Published in final edited form as:
Am J Obstet Gynecol. 2011 February ; 204(2): 177.e15–177.e33. doi:10.1016/j.ajog.2010.09.025.

A molecular signature of an arrest of descent in human parturition

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Abstract

Objective—This study was undertaken to identify the molecular basis of an arrest of descent.

Study Design—Human myometrium was obtained from women in term labor (TL; n=29) and arrest of descent (AODes, n=21). Gene expression was characterized using Illumina® HumanHT-12 microarrays. A moderated t-test and false discovery rate adjustment were applied for analysis. Confirmatory qRT-PCR and immunoblot was performed in an independent sample set.

Results—400 genes were differentially expressed between women with an AODes compared to those with TL. Gene Ontology analysis indicated enrichment of biological processes and molecular functions related to inflammation and muscle function. Impacted pathways included inflammation and the actin cytoskeleton. Overexpression of HIF1A, IL-6, and PTGS2 in AODES was confirmed.

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This manuscript was presented in abstract form at the 30th Annual Meeting of the Society for Maternal-Fetal Medicine, 2010, Chicago, Illinois, February 4th, 2010.

Conclusion—We have identified a stereotypic pattern of gene expression in the myometrium of women with an arrest of descent. This represents the first study examining the molecular basis of an arrest of descent using a genome-wide approach.

Keywords

pregnancy; parturition; myometrium; spontaneous term labor; systems biology; inflammation; transcriptomics; interleukin-6; IL6; prostaglandin-endoperoxide synthase 2; COX2; PTGS2; hypoxia inducible factor-1a; HIF1A; ATPase, Na+/K+ transporting, alpha 1 polypeptide; ATP1A1

Introduction

The common pathway of parturition is a complex process involving concomitant myometrial activation, cervical ripening, and membrane-decidual activation.[1-26] While the process of labor is vital to the survival of viviparous species, its physiology and pathology incompletely understood. Dysfunctional term labor (failure to dilate and/or descend) necessitates surgical intervention for delivery. Indeed, the frequent diagnosis of labor arrest disorders contributed to the performance of primary cesarean section rate of 23.5% of parturients in the United States in 2006.[27]

Labor arrest disorders are often attributed to cephalopelvic disproportion. However, while cephalopelvic disproportion contributes to arrest of descent and dilatation, a subset of women who undergo cesarean section for an arrest disorder subsequently deliver a larger neonate vaginally. It is more likely that “failure to progress” represents a functional disorder of labor whose etiology is yet to be elucidated. Such functional disorders may result from inadequate or uncoordinated activation of the common pathway of parturition. Evidence suggests that in natural preparation for labor, the myometrium attains an increasingly contractile phenotype,[28-64] while the cervix also undergoes preparatory changes.[36;57;65-86] Insufficient preparation of the uterus or cervix for labor may prevent the successful coordinated efforts necessary for normal parturition.

High-dimensional biology techniques such as genomics, transcriptomics, and proteomics can be applied to determine the molecular signatures of both pathologic and physiologic states and provide insight into the biological processes involved.[87-94] While the transcriptome (tissue-specific) of myometrium in normal term labor has been investigated, [95-101] that of an arrest of descent has never been reported. We undertook this study in order to characterize the differential gene expression of human myometrium in patients with an arrest of descent and to explore the mechanisms leading to this common labor disorder.

Materials and Methods

A prospective study was performed in which human myometrium was obtained from women undergoing primary cesarean section at term (>37 weeks gestation) in the following groups: 1) term spontaneous labor (n=29); and 2) arrest of descent (n=21). Labor was diagnosed in the presence of spontaneous regular uterine contractions occurring at a minimum frequency of 2 every 10 minutes with cervical change that required hospital admission. Women in the term labor group underwent cesarean section due to a non-reassuring fetal status as determined by the primary physician or fetal malpresentation. The diagnosis of arrest of descent was made in patients with complete cervical dilation without continued fetal descent after greater than 1 hour.[102-104] Only patients presenting in spontaneous labor were included. The placentas of all participating women were examined by an experienced pathologist (CJK) who was blinded to the clinical diagnosis. Patients with

clinical[105] or histological[106;107] chorioamnionitis and those undergoing labor induction were excluded.

All women provided written informed consent prior to the collection of myometrial samples. The collection and utilization of the samples for research purposes was approved by the Institutional Review Board of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD/NIH/DHHS, Bethesda, Maryland), and the Human Investigation Committees of Wayne State University (Detroit, Michigan) and the Sotero del Rio Hospital (Santiago, Chile).

Sample collection

Samples of myometrium were obtained from the lower uterine segment at the time of cesarean section, following delivery of the placenta. The biopsies were obtained from the midpoint of the superior aspect of the uterine incision using Metzenbaum scissors. All specimens measured approximately 1.0×1.0×1.0 cm. Tissue was ground under liquid nitrogen, placed in TRI Reagent® (Applied Biosystems, Foster City, CA) and kept at −80° Celsius until analysis.

Total RNA Extraction

Total RNA was isolated from snap-frozen myometrium using TRI Reagent® combined with the Qiagen RNeasy Lipid Tissue kit protocol (Qiagen, Valencia, CA, USA) according to the manufacturers' recommendation. The RNA concentrations and the A260nm/A280nm ratio were assessed using a NanoDrop 1000 (Thermo Scientific, Wilmington, DE, USA). RNA integrity numbers (RIN) were determined using the Bioanalyzer 2100 (Agilent Technologies, Wilmington, DE, USA). An A260nm/A280nm ratio of 1.66, a 28S/18S ratio of 0.2, and a RIN of 3.8 were minimum requirements for inclusion in expression analysis.

