extensive review of the literature, we identified unique phenotypes of inflammation in each gestational tissue at the time of term labor compared to term not in labor status of these tissues. Our review identified those inflammatory biomarkers common among all

gestational tissue at term labor. The included studies report that in healthy women at term in labor, the amnion, chorion, placenta, decidua and myometrium increase the production of seven proinflammatory cytokines, IL-6, IL-8, IL-1 β , TNF- α , COX-2, PGE₂, and hCAP18, in comparison to healthy women at term not in labor. Their synergistic increase in all tissues validates their reported functional roles as uterotons. These common biomarkers should be the focus of future investigations of labor at term. We expect that this information can fill a major knowledge gap in the literature and assist future research based on the biomarker profiles of different gestational tissues. Determination of functional contributions by various biomarkers in any of the compartment was beyond the scope of this review. However, the seven common biomarkers present in all gestational tissues at the time of term labor are in general pro-inflammatory mediators.

IL-6 is a well-studied inflammatory cytokine documented to present with intra-uterine infection,^{11,12,13} preterm labor,¹⁴ and term labor.² In our review, of the 27 articles that reported on IL-6, 13 articles reported on IL-6 protein, 12 reported on IL-6 mRNA and 2 that reported on both protein and mRNA in various gestational tissues. An increase in IL-6 protein was reported in all gestational tissues at the time of term labor or after *in vitro* stimulation.^{7, 11, 15,16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26} There was also an increase in IL-6 mRNA in all the gestational tissues investigated at term labor or not in labor tissues placed in an *in vitro* organ explant environment where labor was induced by various agents.^{15, 18, 19, 27–37} However, discrepancies were reported in IL-6 concentrations in term labor placenta. Both Keelan et al 1999 and Gunn et al. 1996 reported no change in IL-6 protein levels in labor placenta.^{7,16} Whereas Zhou et al. 2015 found an increase in IL-6 protein in placenta at preterm and term labor.²⁶ Yadav et al. 2014 saw an increase in IL-6, amongst other labor cytokines, in placental explants after treatment with surfactant protein-D, a secretory collection protein important in immunomodulation.²³ Steinborn et al. 1998 also saw an increase in IL-6 production from villous trophoblasts in labor.²¹ Pasetto et al. 1993 also reported contradictory results, finding that there was no change in IL-6 protein levels in term labor fetal membranes and decidua.³⁸ Simpson et al. 1999 also found that IL-6 protein level did not increase in amnion explants after labor, but that IL-6 protein did increase after stimulation with IL-1 β , TNF- α , and LPS.³⁹ Fortunato et al. 1996 showed that amniochorion from term not in labor membranes has minimal IL-6 expression, but was inducible after treatment with LPS.⁴⁰ Taking into account all the included articles, it appears that IL-6 is cytokine common to all gestational tissues at the time of term labor and its functional role is difficult to assess. It is likely that IL-6 functions as a biomarker of overall and nonspecific inflammation and not necessarily indicative of an underlying mechanism.

The discrepancy in data are due to multiple facts; *in vitro* data are often generated using not in labor tissues in culture stimulated with specific stimulants that not always mimic normal labor associated signals, but often resemble infectious or other risk associated stimuli associated with preterm labor. Discrepancy among *in vitro* data may suggest differences in stimuli (various types of LPS, SP-D, Poly-IC, cigarette smoke etc.), their doses, region of tissue sample (e.g. mid zone membrane vs membrane laying over cervix, cytotrophoblast vs syncytiotrophoblast) being processed and *in vitro* conditions (oxygen, presence of endocrine mediators, dose of fetal bovine serum and other growth factors) among other variables. *In vitro*, the interaction between tissue layers are often lost and this can produce distinct

changes in data. Additionally, assay and analytical approaches have changed during the course of these publications. Assays reported in literature from the 2000s are likely more accurate as more specific and sensitive assays are available now as compared to the late 1980s and early 1990s.

IL-8 is another well-known inflammatory cytokine which is known to have chemotactic properties.^{41, 42, 43, 44} Our review yielded 33 articles which reported on IL-8; 9 of the articles reported on IL-8 protein, 18 on IL-8 mRNA levels, and 6 reported on both protein and mRNA. The majority of articles found that term labor or *in vitro* agents that mimic labor was associated with increased IL-8 protein in all gestational tissues investigated.

7, 17, 18, 23, 24, 25, 41, 42, 45, 46, 47, 48, 49 Increased IL-8 mRNA was also seen in term labor tissues and *in vitro* labor experiments.

18, 19, 28, 29, 30, 31, 32, 34, 35, 37, 42, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55 There were some contradictory findings to the conclusions above. Keelan et al. 1999 found that there was no change in IL-8 protein in the placenta⁶ and Kelly et al. 1992 found no change in IL-8 protein levels in choriodecidua after labor onset.⁵⁴ Laham et al 1999 saw no change in IL-8 mRNA in amnion, chorion, decidua or placental explants between non labor and labor samples.⁵⁵ Based on the overall findings, we conclude that IL-8 levels are increased in gestational tissues at term labor. The discrepancies reported in IL-6 literature may apply for IL-8 and all other cytokine reporting as well.

TNF- α is an inflammatory cytokine commonly increased at the time of infection and is known to increase prostaglandin production in gestational tissues^{50, 58} and can activate the NF- κ B signaling pathway.⁵⁹ Our review found 13 articles that reported on TNF- α . Five articles reported on TNF- α protein, 5 reported on mRNA production, and 3 reported on both protein and mRNA productions from term labor tissues or simulated *in vitro* labor. The overall consensus was an increase in TNF- α protein.^{23, 25, 46, 59, 60, 61} and an increase in TNF- α mRNA^{27, 28, 33, 55, 58, 60, 61} at the time of term labor or when labor was simulated *in vitro*. Interestingly, Alexander et al. 2012 found that TNF- α 1A receptor mRNA increases in the myometrium with labor.⁵⁰ Sato et al. 2003 showed that TNF- α protein was increased in choriodecidua explants after treatment with LPS and that TNF- α induced production of IL-1 β , PGE2 and IL-10 from the explants.⁶²

Prostaglandin E₂ (PGE₂) is a common prostaglandin present at the time of term labor, which contributes to uterotonic effects and cervical ripening.^{63, 64} We found 28 articles that reported on PGE₂ in our gestational tissues of interest. There were 28 articles that reported on PGE₂ protein levels. The majority of articles reviewed found an increase in PGE₂ protein at term labor or with *in vitro* simulated labor.

21, 30, 36, 39, 62, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83

There were a few incongruent findings for PGE₂. Lopez-Bernal et al. 1987 found that PGE₂ was produced by chorion and decidual cells and that the production was increased by arachidonic acid treatment, but found no significant change in PGE₂ protein level in labor versus no labor⁷³. Similarly, Satoh et al. 1981 found that the PGE₂ protein production was the same between labor and non-labor amnion, decidua, and myometrium.⁸⁴ McCoshen et al. 1987 also found that in fetal membranes after labor there was increased PGE₂ protein

release on the fetal side, but decreased on the maternal side.⁸⁵ Skinner et al. 1985 found no change in PGE2 protein in the chorion with labor⁷⁸, while So et al. 1992 found that PGE2 protein increased with stimulation from TNF- α .⁷⁹ These contradictory studies are from the 1980s and thus the bioassays may not have high sensitivity compared to reports in more recent years. Taking all the included studies into consideration it appears that PGE₂ is increased with term labor in the gestational tissues studied.

IL-1 β is an inflammatory mediator that can induce the production of other pro-labor mediators.^{22, 60, 62, 86} IL-1 β promotes adhesion of white blood cells by increasing expression of adhesion molecules.²⁵ Our review found 19 articles that reported on IL-1 β . 6 articles reported on IL-1 β mRNA, 11 reported on IL-1 β protein, and 2 reported both protein and mRNA results. The majority of the included papers confirmed an increase in IL-1 β protein levels with term labor and *in vitro* in response to agents that will mimic labor.^{7, 24, 25, 39, 46, 62, 70, 86, 87} The majority of the articles also confirmed an increase in IL-1 β mRNA during term labor or *in vitro* labor.^{28, 33, 34, 35, 37, 86, 87}

The results for the response of IL-1 β in the placenta at the time of labor was varied. Keelan et al. 1999 found that there was no significant change in IL-1 β protein levels with labor in the placenta⁶ and Mitchell et al 2012 reported no stimulation of IL-1 β production from placental explants after treatment with LPS.⁸⁶ While Turner et al 2002 found that there was no difference in the production of IL-1 β protein by placental fragments from term labor and not in labor, but placental IL-1 β production was more sensitive to stimulation with TNF- α after labor.²¹ Yadav et al. 2014 also found an increased production of IL-1 β by placental explants after treatment with SP-D.²² In general, it appears that IL-1 β is a pro-labor biomarker in all the tissues evaluated in this review, but its utility as a marker in the placenta may be more limited.

COX-2 is a cyclooxygenase that is involved in prostaglandin production.^{89, 90} We reviewed 28 articles that reported on COX-2. Of these articles, 9 reported on COX-2 protein, 14 reported on COX-2 mRNA, and 5 reported on both protein and mRNA at term labor or *in vitro* term labor. The majority of articles identified an increase in COX-2 protein^{37, 59, 64, 65, 76, 89, 90, 91, 92, 93, 94, 95, 96} and an increase in COX-2 mRNA at the time of term labor or when labor was simulated *in vitro*.^{19, 30, 34, 64, 65, 76, 81, 95, 97, 98, 99, 100, 101, 102, 103, 104, 105}

There were some findings that conflicted with the majority of reports. Dunn-Albanese et al. 2004 found that COX-2 staining was rare in the placenta while it was prominent in the membranes especially the amnion.⁹⁴ Fuentes et al. 1996 found that COX-2 protein did not increase in the decidua with labor.⁹⁰ Zuo et al. 1994 found that COX-2 mRNA and protein were present in term myometrium prior to labor, and their levels decreased after labor.⁸³ Johansen et al. 2000 found that COX-2 mRNA was present in amnion, chorion, and placenta with labor but COX-2 mRNA was not seen in chorion cell lines.¹⁰⁰ Another interesting finding by Sparey et al. 1999 showed that COX-2 was higher in the lower myometrium than the upper in labor, which may reflect the role of COX-2 in the production of prostaglandins to ripen the cervix.¹⁰⁶

Human cationic antimicrobial peptide 18 (hCAP-18) is a cationic host defense peptide which had immunomodulatory properties. hCAP18 is a cathelicidin which is commonly found at sites of inflammation and protects against bacteria by inducing cytokine release and chemotaxis (29Lim 2015).²⁹ We reviewed 1 article that reported on hCAP18 by Lim et al. in 2015 that found an increase in hCAP18 protein with term labor fetal membranes, cytotrophoblast, and myometrium. They also found that treatment of membranes and myometrium with hCAP18 lead to an increase in IL-6 and TNF- α .²⁹ There is a paucity of articles about hCAP18 and it seems prudent to investigate hCAP18's role in parturition further as it is reported in all term samples.

It is interesting to note that all the common biomarkers reported in all tissues reported here are pro-inflammatory type and no common anti-inflammatory (e.g. IL-2, IL-4, IL-10, and TGF- β) biomarkers have been reported. Several anti-inflammatory cytokines and growth factors have been associated with normal parturition. This is likely not due to lack of common anti-inflammatory markers in these tissues but demonstrates a generalized bias towards examination of pro-inflammatory factors. We speculate that a balance between pro- and anti-inflammatory cytokines is essential to maintain pregnancy. Higher loads of common pro-inflammatory biomarkers in all gestational tissues signifies their harmonious functional role in promoting parturition. The biomarkers that are unique to each of the compartments have their own tissue specific functions, which may or may not be linked to parturition but linked to maintenance of pregnancy.

In summary, our extensive review of the literature on biomarkers of term labor identified a unique biomarker profile in all gestational tissues. Synthesis of this knowledge will serve to help future research in many ways. Feto-maternal signals that can increase these common markers or promote their imbalance can be the focus of future studies to better understand the mechanisms initiating human parturition. Similarly, understanding the functional role of unique markers in each of the tissues during pregnancy and in preparing for parturition will be of significant value.

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Appendix 1: Search Strategy

Medline and Embase via Ovid Search Strategy

ID #	Search	Results
1	exp labor, obstetric/or exp cervical ripening/or exp labor onset/or exp labor stage, first/or exp labor stage, second/or exp labor stage, third/or exp labor presentation/or exp breech presentation/or exp "trial of labor"/or exp uterine contraction/	46744
2	exp Parturition/	15045

ID #	Search	Results
3	(Childbirth* or child birth* or birth or births or parturition*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	360140
4	((cervix or cervical) adj2 ripen\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	2145
5	((uterus or uteri or uterine) adj2 contraction*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10308
6	(labor or labors or laboring or labour or labours or labouring).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	140637
7	transition to labor.mp.	8
8	quiescen*.mp.	29114
9	exp Pregnancy/or pregnancy.mp.	957949
10	uterus.mp. or exp Uterus/	152160
11	9 or 10	1050177
12	8 and 11	1207
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 12	474206
14	((inflamm* adj2 biomarker*) or (inflamm* adj2 mediator*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	61221
15	(pro-inflamm* or proinflamm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	110289
16	(Biomarker* or bio-marker* or viral marker* or ((immune* or immunologic* or biologic*) adj marker*) or laboratory marker* or ((endpoint* or end point* or marker) adj surrogate*) or biochemical marker* or clinical marker*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	485123
17	((inflamm* adj2 process*) or proinflamm* or pro-inflamm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	141528
18	exp interleukin-1beta/or exp interleukin-6/or exp interleukin-8/	91955
19	(il-1beta or interleukin 1 beta or il-6 or interleukin 6 or il-8 or interleukin 8).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	181473
20	exp Leukocytes/	777542
21	leukocyt*.mp.	295119
22	exp Cytokines/	701486
23	exp Prostaglandins/	105625
24	(cytokine* or prostaglandin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	506488
25	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	2073691
26	13 and 25	28407
27	limit 26 to english language	26014
28	Animals/	6799094
29	27 not 28	17222

