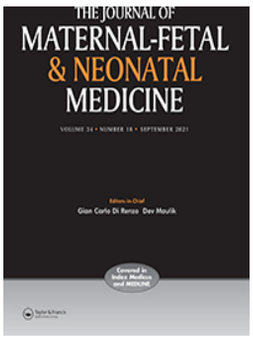

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ORIGINAL ARTICLE

Duration of the pushing phase of labor is inversely associated with expression of *TNF, IL6, IGF1* and *IGF2* in human placenta

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ABSTRACT

Objective: Gene expression in placenta differs between vaginal and cesarean deliveries, but the influence of the duration of labor on placental gene expression is incompletely known. Our aim was to investigate associations between duration of labor and expression of some genes involved in growth or inflammation in human placental tissue.

Methods: Placenta samples ($n = 126$) were collected after an uncomplicated, singleton pregnancy and term vaginal delivery at Örebro University Hospital, Sweden. Duration of labor was recorded by the midwife in the delivery room. The expression of the following genes was analyzed by RT-qPCR: *tumor necrosis factor (TNF), interleukin-6 (IL6), C-X-C motif chemokine ligand 8, toll-like receptor (TLR) 2, TLR4, insulin receptor, insulin-like growth factor (IGF) 1, IGF2, leptin, hepatocyte growth factor (HGF)* and *HGF receptor (MET)*. Multivariable linear regression models were used for the evaluation of associations with labor duration adjusting for potential confounding factors. The Benjamini-Hoschberg method was used to correct for multiple testing.

Results: The expression of *TNF, IL6, IGF1* and *IGF2* was inversely associated with the duration of the pushing phase of labor (B coefficients (95% confidence interval) = −0.150 (−0.277 to −0.023), −0.159 (−0.289 to −0.029), −0.099 (−0.176 to −0.021), and −0.081 (−0.145 to −0.017), respectively).

Conclusions: Longer duration of pushing is associated with downregulation of the expression of genes in placenta from vaginal deliveries. Future research on gene expression in labored placenta should take into account associations with labor duration and especially the pushing phase. Potential impact of these associations on the mother, the fetus and the new-born infant should also be explored.

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Gene expression; insulin-like growth factors; interleukin-6; labor duration; placenta; pushing phase

Introduction

The interest in studying the placenta is considerable due to the need of improvements in our understanding of the pathophysiology of important placental disorders like preeclampsia (PE) [1], but also to explore molecular placental changes that may influence the health of the new-born infant and perhaps also the older child in accordance with the theory of fetal programming [2,3]. However, placental gene expression studies may be affected by the lack of standardized sampling. For example, sampling site has been found to impact the expression of some genes in human placenta [4,5]. Thus, efforts have been made to optimize the sampling procedure and it has been recommended that sampling for research purposes should be performed only on non-labored placenta, i.e. placenta from elective cesarean deliveries [6]. However, such a restriction would withhold the majority of human placenta from research, and further, elective cesarean deliveries are associated with an increased risk for both the child [7] and the mother [8], emphasizing the need to reduce the rates of cesarean deliveries.

Significant differences in gene expression between placenta from vaginal and cesarean deliveries have been reported [9], while others have only found minor differences in gene expression in labored as compared to non-labored placenta [10,11]. The rationale behind

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differences in gene expression in placenta in relation to delivery mode may be linked to placental hypoxia induced by the uterine contractions during labor. Labor, as opposed to an elective cesarean delivery, is associated with profound uterine contractions, which may lead to intermittent blood supply to the placenta [12,13]. This may in turn lead to an "ischemia-reperfusion type injury of the placenta" [14], which potentially could upregulate some genes and downregulate other genes. Other differences between non-labored and labored placentas may be linked to the processes that initiate spontaneous labor. While keeping in mind that these processes are incompletely understood, one suggested pathway of importance to the initiation of labor is inflammation [15,16]. Further, it is also possible that the reason for choosing elective cesarean delivery instead of vaginal delivery may by itself be associated with gene expression in placental tissue.