Microarray Experiments

The Illumina® HumanHT-12 v3 expression microarray (Illumina, San Diego, CA, USA) platform was used to measure the expression levels in each unpooled specimen per manufacturer's instructions. In brief, after purification of RNA using an RNeasy Mini Kit, 500ng of total RNA was amplified and biotin-labeled with the Illumina® TotalPrep RNA Amplification Kit (Ambion, Austin, TX, USA). Labeled cRNAs were hybridized to the Illumina HumanHT-12 v3 expression BeadChip and imaged using a BeadArray Reader. Raw data was obtained with BeadStudio Software (Illumina).

Quantitative Real-time Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

A separate set of specimens for each group (term labor n=10; arrest of descent n=7) were obtained for qRT-PCR assays of select genes differentially expressed by microarray analysis. Total RNA (3 μg) was reverse transcribed using the SuperScript® III First-Strand Synthesis System and oligo$(dT)_{20}$ primers (Invitrogen, Carlsbad, CA, USA). PCR analyses were performed with TaqMan® Gene Expression Assays (HIF1-A: Hs00936368_m1, IL-6: Hs00174131_m1, PTGS2: Hs01573471_m1, ATP1A1: Hs00167556_m1, GPR4: Hs00947870_m1, CNN1: Hs00154543_m1, CALD1: Hs00189021m1, EXOG: Hs00270782_m1, FLNC: Hs00155124_m1, MYLK: Hs00364926_m1, SLPI: Hs01070946_m1, SOD2: Hs00167309_m1, and SORBS1: Hs00908953_m1; Applied Biosystems, Foster City, CA, USA). The human RPLPO (large ribosomal protein) TaqMan® Endogenous Control (part number: 4326314E) was used as the housekeeping gene for relative quantification. The gene specific TaqMan® assays and the RPLPO housekeeping gene were run in triplicate (50ng) for each case to allow for the assessment of technical variability.

Enzyme-linked immunosorbent assay and immunoblot

The myometrial protein concentration of IL-6 was determined with a specific enzyme-linked immunoassay (R&D Systems, Inc, Minneapolis, MN) according to the manufacturer's instructions (term labor n=6; arrest of descent n=5).

Statistical analysis

Clinical data—Statistical analysis of clinical data was performed with Kruskal-Wallis and Mann Whitney U test for post-hoc analysis, Chi-square and Fisher Exact tests. The statistical package used was SPSS v.12 (SPSS Inc,. Chicago, IL). A *p* value of less than 0.05 was considered significant.

Microarray analysis—The Illumina BeadStudio software suite was used to extract raw gene expression values from the array images. Data quality was assessed based on Illumina's positive and negative control probes on each array as well as by inspection of the distributions of probe intensities. Data was normalized using the quantile normalization method.[108] Probes that were called present (detection p value <0.1) in at least 5 samples were retained for further analysis. A moderated t-test implemented in the *limma*[109] library of Bioconductor was applied to test differential expression, and a false discovery rate (FDR) adjustment of the p-value was performed to correct for multiple testing. Probes were considered significantly different if the adjusted p-value was less than 0.1 and the fold change difference between groups was at least 1.5.

Gene ontology analysis was conducted using an over-representation approach described elsewhere[110] and implemented in the GOstats[111] software package that uses an established approach to deal with the correlation of p-values between related GO terms.[112] Pathway analysis was performed on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway database using both the over-representation approach as well as the Signaling Pathway Impact Analysis (SPIA).[113;114] The SPIA impact analysis is a systems biology approach that takes into account the gene-gene signaling interactions as well as the magnitude and direction of gene expression changes to determine significantly impacted pathways.[113]

qRT-PCR assays and ELISA—Thirteen genes among those differentially expressed by microarray analysis were selected for confirmation with qRT-PCR based upon their rank in the list of all differentially expressed genes as well as biological plausibility. Data analysis was performed using an equal variance two-sample one-tailed t-test based on the hypothesis provided by the microarray data. qRT-PCR results were considered significant with a P-value <0.05 and if the direction of gene expression change between the groups was concordant with the microarray data. IL-6 concentrations were compared using the Mann-Whitney U test.

Results

Demographic and clinical characteristics of the study groups are displayed in Table 1. There were no significant differences in gestational age at delivery among the groups.

Microarray Analysis

Four hundred genes were differentially expressed between the myometrium of women at term in labor and those with an arrest of descent. Table 2 lists the top 100 genes differentially expressed between the two study groups ranked by p-values. The differential expression results are depicted in Figure 1. The volcano plot (Figure 1A) shows the magnitude versus the significance of gene expression changes. Principal component analysis

based visualization of the microarray data (Figure 1B) was performed as previously described.[94] This visualization of the samples in a 3-dimensional plot allows for inspection of the within-group transcriptome variability, and partly, the between-group differences.

Gene ontology meta-analysis was applied to obtain insight into the biology related to the stereotypic differences between the myometrial transcriptomes of arrest of descent and spontaneous term labor. Significant enrichment of 28 distinct biological processes, and 7 molecular functions (Table 3) was noted including: inflammatory response, response to hypoxia, muscle contraction, regulation of muscle contraction, actin binding, and structural constituent of muscle. While simple over-representation analysis did not indicate enrichment of any pathways in the comparison, Signaling Pathway Impact Analysis (SPIA) yielded 4 significant pathways associated with an arrest of descent: cytokine-cytokine receptor interaction, complement and coagulation cascade, regulation of actin cytoskeleton, and focal adhesion (Table 4).

qRT-PCR

Given the number of enriched biological processes and molecular functions related to muscle function and inflammation in this comparison, we were interested in further evaluating the differential expression of genes involved in these processes. qRT-PCR assays were performed on an independent set of myometrium samples for confirmation of the microarray results. A total of 13 genes were selected based upon microarray data and biological significance.