ID #	Search	Results
30	(Cat or cats or feline or cattle or cow or cows or bovine or dog or dogs or canine or goat or goats or guinea pig* or pig or pigs or swine or porcine or horse or horses or equine or mare or mares or hamster* or gerbil* or rabbit* or mouse or mice or rodent* or sheep or animal*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7261208
31	29 not 30	16570
32	exp Amnion/	9074
33	exp Chorion/	8131
34	(amnion* or chorion* or amnio-chorion* or amniochorion* or (fetal adj2 membrane*) or (membrane* adj2 fetus)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	71606
35	exp Decidua/	5831
36	(decidua or deciduas or deciduum or decidual or (deciduous adj2 membrane*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	10145
37	exp Myometrium/	7563
38	(Myometrium* or uterine muscle* or (uterus adj2 muscle*) or (uterine adj2 myocyte*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	12849
39	32 or 33 or 34 or 35 or 36 or 37 or 38	91620
40	31 and 39	2285
41	limit 40 to yr="1980 -Current"	2158
42	remove duplicates from 41	1944
43	(serum adj3 marker*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	14827
44	42 not 43	1907

CINAHL Search Strategy

ID #	Search
S1	(MH "Labor+") OR (MH "Cervix Dilatation and Effacement") OR (MH "Labor Stages+") OR (MH "Labor Stage, First") OR (MH "Labor Stage, Second") OR (MH "Labor Stage, Third") OR (MH "Uterine Contraction") OR (MH "Labor Presentation+") OR (MH "Breech Presentation")
S2	childbirth* or child birth* or birth or births or parturition*
S3	(cervix or cervical) N2 ripen*
S4	(uterus or uteri or uterine) N2 contraction*
S5	labor or labors or laboring or labour or labours or labouring
S6	transition to labor
S7	quiescen*
S8	(MH "Pregnancy+") OR "pregnancy"
S9	(MH "Uterus+") OR "uterus"
S10	S8 OR S9
S11	S7 AND S10
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S11

ID #	Search
S13	(inflamm* N2 biomarker*) or (inflamm* N2 mediator*)
S14	pro-inflamm* or proinflamm*
S15	biomarker* or bio-marker* or viral marker* or ((immune* or immunologic* or biologic*) N2 marker*) or laboratory marker* or ((endpoint* or end point* or marker*) N2 surrogate*) or biochemical marker* or clinical marker*
S16	(inflamm* N2 process*) or proinflamm* or pro-inflamm*
S17	il-1 beta or interleukin 1 beta or il-6 or interleukin 6 or il-8 or interleukin 8
S18	(MH "Leukocytes+")
S19	leukocyt*
S20	(MH "Cytokines+")
S21	(MH "Prostaglandins+")
S22	cytokine* or prostaglandin*
S23	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22
S24	S12 AND S23
S25	S12 AND S23
S26	(MH "Animals+")
S27	S25 NOT S26
S28	cat or cats or feline or felines or cattle or cow or cows or bovine* or dog or dogs or canine or canines or goat or goats or guinea pig* or pig or pigs or swine or porcine or horse or horses or equine* or mare or mares or hamster* or gerbil* or rabbit* or mouse or mice or rodent* or sheep or animal*
S29	S27 not S28
S30	(MH "Amnion")
S31	(MH "Chorion")
S32	amnion* or chorion* or amnio-chorion* or amniochorion* or (fetal N2 membrane*) or (membrane* N2 fetus)
S33	decidua or deciduas or deciduum or decidual or (deciduous N2 membrane*)
S34	(MH "Myometrium")
S35	myometrium* or uterine muscle* or (uterus N2 muscle*) or (uterine N2 myocyte*)
S36	S30 OR S31 OR S32 OR S33 OR S34 OR S35
S37	S29 AND S36
S38	serum N3 marker*
S39	S37 not S38

Web of Science Search Strategy

ID #	Search
#35	#33 NOT #34
	<i>DocType=All document types; Language=All languages;</i>
#34	TOPIC: (serum NEAR/3 marker*)
	<i>DocType=All document types; Language=All languages;</i>
#33	#32
	<i>DocType=All document types; Language=All languages;</i>

ID #	Search
#32	#31 AND #26
	<i>DocType=All document types; Language=All languages;</i>
#31	#30 OR #29 OR #28 OR #27
	<i>DocType=All document types; Language=All languages;</i>
#30	TOPIC: (myometrium*) <i>OR TOPIC:</i> (uterine muscle*) <i>OR TOPIC:</i> (uterus NEAR/2 muscle*) <i>OR TOPIC:</i> (uterine NEAR/2 myocyte*)
	<i>DocType=All document types; Language=All languages;</i>
#29	TOPIC: (decidua) <i>OR TOPIC:</i> (deciduas) <i>OR TOPIC:</i> (deciduum) <i>OR TOPIC:</i> (decidual) <i>OR TOPIC:</i> (deciduous NEAR/2 membrane*)
	<i>DocType=All document types; Language=All languages;</i>
#28	TOPIC: (fetal NEAR/2 membrane*) <i>OR TOPIC:</i> (membrane* NEAR/2 fetus)
	<i>DocType=All document types; Language=All languages;</i>
#27	TOPIC: (amnion*) <i>OR TOPIC:</i> (chorion*) <i>OR TOPIC:</i> (amnio-chorion*) <i>OR TOPIC:</i> (amniochorion*)
	<i>DocType=All document types; Language=All languages;</i>
#26	#22 NOT #25
	<i>DocType=All document types; Language=All languages;</i>
#25	#24 OR #23
	<i>DocType=All document types; Language=All languages;</i>
#24	TS=(gerbil*) <i>OR TS=(rabbit*) OR TS=(mouse) OR TS=(mice) OR TS=(rodent) OR TS=(rodents) OR TS=(sheep)</i>
	<i>DocType=All document types; Language=All languages;</i>
#23	TOPIC: (animal*) <i>OR TOPIC:</i> (cat) <i>OR TOPIC:</i> (cats) <i>OR TOPIC:</i> (feline*) <i>OR TOPIC:</i> (cattle) <i>OR TOPIC:</i> (cows) <i>OR TOPIC:</i> (cows) <i>OR TOPIC:</i> (bovine*) <i>OR TOPIC:</i> (dog) <i>OR TOPIC:</i> (dogs) <i>OR TOPIC:</i> (canine) <i>OR TOPIC:</i> (canines) <i>OR TOPIC:</i> (goat) <i>OR TOPIC:</i> (goats) <i>OR TOPIC:</i> (guinea pig*) <i>OR TOPIC:</i> (pig*) <i>OR TOPIC:</i> (pigs) <i>OR TOPIC:</i> (swine) <i>OR TOPIC:</i> (porcine) <i>OR TOPIC:</i> (horse) <i>OR TOPIC:</i> (horses) <i>OR TOPIC:</i> (equine*) <i>OR TOPIC:</i> (mare) <i>OR TOPIC:</i> (mares) <i>OR TOPIC:</i> (hamster*)
	<i>DocType=All document types; Language=All languages;</i>
#22	#20 AND #9
	Refined by: LANGUAGES: (ENGLISH)
	<i>DocType=All document types; Language=All languages;</i>
#21	#20 AND #9
	<i>DocType=All document types; Language=All languages;</i>
#20	#19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10
	<i>DocType=All document types; Language=All languages;</i>
#19	TOPIC: (leukocyt*) <i>OR TOPIC:</i> (cytokine*) <i>OR TOPIC:</i> (prostaglandin*)
	<i>DocType=All document types; Language=All languages;</i>
#18	TOPIC: (interleukin-1 beta) <i>OR TOPIC:</i> (interleukin-6) <i>OR TOPIC:</i> (interleukin-8) <i>OR TOPIC:</i> (il-1 beta) <i>OR TOPIC:</i> (il-6) <i>OR TOPIC:</i> (il-8)
	<i>DocType=All document types; Language=All languages;</i>
#17	TOPIC: (inflamm* NEAR/2 process*)
	<i>DocType=All document types; Language=All languages;</i>
#16	TOPIC: (marker* NEAR/2 surrogate*)

ID #	Search
	<i>DocType=All document types; Language=All languages;</i>
#15	TOPIC: (end NEAR/2 point* NEAR/2 surrogate*) <i>DocType=All document types; Language=All languages;</i>
#14	TOPIC: (endpoint* NEAR/2 surrogate*) <i>DocType=All document types; Language=All languages;</i>
#13	TOPIC: (immune* NEAR/2 marker*) <i>OR</i> TOPIC: (immunologic* NEAR/2 marker*) <i>OR</i> TOPIC: (biologic* NEAR/2 marker*) <i>DocType=All document types; Language=All languages;</i>
#12	TOPIC: (biomarker*) <i>OR</i> TOPIC: (bio-marker*) <i>OR</i> TOPIC: (viral marker*) <i>OR</i> TOPIC: (laboratory marker*) <i>OR</i> TOPIC: (biochemical marker*) <i>OR</i> TOPIC: (clinical marker*) <i>DocType=All document types; Language=All languages;</i>
#11	TOPIC: (pro-inflamm*) <i>OR</i> TOPIC: (proinflamm*) <i>DocType=All document types; Language=All languages;</i>
#10	TOPIC: (inflamm* NEAR/2 biomarker*) <i>OR</i> TOPIC: (inflamm* NEAR/2 mediator*) <i>DocType=All document types; Language=All languages;</i>
#9	#8 <i>OR</i> #5 <i>OR</i> #4 <i>OR</i> #3 <i>OR</i> #2 <i>OR</i> #1 <i>DocType=All document types; Language=All languages;</i>
#8	#7 <i>AND</i> #6 <i>DocType=All document types; Language=All languages;</i>
#7	TOPIC: (pregnancy) <i>OR</i> TOPIC: (uterus) <i>DocType=All document types; Language=All languages;</i>
#6	TOPIC: (quiescen*) <i>DocType=All document types; Language=All languages;</i>
#5	TOPIC: ("transition to labor") <i>DocType=All document types; Language=All languages;</i>
#4	TOPIC: ("trial of labor") <i>DocType=All document types; Language=All languages;</i>
#3	TOPIC: (uterus NEAR/2 contraction*) <i>OR</i> TOPIC: (uteri NEAR/2 contraction*) <i>OR</i> TOPIC: (uterine NEAR/2 contraction*) <i>DocType=All document types; Language=All languages;</i>
#2	TOPIC: (cervix NEAR/2 ripen*) <i>OR</i> TOPIC: (cervical NEAR/2 ripen*) <i>DocType=All document types; Language=All languages;</i>
#1	TS=(parturition) <i>OR</i> TS=(childbirth*) <i>OR</i> TS=(child birth*) <i>OR</i> TS=(birth) <i>OR</i> TS=(births) <i>OR</i> TS=(labor) <i>OR</i> TS=(labors) <i>OR</i> TS=(laboring) <i>OR</i> TS=(labour) <i>OR</i> TS=(labours) <i>OR</i> TS=(labouring) <i>OR</i> TS=(breach presentation*) <i>DocType=All document types; Language=All languages;</i>

Figure 1.
PRISMA flow diagram of record processing and elimination

Figure 2.

The five gestational cell types included in our review are shown as different colored ovals. The numbers listed represent the number of unique biomarker (protein or mRNA) present in the tissue at the time of term labor. The numbers present in overlapping section represent the number of common biomarkers between the two tissues. The central number, 7, is the number of biomarkers present in all tissues at the time of term labor.

Figure 3.

Results of quality assessment of included reports. Q1–Q10 correspond to questions 1–10 as listed in table 1. The Y axis is the value assigned for the component question for the study evaluated and the x axis is the number of high, acceptable and low quality studies in each response category.

Table 1

Quality assessment tool template used for determining the quality of reports included for systematic review.

Quality Assessment	
1) Question/objective sufficiently described?	
2) Design appropriate to answer study question?	
3) Samples, reagents, assays sufficiently described?	
4) Methods described in sufficient detail?	
5) Study can be easily replicated?	
6) Sample/experiment number sufficient for internal validity?	
7) Appropriate negative controls?	
8) Appropriate statistical analysis?	
9) Results reported in sufficient detail?	
10) Do the results support the conclusion?	
Scoring: Fully compliant=2 points, Partially compliant=1 point, No=0; N/A= not applicable Total score: 17–20 = High quality, 11–16= Regular quality, 0–10= Low quality	

Table 2

Description of 5 full text articles excluded

Study ID (author, year, journal)	Reason for exclusion
1. EG Olivares et al., 1997, Biology of Reproduction	Cells studied were from early pregnancy loss, not term pregnancy.
2. M Lappas et al., 2004, Prostaglandins, Leukotrienes and Essential Fatty Acids	Review article
3. S Goldman & E Shalev, 2007, Frontiers in Bioscience	Review article
4. N Gomez-Lopez et al., 2010, Biology of Reproduction	Review article
5. L Carbillon et al., 2001, Annals of Medicine	Review article

Table 3

Study characteristics grouped by gestational tissue investigated

	Number of studies	Type of analysis	Total N clinical specimen analysis	Total N <i>in vitro</i> culture and analysis
Amnion	106	mRNA= 57 Protein= 94	77	53
Chorion	96	mRNA= 54 Protein= 86	72	48
Decidua	81	mRNA= 36 Protein= 69	57	29
Myometrium	53	mRNA= 39 Protein= 50	45	28
Placenta	40	mRNA= 21 Protein= 32	29	17

Table 4

List of biomarkers found in each tissue and common markers

Amnion		Chorion		Decidua		Placenta	Myometrium	
COX-2	NOD1	COX-2	PECAM	COX-2	BCL2A	COX-2	COX-2	oxytocin
IL-6	NOD2	IL-6	MMP-1	IL-6	IDO	IL-6	IL-6	cFos
IL-8	Slit 3	IL-8	MMP-2	IL-8	TLR4	IL-8	IL-8	JunB
PGE2	p53	PGE2	TLR4	PGE2	GROa	PGE2	PGE2	Slit3
TNF- α	IL-24	TNF- α	p53	TNF- α	MMP-9	TNF- α	TNF- α	SOCS3
IL-1 β	IL-29	IL-1 β	IL-24	IL-1 β	PBEF	IL-1 β	IL-1 β	GROa
hCAP18	PBEF	hCAP18	IL-29	hCAP18	ICAM-2	hCAP18	hCAP18	MMP-1
PGF2 α	ICAM-1	PGF2 α	PBEF	PGF2 α	CXCR4	PGF2 α	PGF receptor	PGI ₂
NF- κ B activity	MnSOD	AKR1B1	ICAM-1	AKR1B2		MMP-9	Collagenase activity	Connexin-43
SA β -galactosidase	F2 IsoP	SA β -galactosidase	MnSOD	IL-1		pSTAT3	MCP-1	MMP-9
PPAR- δ	TGF-1	PPAR- δ	F2 IsoP	PPAR- δ		PPAR- δ	MnSOD	
SPHK-1		Annexin 5	TGF-1	IL-1ra		mPR-B	cyclophilin	
MCP-1		MCP-1	CXCR4	IL-10		SP-D	S100A9	
IL-10		IL-10	CD44	MIP-1		GDF15	CCL2	
MIP-1 α		MIP-1	BCL2A	CD44		HMGB3	cIAP1	
IL-1 α		IL-1 α	IDO	MIP-3		SERPINE1	cIAP2	
cIAP 1		cIAP 1	Nitric oxide	PG synthetase		MAPK	Caspase 1	
cIAP2		cIAP2	SOCS3	AKR1C3		IL-1 α	FOXO1	
Caspase-1		Caspase-1		MMP-2		SOCS3	KLF5	
Caspase-3		Caspase-3		SOCS3		PPAR- α	NOD1	
MAPK		PLA-2		PECAM		PLA-2	NOD2	