Besides mode of delivery, the duration of labor may have an impact on gene expression in placenta from vaginal deliveries, possibly through similar processes as those leading to changes between vaginal and cesarean deliveries. However, studies examining associations between duration of labor and gene expression in human placenta are extremely few. An inverse association between the placental expression of the *AKR1C3* gene and the duration of labor was reported in a study investigating 20 genes in 11 placenta samples from vaginal deliveries [17]. Due to the small sample size, it was not possible to adjust for potential modifying factors in that study. Another study found differences in protein expression between five placenta samples delivered after short (<5 h) labor and five samples delivered after long (>15 h) labor [14].

The aim of this study was to investigate associations between duration of labor, or different stages or phases of labor, and expression of some genes involved in inflammation or growth in a larger sample set of human placenta samples, with adjustment for potential confounding factors. The genes were chosen as they are involved in important placental functions. Women with different parity and different body mass index (BMI) categories were included as duration of labor usually differs by parity [18] and obesity is associated with prolonged labor [19,20] and further, obesity is a common condition during pregnancy nowadays [21].

Materials and methods

Subjects

All placental samples ($n = 126$) were delivered vaginally at the Department of Women's Health, Örebro University Hospital, Örebro, Sweden, during 2008–2012 after written informed consent from each pregnant woman. Inclusion criteria were: an uncomplicated and singleton pregnancy, an uncomplicated vaginal delivery at full term (gestational weeks 37–42), and an Apgar score of the new-born infant at 5 min of the age of >7 points. Exclusion criteria were: maternal diabetes mellitus or hypertension prior to the pregnancy, maternal smoking during pregnancy, any pregnancy-induced disorder (hypertension, gestational diabetes mellitus, PE), chorioamnionitis and other infections, and any moderate or severe malformation or sign of chromosomal abnormality in the new-born infant. Both obese (BMI ≥35 kg/m^2 in early pregnancy) and normal weight (BMI = 18.5–24.9 kg/m^2 in early pregnancy) women were included, and a comparison of their gene expression has already been published [22]. However, that earlier study did not consider duration of labor. This study was conducted in accordance to the Helsinki declaration and the Regional Board of Ethics in Uppsala, Sweden, approved it (Dnr 2010-189).

Procedures, definitions and genes of interest

Data on maternal and new-born infant characteristics were collected from medical records at the antenatal care units and the Department of Women's Health, as reported previously [22]. For this study, data on the duration of labor were collected from each woman's medical record. The following events to define the different phases of labor are routinely recorded by the midwife in the delivery room in Sweden: rupture of the membranes; start of mild contractions; start of regular, painful contractions with an interval of 3–4/10 min; start of pushing; delivery of the baby; and delivery of the placenta [20]. The latent phase of labor was calculated as the interval between start of regular, painful contractions and start of mild contractions; the active phase as the interval between start of pushing and start of regular, painful contractions; the pushing phase as the interval between delivery of the baby and start of pushing, and finally, the third stage of labor was calculated as the interval between delivery of the placenta and delivery of the baby. If the latent or the active phase had started before arrival to the delivery ward, the pregnant woman reported those time points to the midwife. To minimize the impact of outliers, durations of the active and the pushing phases were categorized as follows: <2.5 h, 2.5 to <5 h, 5 to <7.5 h, 7.5 to <10 h, and ≥10 h, for the active phase; and <15 min, 15 to <30 min, 30 to

<45 min, 45 to <60 min, and ≥60 min, for the pushing phase, in accordance with a previous report [23].

Weight and height of each woman were measured in first trimester and used for calculation of early pregnancy BMI, which was categorized into six classes (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, and ≥40) according to WHO [24]. Weight was also measured at the time of delivery and gestational weight gain (GWG) was calculated as the difference between late and early pregnancy weight.