Consistent with the microarray results, qRT-PCR confirmed differential expression of 3 genes. Genes with significantly increased expression in an arrest of descent included hypoxia inducible factor-1a (HIF1A), interleukin-6 (IL-6), and prostaglandin-endoperoxide synthase 2 (PTGS2; alias COX2) (Figure 2). Although not significant at a 0.05 level, there was a trend for increased expression of Na+/K+ transporting, alpha 1 polypeptide (ATP1A1; p=0.05) in arrest of descent. Four additional genes had a p-value between 0.05 and 0.1 while matching the microarray determined directions of change. Overall, the direction of change was the same between the microarray data and the qRT-PCR data in 10 out of 13 tests (76.9%). Comparison of the qRT-PCR results with the microarray data of the selected genes is described in Table 5.

ELISA—The median protein expression of IL-6 was significantly higher in arrest of descent compared to the term labor group as shown in Figure 3. This result is consistent with the microarray and qRT-PCR data.

Comment

Principal findings of the study

1) The myometrial transcriptome of an arrest of descent is significantly different than that of spontaneous term labor with differential expression of 400 genes; 2) the stereotypic transcriptome detected in the myometrium from women with an arrest of descent was characterized by the increased expression of genes involved in inflammation and muscle contraction; 3) Gene Ontology analysis revealed enrichment of multiple biological processes and molecular functions supporting a role for the immune response and muscle contraction in an arrest of descent. Moreover, SPIA indicated 4 significant pathways involved in the biology of an arrest of descent including cytokine-cytokine receptor interaction, complement and coagulation cascade, regulation of actin cytoskeleton, and focal adhesion; 4) using independent sample groups for qRT-PCR confirmation of microarray results, increased mRNA expression of IL-6, PTGS2, and HIF1A as well as increased protein expression of

IL-6 was confirmed in the myometrium of women with an arrest of descent. These results are the first to describe a molecular fingerprint underlying dysfunction of the second stage of labor.

High-dimensional biology and human parturition—Discovery driven high-dimensional biology techniques have provided significant insight into normal human parturition. Studies using transcriptomics have demonstrated that uncomplicated spontaneous term labor is characterized by the overexpression of genes involved in the inflammatory response in the chorioamniontic membranes[115;116], the uterine cervix[69;117;118], and the myometrium,[77;97;98;100;119] thereby implicating inflammation as a component of the common pathway of parturition.

However, the molecular basis of labor dystocia, the leading indication for primary cesarean section, has not been previously investigated. This common labor disorder is diagnosed in as many as 37% of nulliparous deliveries.[120] Arrest of descent, first characterized by Emanuel Friedman,[102;103;121] has been reported to contribute to up to 61% of arrest disorders[120] and has been associated with numerous risk factors including nulliparity, fetal macrosomia, epidural analgesia, hypertensive disorders, and gestational diabetes mellitus.[122] Herein, we report the biological processes characterizing dysfunctional term parturition.

Meaning of the study

Arrest of descent is characterized by over-expression of genes involved in the inflammatory response—The involvement of inflammation in the "Great Obstetrical Syndromes" [123-138] (including preterm labor[139-162]) has been well-documented. However, normal spontaneous human parturition is also characterized by an inflammatory response, [143;144;149;150;153;154;161;163-192] partially attributed to a massive influx of leukocytes into myometrium at the onset of term labor.[77;86;193] Interestingly, our findings indicate that the molecular signature of an arrest of descent in comparison to spontaneous term labor involves a further overexpression of genes involved in inflammation. Indeed, the most enriched biological pathway is "cytokine-cytokine receptor interaction", followed by the "complement and coagulation cascade", which we and others have reported plays a key role in the activation of an inflammatory response.[139;141;142;145;147;151;155-160;194-203] Moreover, significantly enriched biological processes such as "inflammatory response", "chemotaxis" and molecular functions such as "chemokine activity" further support a role for inflammation in this labor disorder.

Our results confirmed increased expression of IL-6 mRNA and protein in myometrium from women with an arrest of descent compared to those with normal spontaneous labor at term. We have previously reported that the median amniotic fluid concentration of IL-6 is higher in women with spontaneous labor at term compared to those not in labor at term[179]-an observation that has since been confirmed in other gestational tissues.[69;77;86;115;204] This pro-inflammatory cytokine has also become an important marker for the assessment of women with preterm labor, preterm prelabor rupture of membranes, and is an essential element for the diagnosis of the Fetal Inflammatory Response Syndrome, which precedes the onset of labor.[173;205-211] Neonatal complications such as bronchopulmonary dysplasia[212;213] and periventricular leukomalacia[214;215] have also been associated with increased concentrations of IL-6.

A pleiotropic cytokine, IL-6 mediates the acute phase response and functions as a "myokine"; [216] IL-6 is well-recognized to play an important role in skeletal[217;218] and smooth muscle contraction.[219;220] Muscle-derived IL-6 expression within the contracting muscle increases in response to a reduction of intramuscular glycogen content, suggesting that the IL-6 response may be a signal that muscle glycogen stores are being depleted.[221;222]

We report significantly higher myometrial IL-6 mRNA and protein expressions in an arrest of descent compared to spontaneous term labor. Indeed, qRT-PCR confirmation of our microarray results in an independent sample group indicated a 7.7 fold increase in IL-6 mRNA expression in myometrium during arrest of the second stage of labor. This finding was further validated using ELISA to confirm increased myometrial IL-6 protein expression in an arrest of descent. Dajani and colleagues[223] investigated the effects of IL-6 on myometrial contractions using a dual chamber-fetal membrane-uterine muscle *in vitro* model. They found that treatment of the tissues with IL-6 actually caused a significant decrease in uterine contractions over time. This finding sheds further light on labor arrest as a functional disorder, and suggests that arrest of descent may be associated with glycogen store depletion in uterine smooth muscle.