Appendix Table 2

Main characteristics of included studies

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
1	Aitken et al., 1990 Reproductive Fertility and Development	Phospholipase A2 (PLA-2) mRNA transcripts were higher in the placenta in the spontaneous labor group than no labor group. No difference in no labor vs labor for membranes	mRNA-Northern Blot	Placenta and membranes	None
2	Alexander et al., 2012 Reproductive Sciences	Tumor necrosis factor receptor 1A (TNFR1A) and 1B mRNA increases with advancing pregnancy and TNFR1A mRNA is increased in term labor compared to no labor. Total TNFR1B protein is increased at term labor vs not labor at term while there was no change in TNFR1B protein. After TNF- α stimulation, TNFR1B mRNA increased significantly. TNFa stimulation increased mRNA expression of IL-8 and PGHS-2. Myometrial sensitivity to TNF- α may increase as gestation nears term and with labor onset.	mRNA-qPCR (for TNFR1A and 1B) Protein-Western blot	Myometrium	Myometrium with TNF- α stimulation
3	Alfaidy et al., 2003 Endocrine	Prostaglandin E synthase (PGES) is involved in converting PGH ₂ to PGE ₂ . Membrane bound PGES (mPGES) is one form of PGES. mPGES protein was present at higher levels in the amnion and chorion as compared to the decidua and placenta. With labor the changes seen in mPGES protein levels were seen as a decrease in the placenta and an increase in the chorion, no changes seen in amnion or decidua. No changes in mPGES mRNA were seen in any of the tissues.	mRNA= In situ hybridization and autoradiography Protein= Immunohistochemistry, Western blot	Amnion, Chorion, Decidua, Placenta	None
4	Allport et al., 2001 Molecular Human Reproduction	Human labor is associated with constitutive NFkB activity in the amnion. Higher NFkB transcriptional activity in amnion cells from term labor than term no labor. There is more binding of NFkB to DNA in labor than not in labor. Both of these are increased by stimulating with IL-1B, except	mRNA= plasmids, EMSA	Amnion	Amnion treated with IL-1B

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		no increase in the NFkB activity in labor amnion when adding IL-1-B. They also found that progesterone receptors decrease with increasing NFkB activity. NFkB activity increases with labor and contributes to labor at term.			
5	Alzamil et al., 2014 Frontiers in Physiology	Prostaglandin F2 synthase (AKR1B1) and human prostaglandin transporter (SLCO2A1) were investigated in TNIL and TL. AKR1B1 protein and cyclooxygenase-2 (PTGS-2) protein was increased in the fetal membranes while SLCO2A1 was decreased at the time of term labor. PTGS2 protein is highly expressed in the amnion, chorion and adjacent decidua while AKR1B1 expression is highest in the chorion and is absent in the amnion.	Protein= Immunohistochemistry, Immunoblotting	Amnion, chorion, decidua	None
6	Amash et al., 2007 European Cytokine Network	Placental cotyledons from term in labor placentas were studied for IL-15 and IL-18 production. IL-15 and IL-18 were present in all cell layers (amnion/chorion/placenta) and both were higher in chorion than the amnion and placenta. IHC showed IL-15 was produced by epithelial and mesenchymal amnion cells, cytotrophoblasts and mesenchymal cells of chorion, and in the syncytiotrophoblasts of villi and decidua cells. IHC showed IL-18 produced by epithelial cells of amnion, cytotrophoblast and mesenchyme of chorion, and decidua cells of decidua. IL-18 was not produced by syncytiotrophoblasts. Stimulation with LPS did not change the expression of IL-15 or 18.	Protein= ELISA and IHC	Amnion, chorion, placenta	None
7	Ammala et al., 1997 Placenta	TNIL and TL placental and decidua samples were evaluated for IL-1 β and IL-1 receptors and IL-1 receptor antagonist (ra). IL-1 β mRNA transcripts were higher in the decidua than placenta. IL-1 β mRNA transcripts were higher in spontaneous labor in both tissues. The IL-1 β protein level was higher	mRNA= Northern blot, qPCR Protein= ELISA	Decidua, placenta	None

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		in laboring decidua cells. No change was seen in IL-1ra in either group with labor, but there was a decreased IL-1ra/IL-1 β level with labor in the decidua.			
8	Arechavalaeta-Velasco et al., 2002 Biology of Reproduction	Amnion and chorion from TNIL pregnancies were stimulated with TNF- α , IL-1 β and LPS and biomarker activity was measured. Levels of proMMP were elevated in amnion after stimulation with all 3. This effect was blocked by a TNFa neutralizing Ab. In the chorion proMMP-9 was not increased after stimulation with any of the 3, but the levels of IL-1b and TNF- α were increased with LPS stimulation. No change was seen in tissue inhibitor of MMP-1 (TIMP-1) in either tissue with stimulation.	Protein=ELISA		Amnion, chorion
9	Astle et al., 2007 Molecular Human Reproduction	PGE2 is synthesized by 3 enzymes, cytosolic PGE synthase (cPGES), microsomal PGES-1 (mPGES-1) and microsomal PGES-2 (mPGES-2). All 3 enzymes mRNA were expressed in myometrium of lower segment. With term labor there was increase in mPGES-1 and -2 mRNA and no change in cPGES mRNA. COX-2 mRNA expression increased in term labor as well. IL-1beta stimulation increased expression of mPGES-1 mRNA, PGE ₂ protein, and COX-2 mRNA and protein. There are three distinct PGES enzymes present in term myometrium which supports the role for locally produced PGE ₂ in the regulation of myometrial activity.	mRNA= RT-PCR Protein= Western blot and IHC	Myometrium	Myometrium stimulated with IL-1B
10	Behnia et al., 2015 American Journal of Obstetrics and Gynecology	In term labor, chorioamniotic membranes have increased levels beta galactosidase, uPAR, MCP-2, and ICAM-3. Levels of PAI1 and PAI2 were not changed with labor.	Protein= SA β -gal staining, Fast Quant-microspot assay	amniochorionic membranes	None
11	Belt et al., 1999 American Journal of Obstetrics and Gynecology	Myometrial cell line was stimulated with IL-1 to mimic labor. Activation of NF-k β was measured by degradation of Ik β - α .	Protein= Western blot, Radioimmunoassay mRNA= EMSA, Northern blot	NA	Myometrial cell line

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		which immediately after stimulation with IL-1, COX-2 mRNA increased within 30 minutes followed by an increase in COX-2 protein and then and increase in PGE ₂ and PGI ₂ .			
12	Bennett et al., 1996 American Journal of Reproductive Immunology	All trophoblast cells (cell lines and term trophoblasts) expressed IL-6, IL-10, IFN- α , IFN- β , GM-CSF mRNA, except JEG-3 which did not express IL-10. Choriocarcinoma cell line cells expressed weak or absent IL-1, TNF- α , and IFN- γ , while these were expressed in the term trophoblast. Human trophoblast cells produce cytokines that may be important in labor initiation.	mRNA= rt-PCR	Term trophoblasts-unclear is term in labor or not in labor	BeWo, JEG-3, JAR placental choriocarcinoma cell lines
13	Bennett et al., 1992 American Journal of Obstetrics and Gynecology	COX mRNA expression increases in the amnion and trophoblasts at the time of term labor. There was a non significant increase in COX mRNA in choriodecidua at term labor.	mRNA= Northern blot	Term amnion, chorion and trophoblasts	None
14	Berry et al., 2003 Molecular Pharmacology	Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors involved in inflammation. In the amnion, PPAR- δ increased while PPAR- α did not at the time of labor. In the choriodecidua, PPAR- δ increased with labor while PPAR- α decreased. In the placenta, PPAR- α and - δ increased significantly with labor. JEG3 choriocarcinoma cells were used to assess the functional roles of PPAR. These results suggest that PPARs may play a role in parturition and pregnancy maintenance.	mRNA= Northern blot	Term amnion, chorion and placenta (TNIL and TIL)	JEG3 choriocarcinoma cell line
15	Bredeson et al., 2014 PLOS ONE	High mobility group box 1 (HMBG1) as a contributor of the non infectious fetal inflammatory response. HMBG1 is increased in membranes in response to cigarette smoke extract (CSE) and lipopolysaccharide (LPS). p38 mitogen-activated protein kinase (p38MAPK) was activated by HMBG1 and promotes senescence	mRNA= RTPCR Protein= ELISA		TNIL fetal membranes

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		phenotype and sterile inflammation.			
16	Brodt-Eppley et al., 1999 Obstetrics and Gynecology	This study evaluated the relaxatory PGE ₂ receptor and the contractile PGE ₂ receptor in myometrium at term and preterm when in labor and not in labor. They found that the expression of PGE ₂ receptor mRNA decreased at TNIL compared with preterm NIL. PGE ₂ receptor mRNA expression was less in the TNIL group than preterm NIL, but the PGE ₂ receptor mRNA increased significantly at the time of term labor.	mRNA= RTPCR	Myometrium	None
17	Bryant-Greenwood et al., 1987 Journal of Endocrinology	Samples from fetal membranes obtained at TL and TNIL were evaluated for relaxin, prolactin and prostaglandin synthase. Relaxin was seen more in the chorion cytotrophoblasts than the decidua and was not seen in the amnion. All chorion and decidua tissues from the TNIL group stained with relaxin, while only half of those in the TL group did. Prolactin was found mostly in the decidua and rare in chorion and amnion. Prostaglandin synthase was found in the amnion, chorion and decidua but there was no difference with labor.	Protein= immunostaining	Amnion, Chorion, Decidua	None
18	Chan et al., 2002 Journal of Clinical Endocrinology and Metabolism	Myometrial samples were evaluated at TL and TNIL. They found genes upregulated at the time of labor included: IL-8, manganese superoxide dismutase (MnSOD), metalloproteinase 9 (MMP-9), interferon-inducible 1-8d, elongation factor 1 α , nucleophosmin, cyclophilin, and a-actin. Increased IL-8, MnSOD and cyclophilin mRNA was seen at term labor. MnSOD was differentially distributed between upper and lower segments of myometrium while there was no difference in IL-8. Induced labor showed higher IL-8 than spontaneous labor, with no difference seen for MnSOD.	mRNA= Suppression subtractive hybridization, Northern blot, RT PCR	Myometrium	NA

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
19	Chan et al., 2013 Placenta	Let-7 micro RNA (miRNA) is negatively regulated by Lin 28 which is a RNA binding protein. Let-7 miRNA and Lin28 are thought to regulate IL-6 expression. They found that Lin28 is expressed in placenta and choriondecidua, but not in amnion. Let-7b and -7c were expressed less in choriondecidua as compared with amnion and placenta. Neither Let-7 or Lin28 varied significantly with labor.	mRNA= RT-PCR Protein= Western blot	Amnion, chorion, decidua, placenta	NA
20	Chapman et al., 2004 Journal of Clinical Endocrinology and Metabolism	NfκB expression and DNA binding were examined in the myometrium in non pregnant conditions and at term NIL and TIL. RelA protein was noted to be decreased in TIL compared to non pregnant and TNIL, but increased RelA-p50 DNA binding was noted in the TIL group. No change was seen in c-Rel, p105, p50, p100 between TNIL and TIL.	mRNA= EMSA Protein= Western Blot	Myometrium from non pregnant, TIL and TNIL	NA
21	Choi et al., 2006 European Journal of Obstetrics and Gynecology	NfκB, COX-2, and MMP-9 were evaluated in myometrial tissues in TNIL and TIL conditions. There was a significant increase in COX-2 and MMP-9 protein in the TIL group. There was a significant decrease in p65 and p50 subunits of NFκB at TIL. IL-1B stimulation caused activation of NF-kB and increased COX-2 and MMP-9.	Protein: immunostaining, Western blot, gel zymography	Myometrium: TNIL and TIL	Myometrium stimulated with IL-1B
22	Denison et al., 1998 Human Reproduction	TNIL placenta samples evaluated for monocyte chemotactic peptide-1 (MCP-1), IL-8, IL-10 and Regulated on Activation and Normally T-cells Expressed and Presumably Secreted (RANTES). MCP-1 is expressed in the chorion, decidua and placenta, but minimally from the amnion. IL-8 is expressed in the amnion, chorion, decidua and placenta. RANTES was not expressed in amnion, but moderately expressed in chorion, decidua and placenta. IL-10 was not expressed in the amnion and had low expression in chorion, decidua and placenta. After an infusion of PGE ₁ MCP-1,	Protein: ELISA	Amnion, chorion, decidua, placenta	Amnion, chorion, decidua, placenta