The following genes were studied: *tumor necrosis factor (TNF), interleukin-6 (IL6), C-X-C motif chemokine ligand 8 (CXCL8), toll-like receptor (TLR) 2, TLR4, insulin receptor (INSR), insulin-like growth factor (IGF) 1, IGF2, leptin (LEP), hepatocyte growth factor (HGF),* and *HGF receptor (MET)*. The housekeeping gene *glyceraldehyde-3-phosphate dehydrogenase (GAPDH)* was chosen for normalization of the genes of interest, as reported before [22].

Sample preparation

The placental samples, approximately 1 cm^3, were collected from the maternal side of the placenta immediately after delivery. The marginal area and the zone near the insertion of the umbilical cord were avoided. The pieces were rinsed in 35 ml of cold phosphate-buffered saline (Gibco, Life Technologies, Stockholm, Sweden), placed in tubes containing RNAlater (3 ml/tube, Ambion, Stockholm, Sweden), and stored frozen at −80 °C until analysis, as described previously [22].

RNA isolation and cDNA production

The RNeasy Midi Kit (Qiagen Nordic, Sollentuna, Sweden) was used for isolation of total RNA according to the manufacturer's instructions. The purity (260/280) was >1 in all samples as measured by Thermo Scientific NanoDrop 2000 (Fisher Scientific, Göteborg, Sweden). The RNA integrity number as measured by Agilent Bioanalyzer 2100 (Agilent Technology, Kista, Sweden) was 6.2–8.8, indicating almost no degradation. 5 μg of RNA per sample was used as the template for cDNA production. cDNA was synthesized using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA), as stated earlier [22].

RT-qPCR

The 7900 Fast Real-Time PCR System (Applied Biosystems) was used for the RT-qPCR analyses with fluorescent probes (Taq-Man Gene Expression Assays), reagents, and 384-well plates from the same company. The primers and assay IDs used have been reported before [22]. The crossing threshold (Ct) values were calculated using the second-derivative maximum method and the software provided from 7900 Fast Real-Time PCR System. All *Ct* values >35 or "not detected" were considered negative. A reference placenta sample was used as an internal control in triplicate for each PCR run. Relative gene expression was calculated using the 2-delta delta method [25].

Statistical analysis

Data are presented as median (min–max), mean ± SD or absolute numbers (%). The Shapiro–Wilk test was used for normality testing. Comparisons of continuous variables were performed using Mann–Whitney *U* test or Student's *t*-test and comparisons of categorical variables were performed using χ^2 or Fisher's exact test, as appropriate. The normalized gene expression had skewed distributions, so these variables were natural-log transformed. Each gene expression was analyzed as the dependent variable in separate linear regression models with duration of labor as an independent variable. Adjustment was for maternal age and maternal age squared (to account for potential non-linear associations), parity, BMI class, self-reported asthma prior to pregnancy, GWG, induction of the delivery, gestational age, birthweight, and sex of the infant. The Benjamini–Hoschberg method was used for the correction of multiple testing. Statistical significance was defined as $p < .05$ for two-sided tests or a 95% confidence interval that did not cross zero. The statistical software program SPSS version 25 (IBM®, Armonk, NY, USA) was used for the analysis.

Results

Maternal and infant characteristics can be seen in Table 1 together with information on labor duration. No gene expression was statistically significantly associated with the duration of total labor, the duration of the first part of labor (from the start of labor until the start of pushing) nor with the duration of the third stage of labor after adjustment for potential confounding factors. Further, no gene expression was associated with the duration of the active phase of labor. However, expression of the *TNF, IL6, IGF1,* and *IGF2* genes was statistically significantly lower with longer duration of the pushing phase both before and after adjustment for potential confounding factors and after

Table 1. Maternal and new-born infant characteristics and labor duration.