PTGS2, or COX2, is the inducible isoform of cyclooxygenase and a key enzyme in prostaglandin synthesis. We and others have described the induction of this enzyme in the amnion, decidua, and myometrium by pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6.[163;170;171;224-236] Increased expression of this enzyme has been associated with the spontaneous onset of labor in myometrium,[100;204;237-246], the uterine cervix, [24;69;241;247-252] and the chorioamniotic membranes[253;254] Our microarray findings indicate an overexpression of PTGS2 in an arrest of descent compared to spontaneous term labor. qRT-PCR confirmed a significant increase in PTGS2 expression in dysfunctional labor (4.7 fold increase). Overexpression of PTGS2 may therefore contribute to dysregulation of normal contraction patterns resulting in abnormal labor patterns, such as arrest disorders.

Dysfunctional labor is associated with dysregulation of muscle contraction elements—The data presented herein also implicate dysregulation of muscle function in the pathophysiology of an arrest of descent. Gene ontology and SPIA comparison of the myometrial transcriptomes of an arrest of descent and spontaneous term labor were significant for enrichment of multiple categories related to muscle function including: 1) biological processes: muscle contraction and regulation of muscle contraction, and cytoskeleton organization; 2) molecular functions: actin binding and structural constituent of muscle; and 3) pathways: regulation of actin cytoskeleton.

While action potentials in myometrium are initiated by a cellular influx of Ca2+ ions, repolarization depends upon K+ ion efflux combined with inhibition of Ca2+ ion channels. A large body of evidence supports the essential role of ion channels in uterine contractility. [255-281] The microarray data was significant for overexpression of ATP1A1 in an arrest of descent ($p<0.001$); confirmatory qRT-PCR was borderline ($p=0.05$). ATP1A1 is the alpha subunit of the Na+/K+ ATPase pump (a sodium pump) which uses the energy of one molecule of ATP to drive 3 sodium ions out of the cell and 2 potassium ions into the cell. This action is performed against considerable concentration gradients and is involved in the sensing of mechanical strain and subsequent adaptation. Na+/K+ ATPase plays a pivotal role in maintaining muscle membrane potential during exercise[282] and has been implicated in the development of muscle fatigue. [283-286] Expression of the Na+/K+ ATPase has been demonstrated to increase in the setting of cyclic, rather than sustained muscular activity. In a skeletal muscle culture, the increase in pump activity was cyclic stretch magnitude dependent,[287] suggesting that the force generated by the activity rather than the duration requires upregulation of this sodium channel. However, while ATP1A1 has long been recognized to play an integral role in skeletal muscle contractility,[288] its differential expression has not previously been described in uterine smooth muscle. The overexpression of this vital contraction-associated pump in an arrest of descent was similarly increased in both the microarray and qRT-PCR analyses (fold change 1.54 and 1.47, respectively). The overexpression of ATP1A1 in myometrium during dysfunctional labor may represent a

compensatory measure to maintain muscle performance and suggests that the condition of dysfunctional labor is associated with mechanical strain.

During gestation, the molecular mechanism of uterine smooth muscle excitability is regulated by a diverse group of ion channels.[259] Myometrial contractility and relaxation are mediated via the interactions between actin and myosin which, in smooth muscle, is regulated by the enzymatic phosphorylation and dephosphorylation of the 20-kD light chain myosin.[289] Increased intracellular Ca2+ activates myosin light chain kinase (MYLK) which catalyzes myosin phosphorylation and results in muscle contraction. Of interest, Word et al.[290] have reported that in pregnancy, the extent of myosin light chain phosphorylation in myometrium is lower than that of non-pregnant women. However, the amount of steady-state stress (measured by a stress/light chain phosphorylation ratio) generated by myometrium from pregnant women was 2.2 fold greater than that of non-pregnant myometrium at any given percentage of phosphorylation. Low levels of myosin light chain phosphorylation were also reported in samples of myometrium from women in labor. Our microarray data reveals the novel finding of significantly decreased expression of MYLK in myometrium from women with arrest of descent compared to those with spontaneous term labor (fold change: −2.3; corrected p-value: 0.0025). qRT-PCR data was consistent in the direction and extent of decreased expression (fold change: −2.9), but the comparison was not statistically significant. However, the consistency in results between the microarray and qRT-PCR data suggests that this vital enzyme for the initiation of muscle contraction may be involved in an arrest of descent.

Hypoxia and human myometrial function—During uterine contractions, reduction of blood flow to the uterus has been reported.[291-293] Moreover, the force of contraction and metabolite production (including ATP) of uterine smooth muscle have been shown to have an inverse linear relationship to uterine blood supply.[294] In cases of decreased blood flow, or hypoxia, the force of uterine contractility was significantly decreased, but returned to baseline following reperfusion.[294] Importantly, even small reductions in uterine perfusion resulted in significant functional changes. In an *in vitro* study, Monir-Bishty et al[295] report that by blocking oxidative metabolism with cyanide, term human myometrium is unable to maintain phasic contractions, despite treatment with oxytocin. The authors proposed that given the inhibitory effects of hypoxia on myometrial contractions, hypoxia itself may contribute to the pathogenesis of dysfunctional labor. Moreover, acidification of uterine artery blood flow resulting from uterine hypoxia/ischemia has been associated with decreased force of uterine contractions.[296-302] In accordance with this hypothesis, we report the novel finding of increased expression of hypoxia inducible factor 1-alpha (HIF1A) in an arrest of descent compared to term spontaneous labor with a 2.4 fold difference in expression as confirmed by qRT-PCR.