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		IL-8, and IL-10 increased on the maternal side and MCP-1 and IL-8 increased on the fetal side.			
23	Dong et al., 2012 Reproductive Sciences	Peroxisome proliferator-activated receptor alpha (PPAR α) is thought to have anti-inflammatory activities. IHC was used to identify PPAR α in the nucleus of myometrial cells. PPAR α mRNA and protein decreased with the onset of labor. IL-1 β mRNA and protein increased with labor onset.	mRNA= RT-PCR Protein= Western Blot, Immunohistochemistry	Myometrium	
24	Drivers et al., 1995 Gynecologic and Obstetric Investigation	IHC staining for COX was performed on TNIL and TL placentas and membranes, along with preterm in labor and not in labor. COX staining was identified in the decidua, placenta, chorion, and amnion in TL and TNIL as well as in preterm, although amnion staining was more heterogeneous. No difference in the amount of COX expression in the membranes, decidua or placenta was described in the article.	Protein= Immunohistochemistry	Placenta, chorion, decidua, amnion	
25	Dudley et al., 1996 Journal of the Society for Gynecologic Investigation	Placentas from TNL, TIL and preterm IL and NIL were collected and mRNA levels for cytokines analyzed. IL-1 β , TNF- α , IL-6, and IL-8 mRNA all increased in decidua, chorion and amnion after labor. The same trend was seen in preterm labor samples.	mRNA= RT-PCR	Decidua, chorion, amnion	
26	Dudley et al., 1993 Journal of Clinical Endocrinology and Metabolism	Chorion and decidua from term not in labor pregnancies constitutively produce IL-8 at baseline. If they are stimulated with IL-1 β or TNF- α the IL-8 protein and mRNA levels increase significantly. The response is attenuated with adding actinomycin-D or cycloheximide. Stimulation with IL-1 β increased IL-8 mRNA production as well.	mRNA= Northern blot Protein=IL-8 Radioimmunoassay	Chorion, decidua	Chorion, decidua
27	Dudley et al., 1992 Journal of Clinical Endocrinology and Metabolism	The chorion produces IL-6 at baseline, and levels significantly increase with stimulation by IL-1 β , TNF, and LPS. The response is attenuated with adding	mRNA= Northern blot Protein= IL-6 RIA, IL-6 ELISA		Chorion

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		actinomycin-D or cycloheximide, IL-6 mRNA also increased with IL-1 β stimulation.			
28	Dunn-Albanese et al., 2004 American Journal of Obstetrics and Gynecology	Peroxisome proliferator-activated receptor- γ is an anti-inflammatory molecule. PPAR- γ was prominent in membranes and placenta before labor. After labor PPAR- γ was decreased in the membranes while the COX-2 increased. PPAR- γ expression in placenta did not change with labor. PPAR- γ stained prominently in the syncytiotrophoblast, cytotrophoblasts, amnion and chorion. COX-2 was seen abundantly in the amnion, but rarely in the placenta.	Protein= Immunoblotting, Immunohistochemistry	Fetal membranes (amnion/chorion) and placenta	
29	Durn et al., 2010 Prostaglandins, Leukotrienes, and Essential Fatty Acids	They applied a lipidomic approach to identify the profile of prostanoids in human non-labouring and laboring myometrium. They identified 19 prostanoids, most predominant were prostacyclin, PGD2 and PGF2a which were present in labor and NL. Total amount of prostanoid increased with labor, the specific ones to increase were: PGE ₂ , 13,14-dihydro-15-keto-PGE ₂ which increased in early and late labor.	Protein= Electrospray ionization, Liquid chromatography, Mass spectrometry	Myometrium	
30	Elliott et al., 2000 American Journal of Reproductive Immunology	IL-8 mRNA and protein levels were evaluated in myometrium of preterm and term not in labor and term in labor patients. IL-8 mRNA and protein increased significantly in the term labor group as compared to the TNL and PNL groups. There was no difference in IL-8 protein or mRNA in PNL vs TNL.	mRNA= RT-PCR Protein= ELISA	Myometrium	
31	El-Maradny et al., 1996 Acta Obstetrica et Gynecologica Scandinavica	IHC was performed on gestational tissues before and during term labor to identify IL-8 receptors. IL-8 receptors were seen in fetal membranes, placenta, umbilical cord and myometrium prior to the onset of labor. With labor, more intense staining for IL-8 receptors was seen in the amnion and	Protein= Immunohistochemistry	Amnion, chorion, placenta, myometrium, and umbilical cord	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		placenta. Myometrial samples at term labor were not evaluated.			
32	El-Maradny et al., 1996 American Journal of Obstetrics and Gynecology	Fetal membranes, amnion and myometrial tissues were placed on stretch to simulate stretching that takes place as the fetus grows. They found that IL-8 concentration and collagenase activity was significantly increased after stretching of the amnion-chorion membrane, amnion alone and myometrium. The amnion, chorion and myometrium stained darker for IL-8 after stretching than the non stretched membranes.	Protein= ELISA, Immunohistochemistry		Amnion, chorion, myometrium
33	Ekkhambattar et al., 2013 Placenta	Sphingosine-1-phosphate (S1P) is a mediator of inflammation. Sphingosine kinase (SPHK-1) leads to production of S1P and S1P lyase (SPL-1) which is an inhibitor of S1P. They evaluated the levels of SPHK-1 and SPL-1 in fetal membranes from TNIL and TIL. They found that SPHK-1 and SPL-1 were expressed in the amnion in TNIL. SPHK-1 and PTGS-2 (COX-2) expression increased in post labor amnion. There was no change in SPL-1 expression between TNIL and TIL. Treatment of the amnion with S1P lead to increased PTGS-2 (COX-2) expression.	mRNA= RT-PCR Protein=Western Blot, IHC	Amnion	Amnion
34	Esplin et al., 2005 Placenta	Microarray was used to characterize the transcriptome of term labor in the myometrium and monocyte chemotactic protein-1 (MCP-1) was found to be upregulated. MCP-1 was evaluated in myometrium, placenta, membranes and amniotic fluid. MCP-1 was upregulated in myometrium and membranes with term labor. There was increased immunoreactive (IR) MCP-1 content in myometrium at term and in the amniotic fluid in PTL. IR MCP-1 increases in myometrium after stimulation with IL-1 β .	mRNA=Microarray, RT-PCR, Northern Blot, in situ hybridization Protein=ELISA	Myometrium, placenta, membranes, and amniotic fluid	
35	Fidel et al., 1994 American Journal of	Interleukin-1 receptor antagonist (IL-1ra) levels were investigated in	Protein=ELISA		Amnion, chorion, decidua

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
	Reproductive Immunology	primary cultures of amnion, chorion and decidua. All layers produced IL-1ra at baseline. The production of IL-1ra was increased after stimulation with IL-1 β and LPS in the decidua. Amnion and chorion did not increase release of IL-1ra with stimulation.			
36	Fortunato et al., 1994 American Journal of Reproductive Immunology	Amniochorion explants from term pregnancies not in labor were investigated for TNF- α and TNF receptor (TNFR). There was increased mRNA for TNF α and TNFR was seen in both amnion and chorion. TNF α peptide was seen only in the amnion. TNFR peptide was seen in both amnion and chorion.	mRNA= RT-PCR, in situ hybridization Protein= IHC		Amniochorion explants
37	Freed et al., 1995 Gynecologic and Obstetrics Investigation	There are 2 isoforms of Prostaglandin G/H synthase (PGHS): PGHS-1 and -2. PGHS-1 is constitutively expressed in all tissues and mRNA level does not change with onset of labor. The authors state that increased mRNA of this enzyme is not necessary for labor associated prostaglandin production.	mRNA= Northern Blot, Southern blot, sequence copy DNA	Amnion, chorion, decidua, placenta	
38	Friebe-Hoffman et al., 2007 Regulatory Peptides	Primary decidual cells were treated with IL-1 β and levels of oxytocin (OT) peptide, OR receptor (OTR) binding, Inositol triphosphate (IP ₃) production, arachidonic acid (AA) and PGE ₂ release were measured. After stimulation with IL-1 β OT peptide initially decreased in the cytoplasm and then increased in the media. OT peptide release was blocked by treatment with indomethacin. OTR mRNA decreased with IL-1 β treatment. IP ₃ production and AA release were reduced. They found that OT mediated PGE ₂ release was enhanced.	mRNA= PCR (for OTR) Protein= ELISA (PGE ₂ level), RIA (for OT peptide), Radioligand-binding-assay (OTR binding), liquid scintillation (for IP ₃ , AA)		Primary decidual cells treated with IL-1 β
39	Fuchs et al., 1981 American Journal of Obstetrics and Gynecology	The investigated the effect of oxytocin stimulation on prostaglandin production in amnion, decidua and myometrium. Oxytocin stimulation lead to	Protein= RIA		Explants of amnion, decidua and myometrium

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		increased PGE and PGF production in the decidua and increased PGE production in the amnion. There was no significant change seen in the myometrium			
40	Fuentes et al., 1996 Prostaglandins	They investigated COX-2 levels in amnion and decidua at term not in labor and term in labor. They found a two fold increase of COX-2 with labor while in the decidua there was no change with labor.	Protein= Western Blot	Amnion, decidua	
41	Fukai et al., 1984 Endocrinologia Japonica	They evaluated myometrium, amnion and decidua for oxytocin receptors (OXT-R) and PGF _{2α} receptors. In the myometrium they saw an increased number of binding sites for OXT as gestational age progressed and a rapid decrease after onset of labor. In the myometrium, the number of PGF _{2α} receptors remained unchanged in pregnancy and with labor. In the amnion and chorion there were no changes in the OXT-R with labor.	Protein= LSC-903 scintillation counter	Myometrium, amnion, decidua	
42	Giannoulas et al., 2002 Journal of Clinical Endocrinology and Metabolism	Prostaglandin E synthase (PGES) synthesizes PGE ₂ and prostaglandin I synthase(PGIS) synthesizes PGI ₂ which causes relaxation. They examined myometrium for membrane bound PGES and PGIS. PGES and PGIS were localized to cytoplasm of myocytes and vascular smooth muscle. PGES was seen in vascular endothelial cells. There was no change in mRNA level of immunoreactive PGES or PGIS with labor in term or preterm. There was a significant decrease in PGIS mRNA and protein with advancing gestational age.	mRNA= in situ hybridization Protein= IHC, Western Blot	Myometrium	
43	Goldman et al., 2005 Molecular Human Reproduction	Fetal membranes and decidua were evaluated for progesterone receptors (PR-A, PR-B and PR-C). In the decidua PR-B was the primary receptor, but several PRs were expressed. PR-B and PR-A were decreased after labor in the decidua. Incubation of decidua	mRNA= RT-PCR Protein= IHC, Western blot	Decidua, fetal membranes	Decidua, fetal membranes

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		with PGF _{2α} caused a decrease in all PR isoforms. When decidua was treated with progesterone, PR-B and PR-C increased. In the membranes IHC showed no PR in the amnion or chorion. Western blot showed the PR-C was dominant in the amnion and that the PR-A levels decreased after labor.			
44	Gomez-Lopez et al., 2009 Journal of Reproductive Immunology	The authors wanted to see if fetal membranes cause chemotaxis. Membranes from TIL and TNL induced chemotaxis, but those in labor induced significantly more chemotaxis of PMNs, T and B lymphocytes, and NK cells. Labor membranes also contained more IL-8, TNF-α, IL-1β, IP-10, and MIP-1α on the multiplex assay. IL-8, MCP-1, MIP-1 and IP-10 immunofluorescence was predominantly localized into the fetal membranes and decidua in the labor group	Protein=Flow cytometry, multiplex suspension array system, immunofluorescence histochemistry		Fetal membranes (amnion, chorion, decidua)
45	Grisby et al., 2006 American Journal of Obstetrics and Gynecology	PGE ₂ receptors (EP) have 4 subtypes (EP1-4). All EP1-4 were expressed in placenta and membranes. Syncytiotrophoblast only had EP-3. EP1-4 were consistently expressed across gestation in membranes, but a different cellular localization in labor was noted in amnion for EP1, 2, and 4. The authors feel that the presence of these receptors indicates a paracrine role for PGE ₂ in parturition.	Protein=Western blot and IHC	Placenta and fetal membranes	
46	Gunn et al., 1996 Reproductive Fertility and Development	Term labor and not in labor amniotic fluid, placenta, umbilical cord, cord blood, and maternal blood were evaluated for levels of IL-1α and IL-6. In the membranes IL-1α and IL-6 were increased after onset of labor. In the placenta there was no change in concentration of IL-1α or IL-6. Fetal membranes and decidua are the main sources of IL-6 and IL-1α at time of labor.	Protein= Radioimmunoassay	Amniotic fluid, placenta, membranes, umbilical cord blood, maternal blood	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
47	Hanna et al., 2004 American Journal Reproductive Immunology	The authors wanted to evaluate the effect of IFN- γ on COX-2 and PGE2 production in the placenta. There was significant expression of IFN- γ in decidua (term and preterm), and not much in placenta. IFN- γ significantly inhibited COX-2 and PGE2 release in placental explants at term and preterm. IFN- γ receptor expression was decreased at time of preterm and term labor.	Protein= IHC, Western blot, ELISA	placenta, decidua	placenta
48	Harirah et al., 2009 American Journal of Obstetrics and Gynecology	The authors looked at catechol-O-methyltransferase (COMT) in fetal membranes at term. In the amnion there were higher levels of COMT in labor than not in labor. COMT was higher in the amnion than the choriondecidua. Inhibition of COMT lead to decreased PGE ₂ release.	mRNA= RT-PCR Protein= IHC, Western blot, ELISA	Fetal membranes	Fetal membranes
49	Havelock et al., 2005 Biology of Reproduction	The investigated the gene expression in myometrium before and after labor. The used PCR to evaluate 3 genes: prostaglandin-endoperoxide synthase-2 (PTGS-2), calgranulin B (S100A9), and oxytocin receptor (OXTR). Few genes were differentially expressed in myometrial fundus with onset of labor. S100A9 was dramatically increased in the cervix and myometrium with labor.	mRNA= Human UniGEM-V microarrays, RT-PCR Protein= IHC	Myometrium	
50	He et al., 2015 American Journal of Pathology	They investigated chorion at term labor for expression of peroxisome proliferator-activated receptors and the effect on prostaglandin dehydrogenase (PGDH). PPAR- α , β , and γ were localized on IHC to the trophoblasts of the chorion. PPAR- α , β , and γ protein were decreased in the TL tissue compared to TNL. All PPAR 3 types correlated with PGDH level in TNL, but only PPAR- γ correlated in TL. No difference in PPAR levels between TL and PTL, but PGDH was decreased in PTL compared to TL. Agonists of PPAR stimulated PGDH activity.	mRNA= RT-PCR Protein= Immunocytochemistry, Western blot	Chorion	Chorion