Maternal characteristics $N = 126$		
Parity		
0		32 (25.4%)
1		69 (54.8%)
2		20 (15.9%)
3		5 (4.0%)
Number of women self-reporting asthma		13 (10.4%)
Age (years)		30 (21–40)
Height (cm)		167 (149–182)
BMI (kg/m^2) in early pregnancy		23.1 (18.8–52.2)
BMI class		
18.5–<25		94 (74.6%)
35–<40		20 (15.9%)
≥40		12 (9.5%)
Gestational weight gain (kg)		13 (−5–33)
Induction of the delivery		4 (3.2%)
Induction was by prostaglandins		1 (0.8%)
Induction was mechanical		3 (2.4%)
New-born infant characteristics $N = 126$		
Sex, number of male infants		69 (54.8%)
Gestational age (weeks)		40.3 (37.9–42.0)
Birth weight (g)		3628 (2725–5310)
Birth length (cm)		50 (46–55)
Birth head circumference (cm)		35 (32–40)
Duration of labor		
Total labor (hours, $n = 118$)	11.3 (2.4–46.0)	
Latent phase (hours, $n = 112$)	4.4 (0.0–38.0)	
Active phase (hours, $n = 117$)	4.5 (0.6–27.5)	
Pushing phase (min, $n = 125$)	21 (1–270)	
Third stage (min, $n = 124$)	10 (2–67)	
Active phase categories	Duration (h)	Number of women
	0–<2.5	27 (23%)
	2.5–<5	38 (32%)
	5–<7.5	22 (19%)
	7.5–<10	13 (11%)
	≥10	17 (14%)
Pushing phase categories	Duration (min)	Number of women
	0–<15	46 (37%)
	15–<30	37 (30%)
	30–<45	17 (14%)
	45–<60	10 (8%)
	≥60	15 (12%)

The values are median (min–max) or absolute numbers (%). Total labor = from the start of labor until the delivery of the placenta. Latent phase = from the start of labor until the start of regular, painful contractions, 3–4 per 10 min. Active phase = from the start of regular, painful contractions until the start of pushing. Pushing phase = from the start of pushing until the delivery of the baby. Third stage = from the delivery of the baby until the delivery of the placenta, in accordance with Swedish standard practice [18]. n = number of individuals with available data on each variable.

correction for multiple testing (Table 2 and Figure 1). As a sensitivity analysis, duration of the active phase was added to the regression models. This resulted in only minor alterations of the associations between gene expression and pushing phase duration.

To investigate whether obesity modified the associations between gene expression and pushing phase duration, the study population was divided into obese ($n = 32$) and normal weight women ($n = 93$). This stratification did not change the associations between gene expression and pushing phase duration. The duration of labor did neither differ significantly between obese and normal weight women.

As expected, nulliparous women had longer duration of total labor, first part of labor (from the start of labor until the start of pushing) and pushing phase compared with multiparous women (16.3 h (3.3–46.0) vs. 8.6 h (2.4–31.1), $p < .001$; 16.0 h (2.0–45.0) vs. 8.0 h (1.8–38.2), $p < .001$; and 0.8 h (0.2–4.5) vs. 0.2 h (0.02–1.3), $p < .001$, respectively). However, the duration of third stage of labor did not differ by parity.

Discussion

In the present study, statistically significant downregulation of four out of eleven studied genes was found in human term placenta with increasing duration of the pushing phase after adjustment for several potential confounding factors and correction for multiple testing. This indicates that labor duration may influence the expression of genes in placenta and the finding is in accordance with previous findings on differences in gene expression between non-labored cesarean delivered and vaginally delivered placenta [9]. An alternative, but possibly less likely, explanation is that preexisting immunological or other factors have an influence on the duration of the pushing phase of labor. To the best of our knowledge, this is the first study reporting associations between gene expression in human placenta and duration of labor after adjustment for multiple confounding factors.