HIF1A is a transcription factor regulating adaptation to hypoxia. Degraded by proteosomes under normoxic conditions, HIF1A is stable only in hypoxic conditions and able to heterodimerize with its constitutively expressed beta subunit. The resultant active product, HIF1, is able to bind specific hypoxia response elements in target genes including erythropoietin, members of the insulin growth factor (IGF) pathway, and vascular endothelial growth factor (VEGF), among others. Increased expression of HIF1: 1) promotes angiogenesis via VEGF transcription, promoting migration of endothelial cells towards hypoxic locations[303;304]; 2) coordinates the shift to anaerobic metabolism for cellular energy production[305-307]; and 3) is implicated in hypoxia-induced apoptosis.[303;308-310] In human pregnancy, HIF1A has also been described to play an essential role in the survival of hematopoietic precursors during development,[311] in the development of embryonic vasculature,[312] and in trophoblast differentiation,[313-315]. However, no previous studies have examined the expression of HIF1A in myometrium. The results we present demonstrate that

not only is HIF1A transcribed in the myometrium, but that its expression is higher in an arrest of descent compared to that of normal labor, supporting a role for myometrial hypoxia in the molecular biology of dysfunctional labor.

Strengths and Weaknesses—Major strengths of this study include: 1) the prospective study design; 2) the use of a large myometrium sample set to characterize the transcriptomes of the study groups; 3) stringent patient selection; and 4) qRT-PCR confirmation in an independent set of specimens, demonstrating biological replication. A shortcoming of the study is the number of myometrium samples in the arrest of descent group available for qRT-PCR confirmation, which may account for the lack of significance in some comparisons. The number of patients receiving intrapartum antibiotics may also be considered a potential confounding factor. However, comparison of the percentage of women in the arrest of descent group and those in the spontaneous term labor group who received intrapartum antibiotics was not significant [32% (9/28) versus 26% (10/39), respectively; p=0.11]. Moreover, no differences in gene expression were detected when correcting the microarray data for the use of intrapartum antibiotics. Additional limitations of the study are that women in the arrest of descent group more frequently received intrapartum oxytocin and were in labor for a longer period of time than women in the term labor group, which could be confounding factors. Differences in the percent of women receiving oxytocin augmentation and the time in which a woman is in labor would clearly be expected when comparing women in normal spontaneous labor and those with an arrest of descent, which is a labor disorder. Nonetheless, comparison of myometrial gene expression in women with and without oxytocin augmentation of labor was significant for differences in gene expression in only 4 of the 444 genes reported herein as differentially expressed between women with spontaneous term labor and those with an arrest of descent [KCNAB1 (potassium channel beta3 subunit), CDKN1C (cyclin-dependent kinase inhibitor 1C), TMEM119 (transmembrane protein 119), and IFI44L (interferon-induced protein 44-like)]. In addition, the duration of labor was associated with only 57 of the 444 gene probes we report. Significantly, this group of 57 gene probes did not include those genes for which differential gene expression between the 2 groups was validated with PCR (IL-6, HIF1A, and PTGS2) or those discussed herein. Moreover, the establishment of causality for the differential gene expression described would require studies with the serial sampling of myometrium in women, which is not feasible.

In conclusion, the common labor disorder “arrest of descent” is characterized by a myometrial transcriptome significantly different from that of spontaneous labor. The findings we report provide insight into the molecular basis of second stage arrest and establish a framework for future studies to explore potential therapeutic avenues for dysfunctional term labor.

Condensation

Arrest of descent is characterized by a unique myometrial transcriptome with enrichment of pathways involving inflammation and the actin cytoskeleton compared to spontaneous term labor.

Acknowledgments

This research was supported by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS. We wish to thank Dr. Susan Land and Dan Lott at the Applied Genomics Technology Center of Wayne State University for performing the microarrays and acknowledge the contributions of the nursing staff of the Perinatology Research Branch and Hutzel Women's Hospital.

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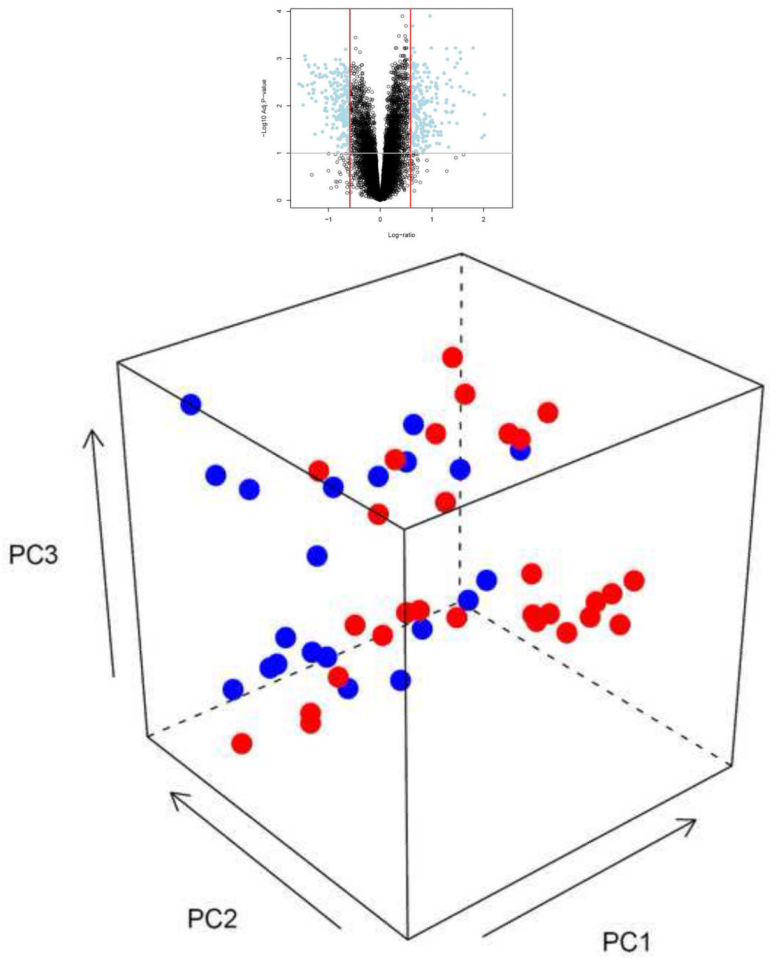

Figure 1. Microarray analysis of the gene expression profiles of myometrium in spontaneous term labor (TL) and arrest of descent (AODES)

Figure 1A. A Volcano plot showing the adjusted significance p-values ($-\log_{10}$ of) against the ratio ($\log_2$ of) between the gene expression of TL and AODES. Dots in the upper right and left quadrants represent genes with a fold change greater than 1.5 and a false discovery fate corrected p-value <0.10. With these criteria for, 400 unique genes (444 probes) were differentially expressed between the myometrial transcriptomes of the two groups.