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
51	Hirst et al., 1995 Journal of Clinical Endocrinology	The authors evaluated prostaglandin endoperoxide-H synthase (PGHS) 1 and 2 in term amnion prior to and after labor. PGHS-2 was higher in labor group than no labor. There was no difference in PGHS-1 in the labor group vs the no labor group. The increase in PGHS-2 mRNA was associated with increased PGHS enzyme activity as well.	mRNA=Northern Blot, in situ hybridization Protein=RIA	Amnion	
52	Hirst et al., 1995 Reproductive Fertility and Development	They examined placenta for PGHS expression and activity. They found that PGHS activity increases with gestation. PGHS-2 mRNA expression increased with labor in amnion and decidua, there was no change in PGHS-1 with labor. The increase in PGHS-2 mRNA correlated with PGHS activity.	mRNA= in situ hybridization Protein= RIA	Amnion and decidua	
53	Holmlund et al., 2007 Immunology	High mobility box group-1 is a proinflammatory molecule. Strong nuclear HMGB1 localization was seen in all cells. HMGB1 mRNA and protein was expressed in the term placenta. More cytoplasmic HMGB1 expression was seen in the syncytiotrophoblast, decidual cells, and amnion cells. Receptors RAGE, TLR2 and TLR4 were abundantly expressed in term placenta. No difference in HMGB1 expression or RAGE, TLR2 or 4 with the change to labor.	mRNA= in situ hybridization Protein=IHC	Amnion, chorion, decidua, placenta	
54	Hua et al., 2013 American Journal of Reproductive Immunology	The authors investigated the expression of 3 chemokine receptors at the time of labor in myometrium: CCR2, CXCR1 and CXCR2. They saw a significant decline in mRNA expression of all the receptors with onset of term labor in the upper and lower myometrium. Chemokine receptor expression was increased by stretch and decreased by oxytocin and PGF ₂ α. The chemokine receptors likely decrease in response to increased chemokine activity.	mRNA= RT-PCR Protein= Western blot, flow cytometry	Myometrium	Myometrium treated with stretch, oxytocin and PGF ₂ α

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
55	Hua et al., 2012 Endocrinology	The authors investigated chemokine expression at preterm and term and in labor in myometrium. Term labor was associated with increased CXCL8 (IL-8) and CCL2 mRNA in the upper and lower myometrium. CXCL1 mRNA increased significantly in the upper segment only. PTL was associated with increased in CCL5, CXCL5, CCL20 in the lower segment only. Chemokine expression (CCL2, CXCL1, and CXCL8 mRNA) was increased by stretch and inflammatory cytokine treatment and decreased by prostaglandins and oxytocin. The authors believe that NF- κ B regulates the response to stretch and cytokines in the myometrium.	mRNA= RT-PCR Protein= Western Blot, ELISA, Chemotaxis assay	Myometrium	Myometrium treated with stretch and IL-1 β and TNF- α
56	Ikoma et al., 2003 Molecular Human Reproduction	Placental leucine aminopeptidase (PLAP) is an oxytocinase that destroys oxytocin. The authors stimulated BeWo cells with cytokines to evaluate for PLAP level. Stimulation with IL-1 β for 72 hours lead to increased PLAP activity at the mRNA and protein levels. There was a dose dependent response to IL-1 β and no response to IL-6 or TNF- α .	mRNA= RT-PCR, Southern blot Protein= Spectrophotometry, Western blot, IHC		BeWo Cells
57	Ishihara et al., 1996 Prostaglandins	The evaluated decidua from TNIL and TIL for PGE ₂ levels and response to IL-1 β . Labor decidua produced more IL-1 β and more PGE ₂ . Both cells responded to the addition of additional IL-1 β with an increase in PGE ₂ . When COX-2 was blocked by an inhibitor, there was decreased production of PGE ₂ and less response to IL-1 β .	Protein= Enzyme immunoassay, Western Blot		Decidua treated with IL-1 β
58	Jiang et al., 2012 Placenta	The authors wanted to investigate the relationship between cytokines and prostaglandin receptors. They saw higher TNF- α immunostaining, higher TNF- α protein levels, higher PR-A/PR-B ratio and higher COX-2 level in labor decidua. NF- κ B was	mRNA= RT-PCR Protein= IHC, Western blot, and ELISA	Decidua	Decidua treated with NF- κ B

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		activated by TNF- α stimulation (for 24 hours).			
59	Johansen et al., 2000 Prostaglandins and other Lipid Mediators	Term labor amnion and chorion and chorion cell lines were evaluated for phospholipase A ₂ (PLA ₂) and COX enzymes. All cell types expressed cytosolic group IV PLA ₂ and COX-1. Secretory forms of PLA ₂ had more restricted expression. Group IIA is most abundant in the placenta and chorion. Group V PLA ₂ is most abundant in the placenta and amnion. COX-2 is in the placenta, chorion, amnion but not in any of chorionic cell lines.	mRNA= PCR	Amnion and chorion	Chorion cell lines: JEG-3, Jar, BeWo
60	Keelan et al., 1997 Biology of Reproduction	Amnion cells from from TNIL were collected and analyzed. IL-6 and 8 were produced by amnion cells over a 7 day culture period. The ratio of IL-8/IL-6 was 5:1 in amnion cells. IL-6 and 8 production was stimulated in amnion by IL-1 β , TNF- α , and bacterial LPS. Dexamethasone decreased the production of cytokines by 50%.	Protein= ELISA, IHC	Amnion	Amnion treated with cytokines
61	Keelan et al., 1999 American Journal of Obstetrics and Gynecology	In the amnion IL-6, IL-8, and IL-1 β were significantly higher in those with spontaneous labor than no labor. IL-6 and IL-8 were significantly higher in chorio-decidual tissues with labor as well. PTL amnion/chorio-decidual had markedly increased IL-6, IL-1 β and IL-8 compared to TL. There was no change in cytokine concentration with labor in the placenta.	Protein= ELISA	Amnion, chorio-decidual, placenta	
62	Keelan et al., 2000 Journal of the Society for Gynecologic and Obstetric Investigation	The authors examined the effect of prostaglandins and thromboxanes on amnion WISH cells. The addition of prostaglandins had no effect on cytokine production in WISH cells. Thromboxane A ₂ agonists stimulated WISH cytokine production of IL-6 and IL-8 protein and mRNA.	mRNA=Northern analysis Protein=ELISA		WISH cells
63	Kelly et al., 1992 Lancet	Choriodecidual cells produce IL-8, but no change was noted between	Protein= Enzyme immunoassay		Choriodecidual cells

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		labor and no labor. Production of IL-8 was stimulated by mifepristone (anti progesterone) and inhibited by progesterone.			
64	Kendal-Wright et al., 2010 Placenta	They investigated the effect of stretching and inflammatory stimuli on the level of IL-8 and pre-B cell colony-enhancing factor (PBEF). Cyclic stretch more robustly stimulated PBEF and IL-8 release than static stretch. When IL-1 β was added to the stretch the effect on increased IL-8 was greater than on PBEF. They concluded that different kinds of stretch affect the expression of these two cytokines from AEC, but inflammation is a much stronger stimulus of IL-8 than PBEF.	mRNA= RT-PCR Protein= Immunofluorescence, Western blot		Amnion cells stimulated with stretch or cytokines
65	Kent et al., 1993 Prostaglandins	They investigated the effect of IL-6 and TNF- α on fetal membrane prostaglandin production. TNF- α treatment on maternal side lead to decidual production of PGF _{2a} but no effect on PGE or PGE ₂ production. IL-6 had no effect on decidual PGF _{2a} . TNF- α on the fetal side lead to increased PGE ₂ production from the amnion and increased PGE ₂ metabolites from chorion. IL-6 treatment to the maternal and fetal side lead to increased production of PGE ₂ from amnion and PGE _{2m} from chorion.	Protein= Radioimmunoassay		Fetal membranes treated with cytokines
66	Kent et al., 1994 Journal of Reproduction and Fertility	IL-1 α and IL-1 β were transferred through placenta in both directions at similar rates. Only 2-4% of IL-1 cytokines were still intact at the opposing side of the membrane. Intact transfer of TNF- α and IL-6 was 5-7% and 8-17% respectively which was greater than the transfer of IL-1 cytokines	Protein= Gamma counter, radioimmunoassay		Fetal membranes treated with cytokines
67	Khan et al., 1992 British Journal of Obstetrics and Gynecology	Decidual stromal and macrophage cells were collected before and after labor. Decidual stromal cells after labor produced 30x more PGE ₂ and PGF _{2a} than prior to labor. This change was associated	Protein= Immunocytochemistry, Radioimmunoassay	Decidual stromal cells and macrophages	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		with increased number of COX+ cells. There were no changes in macrophage function.			
68	Kim et al., 2005 American Journal of Obstetrics and Gynecology	They investigated the levels of bone morphogenetic protein 2 (BMP-2) mRNA and protein in chorioamniotic membranes. BMP-2 mRNA and protein expression were higher in the membranes of patients with spontaneous labor at term than not in labor. BMP-2 was higher in PTL with chorioamnionitis than those without. There was a correlation between BMP-2 and COX-2 protein expression in the chorioamniotic membranes.	mRNA= RT-PCR Protein= IHC	Chorion, amnion	
69	Kim et al., 2015 Molecular and Cellular Endocrinology	Oxytocin (OT) is a mediator of parturition, the authors investigated its effect on myometrium and amnion. OT activates NF- κ B pathway in amnion and myometrium. OT upregulated IL-8, CCL-5, IL-6, COX-2 genes in amnion and myometrium.	mRNA= RT-PCR, EMSA Protein= Western Blot, ELISA		Amnion and myometrium treated with OT
70	Kredentser et al., 1995 American Journal of Obstetrics and Gynecology	Intact and separated fetal membranes were evaluated from TNIL and TIL pregnancies for the PGF2 α level and then treated with PGE2 to assess response of PGF2 α after PGE2 treatment. They found that PGF2 α concentration was higher at the maternal surfaces of intact membranes in labor membranes (but not the separated membranes). Amniotic PGF2 α was increased after labor. No difference was seen after addition of PGE2. They conclude that PGF2 α production on the maternal side is likely independent of the amniotic production of PGE2.	Protein= Radioimmunoassay	Amnion, chorion, decidua	Amnion, chorion, decidua treated with PGE2
71	Laham et al., 1999 Biology of Reproduction	IL-8 produced by all cell types in fetal membranes. IL-8 release in choriodecidual explants was significantly greater than in amnion and placenta. Choriodecidual IL-8 release was	mRNA= DNA assay Protein= ELISA		Amnion, chorion, decidua, and placenta grown in explants

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		higher in term tissues than preterm. No change in IL-8 mRNA level was seen in any tissue term or preterm with labor. No difference was in seen between chorioamnionitis conditions and normal.			
72	Laham et al., 1996 Journal of Endocrinology	IL-1 α concentration did not change in amniotic fluid or serum with labor onset. IL-1 α was released in detectable amounts from amnion and choriondecidual explants only in term labor samples. IL-1 α also increased in the placenta with labor onset. LPS increased IL-1 α release from term tissues.	mRNA=DNA assay with modified diphenylamine method Protein=ELISA	Amnion, chorio-decidea, placenta, amniotic fluid, maternal serum	Tissue explants treated with LPS
73	Lappas et al., 2015 American Journal of Reproductive Immunology	Cellular inhibitor of apoptosis protein (cIAP) 1 and 2 are proteins involved in inflammation. cIAP1 and 2 expression was increased significantly in fetal membranes and myometrium after spontaneous term labor, in preterm labor with chorioamnionitis and with LPS and TNF α stimulation. cIAP2 expression was higher in fetal membranes after spontaneous PTL. Knock down of cIAP1 and 2 leads to lower TNF- α induced expression of IL-6, IL-8 and COX-2 and MMP-9 and NF- κ B.	mRNA=RT-PCR Protein=IHC, ELISA, Gelatin Zymography, NF-kB luciferase assay	Myometrium, fetal membranes	Fetal membranes treated and myometrium treated with LPS and TNF- α
74	Lappas et al., 2012 Biology of Reproduction	Complement C5 is a anaphylatoxin which exerts its effect via receptors C5AR and CD88. IL-6, IL-8, COX-2, PGE2, PGF2 α , MMP9 enzyme production and NF κ B DNA activation were all increased with presence of C5a. This response was reduced with treatment with selective CD88 antagonist and NF κ B inhibitor. They conclude that C5a upregulates prolabor mediators in human gestational tissues via CD88-mediated NFKB activation.	Protein=ELISA, zymography (for MMP activity), Western Blot		placenta, fetal membranes
75	Lappas et al., 2013 American Journal of Reproductive Immunology	Higher caspase-1 gene and protein expression seen in membranes and myometrium in term labor vs no labor. LPS lead to increased	mRNA=RT-PCR Protein= Western Blot, ELISA	Membranes, myometrium	Membranes and myometrium treated with LPS

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		secretion of IL-1B through NF- κ B in myometrium and membranes.			
76	Lappas et al., 2013 Journal of Reproductive Immunology	Levels of FOXO1 at gene and protein levels were higher in labor myometrium than no labor. When FOXO1 was blocked the capacity if IL-1B to induce inflammation was decreased (decreased IL-6, -8, and COX and MMP and PGs).	mRNA=RT-PCR Protein=Western Blot	Myometrium	Myometrium
77	Lappas et al., 2015 Reproduction	No effect on KLF5 expression in membranes. In myometrium: increased KLF5 protein expression in term labor vs no labor. Increased protein expression in myometrium with stimulation with IL-1B. Silencing KLF5 decreased the effect of IL-1B stimulation of IL, PGs, COX-2 release.	mRNA= RT-PCR Protein= NF- κ B luciferase assay, Western blot, IHC, ELISA	fetal membranes, myometrium	fetal membranes and myometrium treated with IL-1 β
78	Lappas et al., 2007 Placenta	Treatment with LPS activated all 3 MAPK proteins and increased IL-6, IL-8, IL-1B, TNF α , PGE2, PGF2 α . Incubation with inhibitors suppressed the release of inflammatory cytokines.	Protein=ELISA, Western Blot		membranes and placenta treated with LPS
79	Lappas et al., 2002 Biology of Reproduction	Treatment of placenta, amnion and chorion with sulfasalazine (SASP) significantly inhibited release of IL-6, IL-8, and TNF- α and NF- κ B activation when coincubated with LPS treatment.	Protein=Electromobility shift binding assay (for NF κ B binding activity), ELISA		placenta, amnion, chorion treated with LPS or LPS+SASP
80	Lappas et al., 2013 Biology of Reproduction	NOD1 and NOD2 expression was higher in membranes and myometrium after labor than no labor. LPS, TNF, IL-1B stimulation lead to sig increase in NOD2 (but not NOD1). Activation of NOD1 and NOD2 by bacterial products lead to NF κ B activation and production of IL6, IL8, COX2, PGE2, PGF2 α , MMP9,	mRNA= RT-PCR Protein= IHC, NF κ B luciferase assay, ELISA, gelatin zymography	Myometrium and membranes	Myometrium, membranes treated with LPS, TNF and IL1B
81	Li et al., 2011 PLoS ONE	Amnion cells stimulated with IL-1B, then upregulated genes evaluated. Up regulation of sterile inflammation genes with labor and after stimulation with IL-1B. It is unclear if NF- κ B was a common binding motif.	mRNA=Microarray analysis, RT PCR, Motif enrichment analysis	Amnion	Amnion stimulated with IL-1B
82	Li et al., 2013 American Journal of Pathology	PGDH was down regulated in chorion tissues during labor. PRB	mRNA=RT-PCR Protein= Western blot, IHC	Chorion	Chorion