Vaginal deliveries can be divided into three stages [26]. The first stage is the opening stage and includes the latent phase with mild pain and the active phase with regular, painful contractions. The first stage results in a full dilatation of the cervix. The second stage is the expulsion stage and starts when cervix is fully dilated and ends with the birth of the child. It also consists of two phases: the passive descent of the fetal head and the active phase with involuntary, expulsive uterine contractions and voluntary maternal pushing. The third stage is the period between the birth of the infant and the delivery of the placenta and membranes. To enable defining an exact time point for the end of the first stage, the cervical dilatation needs to be evaluated at close intervals. Instead of recording the time point for full dilatation, the routine in Sweden is to record the time point for the start of pushing, as described before [20]. As labor progresses, the intensity of the uterine contractions increases [27]. Uterine contractions increase the intrauterine pressure and reduce the placental perfusion, which seems to occur in a dose-dependent way

Table 2. Associations between gene expression and pushing phase duration.

	Unadjusted		Adjusted	
Gene	B coefficient (95% confidence interval)	*p* Value	B coefficient (95% confidence interval)	*p* Value
TNF	−0.138 (−0.248 to −0.027)	.015	−0.150 (−0.277 to −0.023)	.021*
IL6	−0.147 (−0.259 to −0.036)	.010	−0.159 (−0.289 to −0.029)	.017*
CXCL8	−0.019 (−0.144 to 0.107)	.770	−0.019 (−0.161 to 0.123)	.792
TLR2	−0.049 (−0.134 to 0.036)	.258	−0.063 (−0.158 to 0.032)	.193
TLR4	−0.084 (−0.176 to 0.008)	.073	−0.096 (−0.199 to 0.007)	.068
INSR	−0.023 (−0.086 to 0.039)	.461	−0.046 (−0.116 to 0.024)	.195
IGF1	−0.090 (−0.164 to −0.017)	.016	−0.099 (−0.176 to −0.021)	.013*
IGF2	−0.066 (−0.126 to −0.005)	.034	−0.081 (−0.145 to −0.017)	.014*
LEP	−0.048 (−0.295 to 0.199)	.702	−0.179 (−0.439 to 0.081)	.176
HGF	−0.060 (−0.143 to 0.024)	.161	−0.061 (−0.158 to 0.035)	.210
MET	−0.078 (−0.157 to 0.000)	.050	−0.089 (−0.176 to −0.002)	.045

*Statistically significant also after Benjamini–Hoschberg correction for multiple testing.
Adjustment was for parity, age, age squared, BMI class, self-reported asthma, induction, gestational weight gain, gestational age, birth weight, and infant sex.