Figure 1B. Three-dimensional principal component analysis (PCA) plot demonstrating a degree of segregation between the TL and AODES groups. Red dots indicate individual samples from the TL groups while blue dots represent those from the group with AODES.

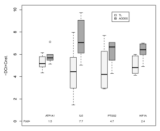

Figure 2. Box plots of qRT-PCR confirmation in human myometrium

The data is presented as -DeltaCt (DCt) values (Ct reference gene-Ct target gene) which is a surrogate for gene expression (on a $\log_2$ scale). The boxes encompass 50% of the data from the 1st quartile to the 3rd quartile. The middle line represents the median value (50%) quantile. The whiskers extend to the most extreme data point, but do not exceed values >1.5 times the interquartile range from the box. The circles represent outliers. Significance was defined as a p-value < 0.05. TL=spontaneous term labor; AODES= arrest of descent; Cnst=constant.

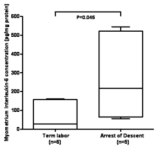

Figure 3.

Comparison of myometrial normalized protein concentrations of interleukin-6 between term labor and arrest of descent. The median interleukin-6 concentration was significantly higher in the arrest of descent group consistent with the microarray and qRT-PCR data (term labor 28.4 pg/mg protein interquartile range [IQR] 0.7-155.8 versus arrest of descent 217.7 IQR 65.2-521.1; p=0.045).

Table 1

Demographic and clinical characteristics of the study groups

	Term labor Microarray (n=29)	Arrest of descent Microarray (n=21)	Term labor qRT-PCR (n=9)	Arrest of Descent qRT-PCR (n=7)	p-value
Maternal age (years)	29 (23.5-34)	23.5 (21.3-30.3)	21 (19.5-27.5)	22 (19-29)	0.04 *a*
BMI (Kg/m^2)	28.7 (23.2-33.3)	23.9 (21.9-27.2)	27.9 (22.6-35.2)	33.3 (24.7-39)	0.03 *b*
Nulliparity (%)	48 (14/29)	70(14/20)	56 (5/9)	43 (3/7)	NS
Smoking (%)	7 (2/29)	5 (1/20)	11 (1/9)	0 (0/7)	NS
African American (%)	52 (14/29)	35 (7/20)	89 (8/9)	86 (6/7)	NS
Gestational age at delivery (weeks)	38.7 (38-40.4)	39.4 (38.8-40.8)	40.1 (38.8-40.6)	40.1 (39.4-40.4)	NS
Birthweight (grams)	3,200 (2,945-3,572)	3,650 (3,332-3,966)	3,240 (2,982-3,632)	3,410 (2,660-3,830)	0.02 *c*

Values are expressed as percentage (number) or median (interquartile range)

BMI: **body mass index;** NS: **not significant.**

a Post-hoc analysis revealed a significant difference between the term labor microarray and term labor qRT-PCR groups (p=0.01).

b Post-hoc analysis was significant for comparisons between term labor microarray versus arrest of descent microarray (p=0.02) and arrest of descent microarray versus arrest of descent PCR groups (p=0.01).

c Post-hoc analysis demonstrated differences between the arrest of descent microarray group and the term labor microarray (p=0.003) and qRT-PCR (p=0.04) groups.

Table 2

List of top 100 microarray probes with differential expression between myometrium from women with an arrest of descent compared to those with spontaneous term labor

Probe ID	Entrez Gene ID	Symbol	Gene name	Fold change	P-value[a]
6580634	2828	GPR4	G protein-coupled receptor 4	1.95	0.0001
4210095	476	ATP1A1	ATPase, Na+/K+ transporting, alpha 1 polypeptide	1.55	0.0002
3370164	476	ATP1A1	ATPase, Na+/K+ transporting, alpha 1 polypeptide	1.51	0.0006
2650730	6781	STC1	stanniocalcin 1	2.75	0.0006
6350184	8771	TNFRSF6B	tumor necrosis factor receptor superfamily, member 6b, decoy	3.48	0.0006
1230630	26207	PITPNC1	phosphatidylinositol transfer protein, cytoplasmic 1	1.98	0.0006
6960072	3329	HSPD1	heat shock 60kDa protein 1 (chaperonin)	1.55	0.0006
3060273	4504	MT3	metallothionein 3	2.44	0.0006
2510201	339768	ESPNL	espin-like	−1.59	0.0006
1580161	81831	NETO2	neuropilin (NRP) and tolloid (TLL)-like 2	1.59	0.0007
6620528	4501	MT1X	metallothionein 1X	2.92	0.0007
1050746	81502	HM13	histocompatibility (minor) 13	1.52	0.0009
5810762	5239	PGM5	phosphoglucomutase 5	−2.74	0.0009
4570008	9941	EXOG	endo/exonuclease (5′-3′), endonuclease G-like	2.94	0.001
2230678	32	ACACB	acetyl-Coenzyme A carboxylase beta	−1.81	0.001
2190255	8771	TNFRSF6B	tumor necrosis factor receptor superfamily, member 6b, decoy	2.46	0.001
770703	9459	ARHGEF6	Rac/Cdc42 guanine nucleotide exchange factor (GEF) 6	−1.71	0.0011
380494	5239	PGM5	phosphoglucomutase 5	−2.73	0.0011
1820504	4830	NME1	non-metastatic cells 1, protein (NM23A) expressed in	1.57	0.0013
4610433	51129	ANGPTL4	angiopoietin-like 4	2.81	0.0013
1820279	90139	TSPAN18	tetraspanin 18	−2.73	0.0013
1400446	123	PLIN2	perilipin 2	1.83	0.0013
2810692	729359	PLIN4	perilipin 4	−2.09	0.0013
4480112	5239	PGM5	phosphoglucomutase 5	−2.62	0.0014
6840156	2762	GMDS	GDP-mannose 4,6-dehydratase	1.65	0.0014
4810026	10205	MPZL2	myelin protein zero-like 2	1.51	0.0014