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		was decreased whereas PRA and GR (glucocorticoid receptor) were increased in the chorion in labor. Glucocorticoids inhibit PGDH expression via GR in chorion. Progesterone enhances PGDH expression through PRB, and inhibits PGDH expression via GR and PRA.			
83	Liedman et al., 2009 Gynecological Endocrinology	Term no labor: higher oxytocin receptor mRNA (than labor and PTL). Women in labor had higher oxytocin peptide mRNA levels than those without labor. PGF2a receptor mRNA levels were higher in those without labor at term than those with labor.	mRNA= RT-PCR	Myometrium	
84	Lim et al., 2014 European Journal of Obstetrics and Gynecology and Reproductive Biology	All proteins were present on IHC stain-present in the cytoplasm. FosB and JunD present in nucleus. Term labor: increased cFos and JunB mRNA and protein expression and decreased JunD mRNA and protein expression. FosB mRNA increased but no protein change. No change in cJun. AP-1 transcriptional activity increased with pro-inflammatory cytokine TNF- α , but no effect from LPS, NOD1, NOD2, TLR2 or TLR5.	mRNA= RT-PCR Protein= IHC, Western blot, luciferase assay	Myometrium	Myometrium
85	Lim et al., 2013 Reproductive Sciences	Preterm and term labor are associated with significantly lower apelin expression in membranes. No change in APJ in membranes. Placenta with no change in apelin or APJ with labor. When apelin was knocked out, there was sig increase in IL-1B, IL-6, IL-8, COX-2, PGE2 and PGF2a release. No change with MMP9.	mRNA= RT-PCR Protein= IHC, Western Blot, Gelatin Zymography, ELISA	Amnion	Amnion
86	Lim et al., 2013 Biology of Reproduction	In Labor: higher FOXO3 gene and protein expression. If FOXO3 silenced: decreased response of myometrial cells to IL-1B induced IL-6 and 8, COX-2, PGs, and MMP9 release. Overexpression of FOXO3 lead to the opposite effect with increased release of inflammatory mediators	mRNA= RT-PCR Protein= IHC, Luciferase assay, Western Blot, ELISA, Gelatin Zymography	Myometrium	Myometrium

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
87	Lim et al., 2012 Placenta	Labor and chorioamnionitis decreases cytoplasmic FoxO4 expression in placenta/chorioamniotum. Knock down of FoxO4 decreases COX-2 & PGF2a expression. In BeWo cells siRNA inhibition of FoxO4 did not lead to inflammation, OS, or apoptosis, while in JEG-3 cells it lead to decreased COX-2 and PGF2a.	mRNA= RT-PCR Protein=Western blot, IHC, ELISA	chorioamniotum, placenta	Chorioamniotum, placenta, BeWo, JEG
88	Lim et al., 2015 Reproduction	GSK3 activity is increased in fetal membranes after term and preterm labor; the amount of serine phosphorylated GSK3a/b was decreased. No change in GSK3 in myometrium at labor. Specific GSK3a/b inhibitor CHIR99021 significantly decreased lipopolysaccharide (ligand to TLR4)-stimulated pro-inflammatory cytokine gene expression and release; COX2 gene expression and prostaglandin release; and MMP9 gene expression and pro MMP9 release in fetal membranes and/or myometrium.	mRNA= RT-PCR Protein=Western blot, cytokine and prostaglandin assay, NFkB luciferase assay	fetal membranes & myometrium	Membranes and myometrium
89	Lim et al., 2015 Journal of Reproductive Immunology	Human labor associated with increased hCAP18 expression in membranes and myometrium. hCAP18/LL-37 induces pro-inflammatory and pro-labor mediators (IL-6 and IL-8 mRNA) via the MyD88/NF-kB pathway. hCAP18 was localized to the amnion epithelium, cytotrophoblasts and decidua in the fetal membranes, and in the longitudinal and transverse muscle fibers of the myometrium.	mRNA= RT-PCR Protein= IHC, Western blot	amnion epithelium, cytotrophoblasts, decidua, myometrium	amnion epithelium, cytotrophoblasts, decidua, myometrium treated with LL-37
90	Lim et al., 2014 Journal of Reproductive Immunology	Slit2 mRNA and protein expression was significantly lower in myometrium after labor onset and after LPS & IL-1B treatments. No difference with term vs Pre term. Slit2 siRNA in myometrial cells increased IL-1B -induced pro inflammatory cytokine expression: IL-6, IL-8, COX2, PGE2, MMP9.	mRNA= RT-PCR, Protein= immunohistochemistry, ELISA, gelatin zymography	Myometrium	Myometrium

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
91	Lim et al., 2014 Journal of Reproductive Immunology	Slit3 was greater in supracervical site and myometrium in TIL tissue (but no change in membranes). Slit3 siRNA in amnion and myometrial cells decreased IL-1B induced pro inflammatory cytokine gene expression: IL-6, IL-8, MMP9, Slit3 siRNA knockdown in amnion reduced COX2, PGE2.	mRNA= RT-PCR Protein= IHC, ELISA	fetal membranes & myometrium, FM from distal site (DS) and supracervical site (SCS)	fetal membranes & myometrium, FM from distal site (DS) and supracervical site (SCS)
92	Lockwood et al., 2010 Journal of Clinical Endocrinology and Metabolism	post- vs. pre-uterine-contraction specimens had lower PR histological scores in decidua cells in nuclei, but not interstitial trophoblasts. Levels of GR did not change in decidua cells and interstitial trophoblasts didn't change suggesting the P4 withdraw may occur in decidua cells and does not likely involve GR.	Protein= IHC, western blot	Decidua basalis and parietalis sections	
93	Loneragan et al., 2003 The Journal of Clinical Endocrinology and Metabolism	TRAIL was found in chorio-decidua but not amnion tissue by ELISA. OPG was found in greater concentrations in fetal membranes than TRAIL. In amniotic fluid OPG levels in preterm birth are elevated but similar to those with PROM. TRAIL in amniotic fluid was elevated in TIL and TNIL but not preterm. TRAIL-R3 and -R4 decoy receptors can be found on amnio epithelial cells and chorionic trophoblasts. TRAIL does not effect amnion or choriodecidua cells viability or apoptosis.	mRNA= cDNA array analysis Protein= ELISA, immunoblotting, immunocytochemistry	amnion epithelium, choriodecidua	
94	Lopez Bernal et al., 1987 British Journal of Obstetrics and Gynecology	Amnion cells from TIL basal PGE output was the highest and lowest in preterm labor group. TNIL and induction group levels were higher than preterm as well. The levels were also lower after induction than spontaneous labor. When adding arachidonic acid all groups increased PGE output but still PTB was the lowest.	Protein= radioimmunoassay	collagenase-dispersed amnion cells	Amnion stimulated with AA
95	Lopez Bernal et al., 1987 British Journal of Obstetrics and Gynecology	Chorionic cells had a high progesterone output with relatively low cortisol and PGE production. Whereas decidua cells had a high	Protein= radioimmunoassay	chorion and decidua	Chorion and decidua stimulated with AA