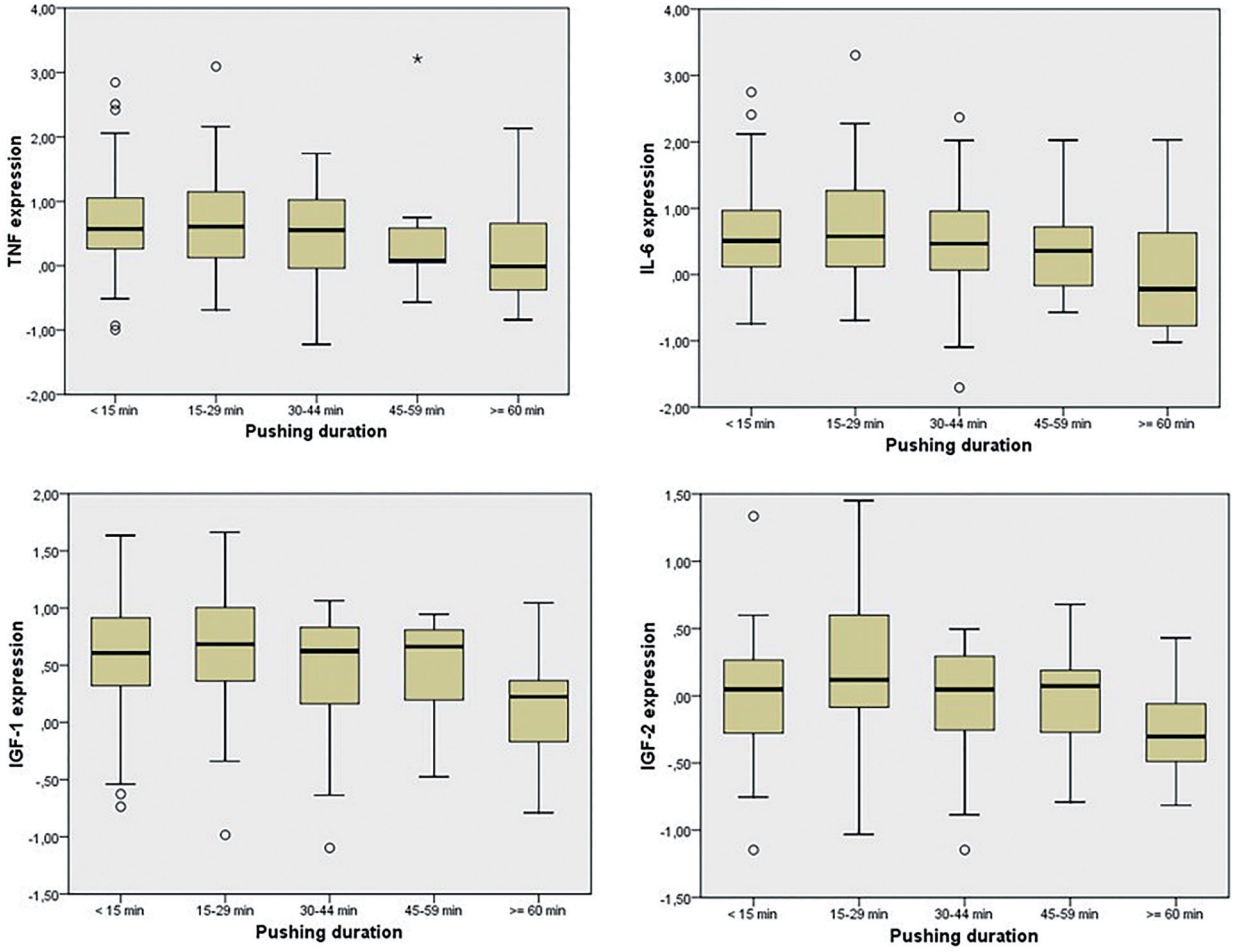

Figure 1. Box plots of natural log transformed gene expression in human, term placental samples ($n = 126$) in different pushing phase duration categories. The gene expression of tumor necrosis factor (TNF), interleukin (IL)-6, insulin-like growth factor (IGF)-1 and IGF-2 was inversely associated with pushing phase duration.

[12,28,29]. This may explain why the pushing phase, and not the earlier phases of labor, was associated with gene expression in the present study. The impact of the pushing phase on the fetoplacental unit is stressed by findings of increased rates of umbilical artery acidosis, admission to neonatal intensive care units and an increased use of continuous positive airway pressure treatment in new-born infants with increasing duration of the pushing phase [23,30]. Infants with asphyxia were excluded from this study. It is possible that larger differences in gene expression in placenta would have been found in relation to

duration of pushing if also infants with asphyxia had been included. Prolonged second stage of labor is also strongly associated with operative delivery [31], and other maternal and neonatal complications, such as postpartum hemorrhage and low Apgar score at 5 min of age [30,32], pointing at the importance of this stage.

It is not known how the downregulation of *TNF, IL6, IGF1* and *IGF2* in the placenta may influence labor, the fetus, the woman, or the new-born infant. TNF is a pro-inflammatory cytokine. The balance between TNF and IL-10 in the placenta seems to be important for normal implantation, placentation and pregnancy outcome [33]. IL-6 is also a pro-inflammatory cytokine and its concentrations in amniotic fluid have been shown to be increased in spontaneous, term labor and in inflammatory conditions of the fetus and the placenta [34]. IGF-1 and particularly IGF-2 are important mediators of fetal growth by facilitating the placental transfer of nutrients to the fetus [35]. Future studies are needed to confirm the associations found here in other populations, to investigate potential effects of downregulated gene expression in the placenta on the mother and the child, and for the broadening of the number of genes studied.