Probe ID	Entrez Gene ID	Symbol	Gene name	Fold change	P-value[a]
6760246	25802	LMOD1	leiomodin 1 (smooth muscle)	−2.40	0.0014
7150292	388610	TRNP1	TMF1-regulated nuclear protein 1	−1.63	0.0014
460204	123	PLIN2	perilipin 2	1.80	0.0014
1510468	80273	GRPEL1	GrpE-like 1, mitochondrial (E. coli)	1.50	0.0014
2650524	6164	RPL34	ribosomal protein L34	1.58	0.0014
6370133	10483	SEC23B	Sec23 homolog B (S. cerevisiae)	1.53	0.0015
6620379	55222	LRRC20	leucine rich repeat containing 20	−1.61	0.0015
4180324	115572	FAM46B	family with sequence similarity 46, member B	−2.60	0.0015
3610193	64321	SOX17	SRY (sex determining region Y)-box 17	1.63	0.0015
1400634	4499	MT1M	metallothionein 1M	2.73	0.0015
2640392	8771	TNFRSF6B	tumor necrosis factor receptor superfamily, member 6b, decoy	1.87	0.0016
6280133	4629	MYH11	myosin, heavy chain 11, smooth muscle	−1.59	0.0016
6860176	139411	PTCHD1	patched domain containing 1	−2.30	0.0016
2000292	92304	SCGB3A1	secretoglobin, family 3A, member 1	1.58	0.0016
3940435	2012	EMP1	epithelial membrane protein 1	1.51	0.0016
2480544	3779	KCNMB1	potassium large conductance calcium-activated channel, subfamily M, beta member 1	−2.07	0.0016
60255	84168	ANTXR1	anthrax toxin receptor 1	−1.51	0.0017
70592	7414	VCL	vinculin	−1.59	0.0017
6420630	51435	SCARA3	scavenger receptor class A, member 3	−1.78	0.0017
5690167	6405	SEMA3F	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	1.60	0.0018
1770333	8654	PDE5A	phosphodiesterase 5A, cGMP-specific	−1.62	0.0019
3610372	84319	C3orf26	chromosome 3 open reading frame 26	1.93	0.002
650689	25999	CLIP3	CAP-GLY domain containing linker protein 3	−1.86	0.002
1710692	23026	MYO16	myosin XVI	−1.55	0.002
580403	1687	DFNA5	deafness, autosomal dominant 5	−1.83	0.002
1500241	10580	SORBS1	sorbin and SH3 domain containing 1	−2.46	0.002
6860424	6318	SERPINB4	serpin peptidase inhibitor, clade B (ovalbumin), member 4	1.81	0.002
5260095	2706	GJB2	gap junction protein, beta 2, 26kDa	1.90	0.002
1570047	6545	SLC7A4	solute carrier family 7 (cationic amino acid transporter,	−1.75	0.002

Probe ID	Entrez Gene ID	Symbol	Gene name	Fold change	P-value[a]
			y+ system), member 4		
7200427	8862	APLN	apelin	1.64	0.002
3140520	7111	TMOD1	tropomodulin 1	1.66	0.002
6100482	493	ATP2B4	ATPase, Ca++ transporting, plasma membrane 4	−1.94	0.002
1470056	6317	SERPINB3	serpin peptidase inhibitor, clade B (ovalbumin), member 3	2.35	0.002
5890064	800	CALD1	caldesmon 1	−2.51	0.002
3140603	6840	SVIL	supervillin	−1.88	0.002
1170300	4495	MT1G	metallothionein 1G	3.20	0.0021
6200402	4489	MT1A	metallothionein 1A	2.36	0.0021
580709	1673	DEFB4	defensin, beta 4	1.57	0.0021
450553	79026	AHNAK	AHNAK nucleoprotein	−1.68	0.0021
5270519	115701	ALPK2	alpha-kinase 2	−2.24	0.0021
4570670	6237	RRAS	related RAS viral (r-ras) oncogene homolog	−1.77	0.0023
1340192	65055	REEP1	receptor accessory protein 1	−2.10	0.0023
580491	2318	FLNC	filamin C, gamma	−2.37	0.0023
1030239	9805	SCRN1	secernin 1	−1.59	0.0023
3190609	22904	SBNO2	strawberry notch homolog 2 (Drosophila)	1.55	0.0024
4280010	55679	LIMS2	LIM and senescent cell antigen-like domains 2	−2.05	0.0024
4670441	10516	FBLN5	fibulin 5	−1.68	0.0025
2970279	7881	KCNAB1	potassium voltage-gated channel, shaker-related subfamily, beta member 1	−2.17	0.0025
50192	2532	DARC	Duffy blood group, chemokine receptor	1.90	0.0025
7330097	104	ADARB1	adenosine deaminase, RNA-specific, B1 (RED1 homolog rat)	−1.56	0.0025
1300286	4638	MYLK	myosin light chain kinase	−2.26	0.0025
270292	2280	FKBP1A	FK506 binding protein 1A, 12kDa	1.70	0.0025
5910440	26872	STEAP1	six transmembrane epithelial antigen of the prostate 1	2.16	0.0026
1940504	2280	FKBP1A	FK506 binding protein 1A, 12kDa	1.61	0.0026
5090315	1804	DPP6	dipeptidyl-peptidase 6	−1.86	0.0027
6220543	3091	HIF1A	hypoxia inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	1.53	0.0028
360053	65258	MPPE1	metallophosphoesterase 1	−1.57	0.0028