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		cortisol and PGE production rate. Free arachidonic acid stimulated PGE production in both decidual and chorionic cells. NO CHANGE WITH LABOR			
96	Lynch-Salamon et al., 1992 American Journal of Obstetrics and Gynecology	Annexin I in the amnion was reduced in TIL compared to TNIL.	mRNA= Northern blot and slot blot Protein= Western blot	amnion	
97	MacIntyre et al., 2009 Proteomics-Clinical Applications	In SL samples, 23 differentially expressed protein spots were detected (9 increased/14 decreased compared to NL, p.0.05). In IL samples, 59 differentially expressed spots were observed (13 increased/46 decreased compared to NL). Comparison of SL and IL proteomes revealed 69 differentially expressed proteins (7 increased/62 decreased). Two proteins consistently decreased in SL and IL samples were identified as transgelin (1.98- and 1.97-fold decrease in SL and IL, respectively) and aB-crystallin (3.27- and 2.49-fold decrease).	Protein= Western blot, 2-D difference in gel electrophoresis (DICE)	Myometrium	
98	Makino et al., 2007 Placenta	Decidua: PGF2a present, no change with labor; MMP2 & 9 were higher at TL than TNIL. Prostaglandin F2a receptor proteins were found in the amnion, chorion trophoblasts, and decidua by IHC. Levels were highest at TNIL. PGF2A levels were higher in PTNIL than TNIL.	mRNA= RT-PCR Protein= ELISA, IHC, Western Blot, Zymography	Amnion, Chorion, Decidua	
99	Markovic et al., 2007 Endocrinology	Any type of labor: preterm or TIL is associate with an increase in CRH-R1 mRNA levels. CRH-R1 is the most prevalent receptor during labor while pre-CRH-R1 & CRH-R1b decline. IL-1B can induce CHR-R1 expression in myometrial cells. ERK 1/2, P38, and NF-KB could regulate CRH-R1 genes during parturition.	mRNA=RT-PCR Protein=Western blot, confocal microscopy	myometrium	myometrium stimulated with IL1B
100	Marvin et al., 2002 Molecular Human Reproduction	They used cDNA arrays to profile genes in PTL and TL. In TL compared to TNL there was increased oncostatin M and PBEF in amnion and choriodecidua. With TL in choriodecidua	mRNA= cDNA array Kit	amnion and choriodecidua	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		CXCR-1 (IL-8) and TGF- β were significantly increased.			
101	McCoshen et al., 1987 American Journal of Obstetrics and Gynecology	TIL amnion released more PGE2 than TNIL on both sides of fetal dual-compartment perfusion chambers system. TIL chorion-decidua released less PGE2 than TNIL on both sides.	Protein=radioimmunoassay	amnion, chorion, decidua	
102	Meadows et al., 2003 The Journal of Clinical Endocrinology and Metabolism	cPGES (cytosolic) was found in the amnion epithelial and associated with fibroblasts and macrophages in the choriodecidua layers, while mPGES (microsomal) was found in the amnion epithelial and chorion trophoblast. No change in cPGES with labor	Protein=IHC, Western blot	amnion, chorion	
103	Menon et al., 2011 Placenta	Explant CSE exposure resulted in significantly more F2-IsoP production from fetal membranes than the control. PGF2a was not different in CSE vs. controls. CSE-exposed tissues demonstrated a dose-dependent decrease in Bcl2 expression and increases in active caspase 3 and nuclear fragmentation in both amnion and chorion cells	Protein= gas chromatography/mass spectrometry, Polyacrylamide gel electrophoresis (PAGE) and Western blot, IHC, TUNEL staining		fetal membrane explant systems treated with CSE
104	Menon et al., 2009 American Journal of Obstetrics and Gynecology	LPS stimulated more cytokines and MMPs than CSE or CSE +LPS. While apoptotic factors (p53 and caspase 3) were higher after CSE or CSE+LPS.	Protein= multiplex assay for cytokines and MMPs		fetal membranes
105	Menon et al., 2006 Journal of Maternal-Fetal and Neonatal Medicine	IL-19/20 were both found in the amnion and chorion layers. LPS stimulated (IL-1, IL-6, IL-8, and TNF- α) when treated. After IL-19/20 stimulation IL-6 was the only one to increase, with no change in IL-8, IL-1 or TNF- α .	mRNA=RT-PCR Protein=IHC, sandwich immunoassays	fetal membranes	fetal membranes
106	Mijovic et al., 1997 American Journal of Physiology	TIL chorion samples had more PGHS specific activity and more PGHS-2 (COX-2) mRNA than TNIL; there was no change in PGHS-1 mRNA. Fetal membranes also showed more PGHS-2 (COX-2) than PGHS-1 overall, but specifically in chorion	mRNA=in situ hybridization, Rnase protection assay Protein=IHC, enzyme activity assay	chorion	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		trophoblasts and mesenchymal cells.			
107	Mitchell et al., 2012 Mediators of Inflammation	Treatment with a histone deacetylation inhibitor can partially abrogate LPS-stimulated TNF α production in villous placenta but not amnion. LPS treatment caused increased release of IL-1B, TNF- α , and IL-10 in villous explants, but no difference in placenta explants.	Protein=ELISA		Amnion explants, Placental villous explants
108	Mitchell et al., 1991 European Journal of Pharmacology	IL-6 induces an increase in prostaglandin (PGE2) production in amnion and decidua. The amount of IL-6 needed was in the range that could be found in amniotic fluid of infection leading to preterm labor.	Protein= radioimmunoassay		amnion, decidua stimulated with IL-6
109	Mital et al., 2010 Journal of Perinatal Medicine	qRT-PCR confirmed over-expression of prostaglandin-endoperoxide synthase-2, heparin binding epi-dermal growth factor (EGF)-like growth factor, chemokine C-C motif ligand 2 (CCL2/MCP1), leukocyte immunoglobulin-like receptor, subfamily A member 5, interleukin (IL)-8, IL-6, chemokine C-X-C motif ligand 6 (CXCL6/GCP2), nuclear factor of kappa light chain gene enhancer in B-cells inhibitor zeta, suppressor of cytokine signaling 3 (SOCS3) and decreased expression of FK506 binding-protein 5 and aldehyde dehydrogenase in labor. IL-6, CXCL6, CCL2 and SOCS3 protein expression was significantly higher in the term labor group compared to the term not in labor group. 0 differentially expressed genes from our study (ENC1, PDE4B, IL-8, PIM1, RGS10, SOD2, IL8RB, IL-1B, NFKBIZ, and IER3) are genomic direct targets of the RelA NF-kB subunit w178x.	mRNA=HumanHT-12 microarray, RT-PCR Protein=ELISA, Western blot	myometrium	
110	Myatt et al., 1992 International Journal of Developmental Biology	Western blot showed that annexin I-5 were in the amnion and chorion/decidua in TNIL & TIL. Each annexin was found in one pool that was dependent on	Protein= Western Blot	amnion and chorion and decidua	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		calcium and the other that wasn't (both located on the membranes). In amnion and chorion cells annexin 1 decreases with labor, while annexin 5 in chorion increases with labor. During labor the calcium dependent pool of annexin 1 and 3 (amnion and chorion) decrease, while annexin 5 increases. The calcium independent pools of annexin 1 in amnion and annexin 1,3,5 in chorion decrease with labor. annexin 1 (calcium independent.) in the amnion show the most decrease overall with labor.			
111	Nace et al., 2010 Journal of Perinatal Medicine	IL-24 and 29 seen in term and PT labor samples but not in term no labor. Not found in amniotic fluid. IL-24 concentrations were higher after LPS stimulation whereas IL-29 concentrations were higher after polyIC-stimulation	mRNA=RT-PCR Protein=ELISA	fetal membranes	fetal membranes treated with LPS
112	Norwitz et al., 2007 American Journal of Obstetrics and Gynecology	Progesterin enhanced PAI-1 and inhibited uPA expression by term Decidua cells. Thrombin augmented PAI-1 expression in the absence of increased uPA or tPA expression by term DCs	mRNA= RT-PCR Protein=ELISA, Western		Decidua
113	O'Brien et al., 2008 Reproductive Science	PSCDBP, TLR2, TWIST1, FLJ35382 and RGS12, EDNRB are upregulated in myometrium with labor	mRNA=microarray, RT-PCR Protein=Western blot, microscopy	myometrium	
114	Ognjajovic et al., 2002 American Journal of Obstetrics and Gynecology	Pre-B-cell colony-enhancing factor (PBECF) was found in the amnion epithelial, mesenchymal cells, chorionic cytotrophoblast, and parietal decidua. It was highest in the amnion though. It also increased with labor and preterm labor in correlation with IL-8. rhPBECF treatment of WISH cells and fetal membranes increased IL-6/8 mRNA.	mRNA= Northern blot Protein= immunolocalization, ELISA	amnion, chorion, decidua, and placenta, wish cells, fetal membrane explants	WISH cells
115	Ognjajovic et al., 2003 American Journal of Obstetrics and Gynecology	Placental explants from 3 patients were treated with PBECF and then RNA expressions assessed. Only 8 genes were up-regulated consistently and significantly in all three patients (three key inflammatory cytokines [tumor	mRNA= gene chip, Qrt-pcr, Protein=ELISA	amnion, chorion, decidua, placenta	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		necrosis factor- α , interleukin-6, and interleukin-1 β , four important chemokines [macrophage inflammatory protein-1 α , macrophage inflammatory protein-1, macrophage inflammatory protein-3 α , and growth-related oncogene- γ], and prostaglandin-endoperoxide synthase			
116	Okazaki et al., 1981 American Journal of Obstetrics and Gynecology	In all placenta layers PG synthetase was increased in TIL vs TNIL. Especially with amnion cells. These increased a lot after labor. PGE2 was formed in the amnion and chorion laeve, while PGE2 and PGF2A was formed in the decidua vera.	Protein= assay of PGDH activity, assay of PG synthetase activity	decidua, amnion, chorion	
117	Osman et al., 2006 Society for Gynecologic Investigation	The area of the membranes overlying the cervix is a site of inflammation during labor and referred to as the zone of altered morphology (ZAM). The ZAM was investigated. There was greater leukocyte density in the periplacental (PP) vs the ZAM region, and the decidua had greater leukocyte density compared to the amnion and chorion. IL-1 β , IL-6, and IL-8 mRNA expression was significantly greater in all regions following spontaneous labor compared with nonlaboring tissues. There were no regional differences in cytokine expression within the fetal membranes. Choriodecidua expressed significantly more IL-1 β mRNA than amnion. Amnion expressed more COX-2 mRNA than choriodecidua.	mRNA= RT-PCR, Northern analysis Protein= IHC	the ZAM, midzone (MZ), and periplacental(PP) regions from fetal membranes and decidua	
118	Osman et al., 2004 Journal of Reproductive Immunology	They found that following labor, ICAM-1 mRNA expression was significantly upregulated in amnion and choriodecidua ($P<0.05$). PECAM mRNA expression was also increased in choriodecidua ($P<0.05$). The main cell types responsible for adhesion molecule expression were leukocytes, amniotic epithelial cells and endothelial cells.	mRNA=Northern blot Protein=IHC	amnion, choriodecidua	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
119	Osman et al., 2003 Molecular Human Reproduction	They found that parturition was associated with a significant increase in IL-1b, IL-6 and IL-8 mRNA expression in cervix and myometrium, IL-6 and IL-8 mRNA expression in chorio-decidual and IL-1b and IL-8 mRNA expression in amnion.	mRNA=RT-PCR, Northern blot Protein= IHC	fetal membranes, decidua and cervix, myometrium, chorio-decidual and amnion.	
120	Pasetto et al., 1993 Placenta	Granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-4 production by human fetal membranes and uterine decidua at term gestation was investigated. GM-CSF and IL-6 were both produced in detectable amounts by tissues. GM-CSF production significantly increased when tissues obtained before labor were stimulated with PHA. IL-6 production was not significantly affected by labor and PHA. IL-4 was not detectable in 10 of 14 samples.	Protein= ELISA	fetal membranes and decidua	fetal membranes and decidua
121	Peng et al., 2011 Kaohsiung Journal of Medical Sciences	Differentially expressed genes in the placenta of the laboring group are involved in nitric oxide transport, gas transport, response to hydrostatic pressure, oxygen transport, acute phase responses, and the tumor necrosis factor-mediated signaling pathway which are important during the transient hypoxemia and hypoperfusion that occur in the placenta during uterine contractions TOP three induced genes are: GDF15, HMOX3, SERPINE1	mRNA=microarray, RT-PCR	Placenta	
122	Phillips et al., 2011 Molecular Human Reproduction	In placenta, the PG synthase expression profile favors production of PGE2 and PGF2, with high levels of PG transporters and catabolic PG dehydrogenase suggesting rapid PG turnover. Choriodecidual is primed for PGE2, PGF2 and PGD2 production and high PG turnover, whereas amnion expresses genes for PGE2 synthesis with low levels of PG transporters and dehydrogenase. In pregnant myometrium, PGI2, PGD2 and PGF2 synthases are highly expressed, whereas PG	mRNA=RT-PCR Protein=Western blot	myometrium, placenta, choriodecidual	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		dehydrogenase is under expressed. Myometrium from women with spontaneous or induced labor had higher mRNA expression of the PGH2 Synthase PTGS2 (COX-2) than tissue from women not-in-labor.			
123	Phillips et al., 2014 BMC Pregnancy and Childbirth	Amnion with labor: increased PTGES, lower PTGIS, ABCC4, HPGD. Choriondecidua with labor: increased AKR1C3.	mRNA=RT-PCR Protein=IHC	amnion, choriondecidua	
124	Rauk et al., 2000 American Journal of Reproductive Immunology	IL-1 stimulation lead to increased PG (Pge and PGF2a) production at 6 hr, COX-2 protein increased at 4 h and continued at 24 h, COX-2 mRNA peaked at 4 h.	mRNA= Northern Blot (COX) Protein=ELISA (PGs), Western blot (COX protein)		Myocytes stimulated with IL-1
125	Rehnstrom et al., 1983 Prostaglandins	Decidua and myometrium: increased PGE and PGF production after treatment with term AF (NL and L). In the amnion, no change in total PG level but increased ratio of PGF to PGE with term AF. Second tri AF made no change in PG production	Protein= RIA		amnion, decidua, myometrium
126	Roh et al., 2000 Molecular Human Reproduction	MMP-9 was present in smooth muscle cells, interstitial fibroblasts and immune cells. ProMMP-9 increased dramatically in labor. IL-1B and TNF-a induced pro-MMP9. Progesterone did not down regulate the IL-1B or TNF-a mediated increase in MMP9.	Protein=Immunostaining, Immunoblotting, Gelatin zymography	Myometrium	Myometrium treated with IL-B or TNF-a
127	Saito et al., 1994 Journal of Reproductive Immunology	IL-8 mRNA and protein were localized to cytotrophoblasts, syncytiotrophoblasts and Hofbauer cells of placenta, decidual stromal and lymphocyte cells, and endometrial gland cells. BeWo cells and Endometrial cancer cells line produced IL-8 mRNA and protein too.	mRNA= in situ hybridization, RT-PCR Protein= IHC, ELISA	placenta, decidua	BeWo, Ishikawa (endometrial CA line)
128	Sato et al., 2003 Journal of Immunology	Treatment with LPS induced TNF-a at 4 h, IL-10 peaked at 8h, IL-1B peaked at 12h, and PGE2 peaked at 24 hours. IL-1B stimulated only PGE2 production, while TNF-a stimulated IL-1B, PGE2 and IL-10. Treatment with IL-10 markedly decreased TNF-a and	Protein= Immunoneutralization, ELISA (IL-1B, TNF-a, IL-10), RIA (PGE2)		Choriondecidua explants stimulated with LPS, IL-1 B and TNF-a

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		IL-1B production, but no effect on PGE ₂ .			
129	Satoh et al., 1981 Prostaglandins and Medicine	PGE ₂ produced at steady rates regardless of condition (NL vs L). Amnion showed the highest production of PGE ₂ . PGF ₂ increased in labor in myometrium and decidua, but not in amnion. 6-keto PGF ₁ α was lower with labor	Protein= Radioimmunoassay	amnion, decidua, myometrium	
130	Schringer et al., 2000 Journal of Clinical Endocrinology and Metabolism	IL-6 and IL-8 were the main cytokines released at 24 h. All cytokines were stimulated by LPS and not by CRH. mRNA IL-1β and IL6 were present in preterm and term regardless of labor. IL-8 and TNF-α mRNA were expressed only in myometrium in active labor	mRNA= RT-PCR Protein= ELISA, IHC	Myometrium	Myometrium stimulated with LPS or CRH
131	Simpson et al., 1998 Journal of Clinical Endocrinology and Metabolism	In labor: decreased IL-10, increased IL-6 and PGE ₂ . All three had increased production with IL-1B, TNF-α, and LPS stimulation, and all were decreased with dexamethasone. There was significantly increased responsiveness of IL-10 production to inflammatory stimuli after labor.	Protein=Radioimmunoassay, ELISA	Choriodecidea	Choriodecidea treated with IL-1B, TNF-α and LPS
132	Simpson et al., 1999 Journal of Reproduction and Fertility	Basal IL-10 production was the same and low both TL and TNL. PGE ₂ was significantly increased in TL vs TNL. IL-6 was not significantly changed by labor. IL-6 and PGE ₂ production increased with IL-1B, TNFα and LPS in both TL and TNL, responsiveness of IL-10 was variable. Dexa suppressed PGE ₂ production, but not as much in TL samples	Protein= Radioimmunoassay, ELISA		Amnion explants
133	Skinner et al., 1985 American Journal of Obstetrics and Gynecology	Output of all 3 PGs was low prior to labor. Amnion: increased production of PGE ₂ and PGF ₂ α with labor. Decidua: small increase production of all 3 with labor. Chorion: with labor increased 13.14 PG, but no net production of PGE ₂ or PGF ₂ α	Protein=Radioimmunoassay	Amnion, chorion, decidua	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
134	Slater et al., 1994 Biochemical and Biophysical Research Communications	There is ~100 fold excess of COX-2 mRNA over COX-1 in term amnion at time of labor.	mRNA=RT-PCR	Amnion	
135	Slater et al., 1995 American Journal of Obstetrics and Gynecology	COX-1 and -2 were localized in the amnion epithelial and mesoderm. COX-1 (not 2) was localized in chorionic mesoderm. COX-2 increased significantly with labor.	mRNA= RT-PCR, in situ hybridization	Fetal membranes	
136	Slater et al., 1999 Journal of Molecular Endocrinology	COX-1 mRNA expression was low throughout pregnancy and labor in amnion and chorio-decidua. COX-1 protein levels did not change with labor or gestational age. COX-2 mRNA increased with gestational age and significant increase prior to and in labor. COX-2 protein level increased with increased gestational age. COX-2 increases prior to labor	mRNA=RT-PCR Protein=Western blot, RIA	fetal membranes	
137	Slater et al., 2004 Molecular Human Reproduction	sPLA2-IIA significantly increased with pregnancy and labor both term and preterm. cPLA2-IV was not altered with pregnancy or labor. IHC showed that cPLA2-IV was mostly in vascular endothelial cells. sPLA2-IIA seen in vascular, endothelial and smooth muscle, but also seen in nuclear and perinuclear location in smooth muscle cells in the lower segment	mRNA=RT-PCR Protein=IHC, Western blot	Myometrium	
138	Slater et al., 1998 British Journal of Obstetrics and Gynecology	Choriodecidua was investigated for COX-1 and COX-2. COX-2 expression exceeded COX-1 by 8-fold in term membranes. COX-2 expression increased by 4-fold with labor.	mRNA=RT-PCR	Chorio-decidua	
139	So et al., 1992 Biology of Reproduction	Chorion cells produced MMP-1 and MMP-3 in response to IL-1. Treatment of chorion with TNF- α led to increased MMP-1, MMP-3, uPa and PGE2. TIMP production was suppressed by TNF α	Protein= fibril assay, Substrate gel electrophoresis, Western Blot, RIA		Chorio-amniotic membranes
140	Sparey et al., 1999 Journal of Clinical Endocrine and Metabolism	Connexin-43: expressed at higher levels in upper segment and more pronounced with labor. COX-1 and COX-2 are expressed at higher levels in the lower segment, but no change with labor. Gsa protein is	Protein=Western Blot	Upper and lower segment myometrium	