We suggest that gene expression studies on vaginally derived placenta should take into account duration of the pushing phase. Similar suggestions have been presented before [6], even though the supporting evidence has been sparse up till now. Strengths of the present study are the relatively large number of placental samples included enabling adjustment for several potentially confounding variables, and the thorough division of labor into different phases. As consistent associations with pushing duration were found for a notable proportion of the genes studied, chance findings seem less likely. This is further emphasized by statistical significance being observed after correction for multiple testing. Limitations of the present study are the low number of genes studied and the lack of protein confirmation data for the relevant genes.

We conclude that longer duration of pushing during labor is associated with downregulation of the expression of *TNF, IL6, IGF1* and *IGF2* in term, human placenta. Future research on gene expression in labored placenta should consider associations with duration of the pushing phase. The potential impact of these alterations on the mother, the fetus and the new-born infant should be explored.

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References

[1] Usta A, Turan G, Sancakli Usta C, et al. Placental fractalkine immunoreactivity in preeclampsia and its correlation with histopathological changes in the placenta and adverse pregnancy outcomes. J Matern Fetal Neonatal Med. 2020;33(5):806–815.

[2] Jansson T, Powell TL. Role of the placenta in fetal programming: underlying mechanisms and potential interventional approaches. Clin Sci. 2007;113(1):1–13.

[3] Nugent BM, Bale TL. The omniscient placenta: metabolic and epigenetic regulation of fetal programming. Front Neuroendocrinol. 2015;39:28–37.

[4] Allbrand M, Aman J, Nilsson K, et al. Expression of genes involved in inflammation and growth - does sampling site in human full-term placenta matter? J Perinat Med. 2019;47(5):539–546.

[5] Wyatt SM, Kraus FT, Roh CR, et al. The correlation between sampling site and gene expression in the term human placenta. Placenta. 2005;26(5):372–379.

[6] Burton GJ, Sebire NJ, Myatt L, et al. Optimising sample collection for placental research. Placenta. 2014;35(1):9–22.

[7] Tribe RM, Taylor PD, Kelly NM, et al. Parturition and the perinatal period: can mode of delivery impact on the future health of the neonate? J Physiol. 2018;596(23):5709–5722.

[8] Mylonas I, Friese K. Indications for and risks of elective cesarean section. Dtsch Arztebl Int. 2015;112(29-30):489–495.

[9] Lee KJ, Shim SH, Kang KM, et al. Global gene expression changes induced in the human placenta during labor. Placenta. 2010;31(8):698–704.

[10] Sitras V, Paulssen RH, Gronaas H, et al. Gene expression profile in labouring and non-labouring human placenta near term. Mol Hum Reprod. 2008;14(1):61–65.

[11] Peng HH, Kao CC, Chang SD, et al. The effects of labor on differential gene expression in parturient women, placentas, and fetuses at term pregnancy. Kaohsiung J Med Sci. 2011;27(11):494–502.