Probe ID	Entrez Gene ID	Symbol	Gene name	Fold change	P-value[a]
2640025	3240	HP	haptoglobin	2.55	0.0029
7400286	3159	HMGA1	high mobility group AT-hook 1	1.76	0.003
5690639	10516	FBLN5	fibulin 5	−1.62	0.003
6560564	5578	PRKCA	protein kinase C, alpha	−1.53	0.0031
5690139	80310	PDGFD	platelet derived growth factor D	−1.54	0.0031
6580056	27189	IL17C	interleukin 17C	1.99	0.0032
5960682	348093	RBPMS2	RNA binding protein with multiple splicing 2	−1.96	0.0032
1710735	23002	DAAM1	dishevelled associated activator of morphogenesis 1	−1.85	0.0032
6380669	6695	SPOCK1	sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 1	−1.51	0.0032
3390551	113146	AHNAK2	AHNAK nucleoprotein 2	−2.42	0.0032
2340241	3613	IMPA2	inositol(myo)-1(or 4)-monophosphatase 2	−1.77	0.0033
5080364	87	ACTN1	actinin, alpha 1	−1.53	0.0033
6420050	4885	NPTX2	neuronal pentraxin II	2.11	0.0033
10543	139728	PNCK	pregnancy up-regulated non-ubiquitously expressed CaM kinase	−2.50	0.0034
670386	3397	ID1	inhibitor of DNA binding 1, dominant negative helix-loop-helix protein	1.67	0.0034
2230379	10135	NAMPT	nicotinamide phosphoribosyltransferase	2.44	0.0034
10296	1674	DES	desmin	−2.98	0.0034

[a] P-values adjusted for multiple comparisons using the False Discovery Rate method

Table 3

Gene Ontology analysis: biological processes and molecular functions associated with differentially expressed genes between arrest of descent and term labor

Biological Process	Number of differentially expressed genes/number of total genes	Corrected P-value
locomotory behavior	21/188	0.0001
inflammatory response	23/234	0.0001
chemotaxis	14/92	0.0001
locomotion	24/309	0.0013
response to hypoxia	14/121	0.0017
muscle contraction	11/93	0.0092
multicellular organismal development	76/1805	0.0101
response to biotic stimulus	19/250	0.0101
response to cytokine stimulus	7/38	0.0101
cellular component movement	19/273	0.0233
system process	14/168	0.0235
acute-phase response	6/32	0.0235
regulation of ion transport	7/45	0.0235
immune response	19/281	0.0247
decidualization	4/13	0.0324
leukocyte differentiation	7/49	0.0335
response to bacterium	8/67	0.0359
cell-cell signaling	18/271	0.0359
response to lipopolysaccharide	8/67	0.0359
regulation of muscle contraction	5/25	0.0359
ion homeostasis	21/348	0.0391
response to heat	7/54	0.0391
cytoskeleton organization	6/40	0.0391
cellular chemical homeostasis	20/324	0.0391
lymphocyte chemotaxis	3/7	0.0391
thyroid hormone catabolic process	2/2	0.0426
localization of cell	22/381	0.0478
response to chemical stimulus	10/124	0.0488
Molecular Functions		
actin binding	22/241	0.0004
cadmium ion binding	5/9	0.0004
chemokine activity	7/38	0.0067
structural constituent of muscle	7/36	0.0067
copper ion binding	8/56	0.0129
G-protein-coupled receptor binding	9/80	0.0249
serine-type endopeptidase inhibitor activity	8/71	0.0479

Table 4

Significant pathways associated with differentially expressed genes between arrest of descent and term labor as determined by Signaling Pathway Impact Analysis (SPIA)

Pathway name	Number of differentially expressed genes/total number of genes in the pathway	Corrected P-value
Cytokine-cytokine receptor interaction	14/218	0.0002
Complement and coagulation cascade	7/57	0.0214
Regulation of actin cytoskeleton	14/197	0.0255
Focal adhesion	11/187	0.0276

Table 5

Comparison of qRT-PCR and microarray results of tested genes between arrest of descent and spontaneous labor at term. (Direction of change denotes change in arrest of descent)

Gene symbol	P-value qRT-PCR	Fold change qRT-PCR	Direction of change in qRT-PCR	P-value microarray	Fold change microarray	Direction of change in microarray
ATP1A1	0.05	1.47	↑	<0.001	1.54	↑
CNN1	0.08	−2.96	↓	0.004	−2.65	↓
GPR4	0.06	2.26	↑	<0.001	1.95	↑
IL-6 [a,b]	0.004	7.72	↑	0.006	3.52	↑
PTGS2 [a]	0.02	4.68	↑	0.004	2.93	↑
HIF1A [a]	0.004	2.36	↑	0.007	1.53	↑
SORBS1	0.09	−2.06	↓	0.002	−2.46	↓
CALD1	0.10	−6.87	↓	0.002	−2.51	↓
EXOG	0.85	−1.54	↓	0.001	2.94	↑
FLNC	0.19	−2.39	↓	0.002	−2.37	↓
MYLK	0.12	−2.95	↓	0.003	−2.26	↓
SLPI	0.76	−1.37	↓	0.04	4.04	↑
SOD2	0.76	−1.78	↓	0.009	2.42	↑

[a] confirmed differential mRNA expression

[b] confirmed differential protein expression

↑: increased expression in the arrest of descent group compared to the spontaneous term labor group

↓: decreased expression in the arrest of descent group compared to the spontaneous term labor group