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
		uniformly expressed in upper and lower segments and decreases in labor.			
141	Steinborn et al., 1995 Prostaglandins	The villous trophoblast (placenta) produced significantly more cytokines and PGs from laboring cells than non labor cells. Membranes from labor produced more IL-6 and PGE2 also. Decidua produced similar amounts before and after labor.	?not documented, some kind of assay	membranes, decidua, placenta (also vaginal secretions and amniotic fluid)	
142	Steinborn et al., 1998 Placenta	IL-6 receptor and TNF receptor were expressed by fetal endothelial cells within placental villi. IL-1 receptor I are exclusively in the stromal cells of the maternal decidua. IL-1 and TNF receptors were expressed in quiescence and labor. IL-6 receptor gp80 subunit was more present with term and preterm labor.	Protein= Immunohistologic staining	Placenta, membranes	
143	Stephen et al., 2015 American Journal of Reproductive Immunology	Extensive inflammatory activation seen in choriondecidua after labor. Genes upregulated regulating leukocyte trafficking and cytokine signaling. Upregulated genes included ICAM1, CXCR4, CD44, TLR4, SOCS3, BCL2A, IDO	mRNA=GeneArray Protein: IHC	Choriondecidua	
144	Siemer et al., 1998 Medical Science Research	IL-8 (radiolabeled) is transferred in both directions across the fetal membranes. 15–20% of the cytokine crossed to the opposite side of membrane intact after 24 hours-not effected by which side it was added to or labor status	Protein= gamma counter		fetal membranes
145	Sun et al., 1996 Placenta	Annexin proteins are calcium binding proteins. Annexin I: in amnion epithelial cells, chorion trophoblasts and syncytiotrophoblast cells of placenta, not in decidua. Annexin II was seen in amnion, mesenchymal cells between chorion and amnion, chorion trophoblast and endothelial cells in decidua. No change in distribution with labor	Protein= IHC	membranes, decidua and placenta	
146	Tan et al., 2012 Journal of Clinical	PR-A and PR-B were transcriptionally active in response	mRNA= RT-PCR, genome wide transcriptome analysis		Myometrium-immortalized

	Author, Year, Journal	Main results	Type of analysis	Clinical specimen analysis	In vitro culture and analysis
	Endocrinology and Metabolism	to progesterone and affected the expression of distinct gene cohorts. Progesterone decreased proinflammatory gene expression when the PR-A:PR-B favored PR-B and it increased pro-inflammatory gene expression when the ratio favored PR-A. Progesterone via PR-B leads to inhibition of NF- κ B and limited basal and LPS-induced proinflammatory gene expression. PR-A inhibited those effects. Data suggest that during most of human pregnancy, when myometrial cells are PR-B dominant, progesterone promotes myometrial quiescence through PR-B-mediated anti-inflammatory actions. At parturition, the rise in PR-A expression promotes labor by inhibiting the anti-inflammatory actions of PR-B and stimulating proinflammatory gene expression.	Protein=Immunoblotting, IHC		
147	Tattersall et al., 2008 Reproduction	Lower segment: TL had sig higher PGHS-2 (COX-2), IL-1B, IL-6, and IL-8 mRNA expression than PTL. TL and PTL both had higher expression of IL-1B and IL-8. PGHS-2 and IL-6 were increased in labor samples over non labor only in TL. Upper segment: no differences between PTL and TL samples. PGHS-2 and IL-1B were increased in TL vs TNL. Neither effected connexin-43 or oxytocin receptor	mRNA=RT-PCR Protein= Western blot	Myometrium-upper and lower segments	
148	Teixeira et al., 1993 Journal of Lipid Mediators	PGHS enzyme activity and PGE2 production are higher in TL than TNL and in PTL over PNL. PGHS enzyme activity and PGE2 production were increased in TNL group over PNL.	Protein=RIA, protein assay, immunoblotting	amnion	
149	Terzidou et al., 2011 Biology of Reproduction	In labor there is increased expression of oxytocin receptor (OXTR) mRNA and protein. IL-1B leads to increase in OXTR mRNA in treated pre-labor amnion cells (peak at 6 h). Incubation of pre-labor cells with OXT leads to increased PGE2 and COX -2 (via a	mRNA= RT-PCR Protein= Western Blot, Immunodetection	amnion	amnion

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		protein kinase signal transduction pathway)			
150	Than et al., 2009 Journal of Maternal-Fetal and Neonatal Medicine	MnSOD mRNA was higher in TL than TNL, also higher in PTL than TL or PPROM. MnSOD higher in those with chorioamnionitis than those without. Mn SOD higher in PTL with chorio than PPROM with chorio	mRNA= RT-PCR	chorion, amnion	
151	Ticconi et al., 2004 American Journal of Reproductive Immunology	Oxytocin stimulation lead to increased nitrite release. mRNA iNOS expression was enhanced by oxytocin also. The effects were more marked in labor tissue than no labor.	mRNA= RT-PCR Protein= Griess reaction, Western Blot	fetal membrane explants	fetal membrane explants treated with oxytocin
152	Topping et al., 2013 Journal of Maternal-Fetal and Neonatal Medicine	Nuclear expression of IL-33 seen in endothelial and smooth muscles of placenta, chorioamniotic membranes and cord. IL-33 was detected in the nucleus of CD14+ macrophages in membranes, chorionic plate and Wharton's jelly. IL-33 expression increased after IL-1b treatment in amnion. IL-33 expressed in acute chorio but not in chronic chorio.	mRNA= RT-PCR Protein= IHC, immunofluorescence staining	placenta, chorioamniotic membrane	placenta, chorioamniotic membrane
153	Trautman et al. 1997 Gynecologic and Obstetric Investigation	Decidua: produced IL-10 in response to IL-1b. Amnion/Chorion: did not produce IL-10 in response to IL-1b	mRNA= in situ hybridization, RT-PCR Protein=ELISA, IHC		Decidua, chorion, amnion treated with IL-1b
154	Turner et al., 2002 Placenta	Term placenta produced IL-1b and IL-6. Post labor placentas are less responsive to TNF- α stimulation than placenta from Cesarean delivery.	Protein=ELISA		placental fragments
155	Ulug et al., 2001 Molecular Human Reproduction	Decidua produced more MMP-2 and 9 than the other fetal membrane layers and decreased TIMP1 level after PGF2a treatment. Chorion and amnion levels of MMP-2, 9 and TIMP1 were not changed by treatment with TIMP1.	Protein= zymography, Western Blot		Amnion, chorion, decidua
156	Vora et al., 2010 Reproductive Biology and Endocrinology	Nuclear p65 (a major component of NF- κ B pathway) labeling was rare in amnion and chorion, irrespective of clinical context. In the decidua, nuclear p65 labeling was greater in the STL group	Protein= IHC, ELISA	Fetal Membrane and myometrium	

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157	Whittle et al., 1999 Placenta	relative to the TNL cohort, but there were no differences among the TNL, PTL, and PNL cohorts. In myometrium, diffuse p65 nuclear labeling was significantly associated with both term and preterm labor. In all tissues studied the IL-1 type I receptor was localized mainly to the decidua and the type II receptor was localized to the decidua and scattered cells in the amnion-chorion mesenchymal layer. The type I and type II receptor protein in the decidua showed a similar pattern of staining as that found for CD-68, a macrophage marker. No evidence for the presence of the type I or type II receptor or their mRNAs in the amnion epithelial cells or chorion laeve trophoblast was found.	mRNA=in situ hybridization Protein= IHC	Fetal Membrane, decidua	
158	Wilson et al. 1988 Prostaglandins	Oxytocin at a physiological concentration stimulated the immediate release of free arachidonic acid from dispersed human decidual cells in a perfusion system. This indicates that oxytocin activates phospholipase(s) thus enhancing prostaglandin synthesis. The effect of oxytocin on the release of [3H]-arachidonic acid from decidual cells of women in labor was significantly greater than from those of women not-in-labor or with endometrial cells of nonpregnant women.	Protein=radioimmunoassay		decidua cells
159	Xu et al., 2005 Molecular Pharmaceutics	PGF2 dose dependently increased CX-43 and PTGS-2 (COX-2) while decreasing PTGFR in upper and lower segments. PGF2 increased OTR in the lower segment while decreasing it in the upper segment. Indomethacin reversed the PGF2 -induced effects on CX-43 and PTGS-2, but it did not alter PGF2 -induced PTGFR and OTR expression.	Protein=Western Blot		Myometrium treated with PGF2a
160	Xue et al., 1995 Prostaglandins	Treatment of WISH cells with IL-1b increase in PGE2 release	Protein= Phospholipase A Assay, Assay of PGE, Western Blot		WISH cells treated with IL-1B

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		and also increased both in total cellular cPLA2, activity and in cPLA2, protein levels. IL-1b could lead to cPLA2 synthase. AACOCF ₃ inhibited IL-1B induced PGE2 production strongly suggesting that cPLA2, mediates IL-1 B-induced PGE2 formation. cPLA2, translocation from cytosol to the membrane is necessary for its bioactivity.			
161	Yadav et al., 2014 PLoS ONE	Collectins are proteins involved in immunomodulation, which include surfactant proteins A and D (SP-A and SP-D). The spontaneous labor group showed significant up-regulation of SP-D, and down-regulation of SP-A. Significant increase SP-D in placental and decidual tissues was associated with the spontaneous labor. In addition, the MMP-9-cleaved form of SP-D was significantly higher in the placenta of labor group compared to the no labor group. Labor associated cytokines IL-1a, IL-1b, IL-6, IL-8, IL-10, TNF-a and MCP-1 proteins were significantly increased in the placental explants treated with nSP-D and rhSP-D.	mRNA= RT-PCR Protein=multiplexed cytokine array, Western Blot, immunohistochemistry		placental/decidual tissues
162	Yan et al., 2002 Placenta	p65 protein was found in the nucleus and cytoplasm of cells in the amnion, chorion laeve and decidua. In the amnion and chorion laeve, no changes occurred in subcellular localization with advancing gestation or term labor. However, in the decidua, there was a marked increase in the nuclear localization of i.r. p 65. IKB was localized to the cytoplasm of cells in all tissues and there was an increase IKB in decidua at term compared to preterm but no change occurred in the amnion or chorion	Protein= Immunohistochemical staining	fetal membranes and decidua	
163	Yonemoto et al., 2006 Placenta	Amnion: MMP-2 and 9 increased with term labor. Chorion: no change in MMP 2 or 9	Protein= Western Blot and Zymography	Amnion and chorion	
164	You et al., 2014 Journal of Clinical	CCL2, CXCL8 (IL-8), IL-1B, IL-6, and activated nuclear factor-	mRNA= RT-PCR	Myometrium	Myometrium

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	Endocrinology and Metabolism	B (NF- κ B) protein levels were increased in the term labor group more than the not term labor group. CRH stimulated production of a number of chemokines and cytokines in cultured uterine smooth muscle cells (USMCs), which induced chemotaxis of monocytes. These effects were mediated by CRH receptor 1 (CRHR1) and dependent on adenylyl cyclase/protein kinase (PKA) and NF- κ B signaling. IL-1, IL-6, and TNF-stimulated the expression of UAPs and output of PGs in USMCs.	Protein= immunofluorescence, ELISA, Multiplexed fluorescent bead-based immunoassays, Chemotaxis assay		
165	Young et al., 2002 Biology of Reproduction	In myometrium, IL-1 β , IL-6, IL-8, and TNF α were restricted to leukocytes, which were present in greater numbers in tissue obtained during labor. In fetal membranes, IL-6 and TNF α were expressed by decidual stromal cells, infiltrating leukocytes, and extravillous trophoblasts. IL-1 β was localized to leukocytes in the decidua of the membranes. IL-8 was expressed in laboring tissues from the decidual cells	Protein= IHC, ELISA, Western Blotting	myometrium (upper and lower segment), cervix, and fetal membranes	
166	Zachariades et al. 2012 Placenta	mPR are present in BeWo cells. 2.8 fold decrease of mPRb in laboring vs non laboring tissue and a 4.6 fold higher levels of mPRg in preterm. The ratio of mPRa to PR-B was increased in term compared to preterm samples, whereas it was decreased in labor compared to non-labor placentas.	mRNA= PCR Protein=cell death assay, immunoblotting	Placenta	BeWo cells
167	Zaga et al., 2014 American Journal of Obstetrics and Gynecology	The presence of PRL during explant incubation significantly decreased the patterns of IL-1 β , TNF- α and MMP-9 secretion along culture. MMP-2 secretion was unaffected by PRL. Tnf- α was not modified by the presence of PRL while MMP-9 was reduced.	mRNA=RT-PCR Protein= ELISA		fetal membranes
168	Zhao et al., 2013 American Journal of Reproductive Immunology	Cyclic mechanical stretch increased IL-8, GRO α , mRNA and protein, and MMP-1 production and activity level. Supernatant from stretched cells induced neutrophil chemotactic activity	mRNA=RT-PCR Protein=ELISA		Decidua

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		significantly. P4 suppressed the effect of stretch.			
169	Zhao et al., 2013 American Journal of Reproductive Immunology	Cyclic stretch increased IL-8 and Groa mRNA and protein and pro-MMP-1 production significantly by non pregnant myometrial cells. Stretch effects were reduced by P4.	mRNA=RT-PCR Protein=ELISA		Myometrium
170	Zhou et al., 2015 Acta Obstetrica et Gynecologica Scandinavica	IL-6, SOCS3 and pSTAT3 protein were elevated in TL compared to TNL	mRNA= TUNEL Protein=Western blot, FLOW, ELISA	placenta, trophoblast cells	HTR-8/SVneo cells (1st trimester trophoblast cell line), placenta
171	Zicari et al., 2002 Journal of Reproductive Immunology	TGF-1 expression in tissues stimulated with oxytocin, hydrocortisone and progesterone was significantly higher than in control tissues. No differences between the effects of oxytocin, hydrocortisone and progesterone were found. TNF- α expression in tissues stimulated with oxytocin was higher than in control tissues. Progesterone and hydrocortisone did not change TNF- α expression by tissues	mRNA=RT-PCR Protein=ELISA		Fetal membrane explants
172	Zuo et al., 1994 Journal of Clinical Endocrine and Metabolism	COX1 & 2 mRNA and proteins are present in the myometrium. Gene expression was different though. COX2 was higher at term pregnancy compared to preterm and TNIL. Cox1 expression was not dependent on labor, while COX2 was. PGE2 and PGF2A were also in the myometrium on immunostains.	mRNA=in situ hybridization, Protein=immunoblotting, immunocytochemistry	Myometrium	