[12] Brar HS, Platt LD, DeVore GR, et al. Qualitative assessment of maternal uterine and fetal umbilical artery blood flow and resistance in laboring patients by Doppler velocimetry. Am J Obstet Gynecol. 1988; 158(4):952–956.
[13] Fleischer A, Anyaegbunam AA, Schulman H, et al. Uterine and umbilical artery velocimetry during normal labor. Am J Obstet Gynecol. 1987;157(1):40–43.
[14] Cindrova-Davies T, Yung HW, Johns J, et al. Oxidative stress, gene expression, and protein changes induced in the human placenta during labor. Am J Pathol. 2007;171(4):1168–1179.
[15] Romero R, Espinoza J, Goncalves LF, et al. Inflammation in preterm and term labour and delivery. Semin Fetal Neonatal Med. 2006;11(5):317–326.
[16] Kumar N, Nandula P, Menden H, et al. Placental TLR/NLR expression signatures are altered with gestational age and inflammation. J Matern Fetal Neonatal Med. 2017;30(13):1588–1595.
[17] Phillips RJ, Fortier MA, Lopez Bernal A. Prostaglandin pathway gene expression in human placenta, amnion and choriodecidua is differentially affected by preterm and term labour and by uterine inflammation. BMC Pregnancy Childbirth. 2014;14(1):241.
[18] Abalos E, Oladapo OT, Chamillard M, et al. Duration of spontaneous labour in 'low-risk' women with 'normal' perinatal outcomes: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2018;223:123–132.
[19] Frolova AI, Raghuraman N, Stout MJ, et al. Obesity, second stage duration, and labor outcomes in nulliparous women. Am J Perinatol. 2021;38(4):342–349.
[20] Carlhall S, Kallen K, Blomberg M. Maternal body mass index and duration of labor. Eur J Obstet Gynecol Reprod Biol. 2013;171(1):49–53.
[21] Poston L, Caleyachetty R, Cnattingius S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol. 2016;4(12):1025–1036.
[22] Allbrand M, Bjorkqvist M, Nilsson K, et al. Placental gene expression of inflammatory markers and growth factors-a case control study of obese and normal weight women. J Perinat Med. 2015;43(2):159–164.
[23] Sandström A, Altman M, Cnattingius S, et al. Durations of second stage of labor and pushing, and adverse neonatal outcomes: a population-based cohort study. J Perinatol. 2017;37(3):236–242.
[24] Organization WH. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 8942000; 2000. p. 252.
[25] Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) method. Methods. 2001;25(4): 402–408.
[26] Intrapartum care for healthy women and babies (CG190) United Kingdom: NICE National Institute for Health and Care Excellence clinical guideline. 2014. [updated 2017 Feb 21; cited 2020 Aug 20]. Available from: https://www.nice.org.uk/guidance/cg190/resources/intrapartum-care-for-healthy-women-and-babies-pdf-35109866447557.
[27] Krapohl AJ, Myers GG, Caldeyro-Barcia R. Uterine contractions in spontaneous labor. A quantitative study. Am J Obstet Gynecol. 1970;106(3):378–387.
[28] Caldeyro-Barcia R. Oxytocin in pregnancy and labour. Acta Endocrinol Suppl. 1960;34(Suppl 50):41–49.
[29] Sinding M, Peters DA, Frøkjaer JB, et al. Reduced placental oxygenation during subclinical uterine contractions as assessed by BOLD MRI. Placenta. 2016;39: 16–20.
[30] Gimovsky AC, Aizman L, Sparks A, et al. Pushing the limits: perinatal outcomes beyond prolonged second stage. J Matern Fetal Neonatal Med. 2021;34(3): 409–415.
[31] Altman MR, Lydon-Rochelle MT. Prolonged second stage of labor and risk of adverse maternal and perinatal outcomes: a systematic review. Birth. 2006;33(4): 315–322.
[32] Allen VM, Baskett TF, O'Connell CM, et al. Maternal and perinatal outcomes with increasing duration of the second stage of labor. Obstet Gynecol. 2009; 113(6):1248–1258.
[33] Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Tumor necrosis factor-alpha and pregnancy: focus on biologics. An updated and comprehensive review. Clinic Rev Allerg Immunol. 2017;53(1):40–53.
[34] Kim CJ, Romero R, Chaemsaithong P, et al. Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance. Am J Obstet Gynecol. 2015;213(4 Suppl):S29–S52.
[35] Sferruzzi-Perri AN, Sandovici I, Constancia M, et al. Placental phenotype and the insulin-like growth factors: resource allocation to fetal growth. J Physiol. 2017;595(15):5057–5093.