



Interleukin-6 in Spontaneous and Induced Vaginal Birth and Neonatal Outcomes: A Cross-Sectional Study

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Abstract

Introduction: The detailed mechanisms fundamentally the onset of spontaneous labor at term remain obscure. Delayed labor means slower progress of the birth process and is associated with childbirth problems and negative birth feelings, resulting in subsequent pregnancy and labor. Inflammatory mechanisms are thought to play a vital role in the physiology of parturition and labor in pre-term and spontaneous term birth. Studies indicated that the mode of birth and labor change interleukin-6 concentrations in maternal and fetal sections. The immunobiological role of inflammatory cytokines in parturition and the onset of spontaneous labor at term, especially without exogenic motivation, remain unspecified yet. The specific role of Interleukin - 6 (IL - 6) in the biosynthesis of prostaglandins, myometrium contractions, cervix ripening, and finally, its role in the process of labor is reported in studies. According to the changes in the physiology of normal birth in induced labor, this study aimed to compare the mean level of IL-6 in pregnancies terminated by selective induction or spontaneous vaginal birth and neonatal outcome.

Methods: This cross-sectional study was conducted on two groups of 40 women with spontaneous and induced birth. All pregnancies were term without clinical or obstetric complications. The enzyme-connected immunosorbent assay measured the level of IL - 6 in the umbilical cord. The obtained data were analyzed by SPSS 22 software.

Results: The mean level of IL-6 in the umbilical cord was not significantly different in spontaneous (250.20 ± 39.36 pg./ml) and induced labor (240.97 ± 39.06 pg./ml) ($P = 0.847$). In the spontaneous birth group, the first and fifth minute Apgar scores were higher than the induced labor group ($P = 0.021$). None of the infants required resuscitation or NICU hospitalization in the neonatal unit. Approximately 97.5% of infants were breastfed in the induced birth group. Only one of the newborns in the induced birth group had jaundice and underwent phototherapy for 8 hours at home. In this study, there was found no association between IL - 6 and pregnancy/infant variables.

Conclusions: Our results indicate that the birth method (induced and spontaneous) had no effect on the level of IL-6 in the umbilical cord blood, but the birth method had just a significant effect on the Apgar score. Induction of labor is associated with adverse birth outcomes. This study investigated interleukin-6 in cord blood in term newborns depending on the mode of delivery and labor. Delayed labor means slower progress of the birth process and is associated with childbirth problems and negative birth feelings, which can have consequences on subsequent pregnancy and labor. We determined whether normal spontaneous birth and induced birth at term was associated with poor newborns outcomes. Current study was a different view helping future studies to investigate other aspects of post term pregnancy and supporting physiological parturition.

INTRODUCTION

The primary mechanism of the term labor is not well known [1-3]. However, it has been stated that the biochemical and physiological aspect of labor is very similar to the inflammatory process [1, 4]. It has been proposed that inflammation can be among one of the theoretical ways for triggering familiar term labor [1-3]. Pro-inflammatory cytokines, including interleukin-1 β , interleukin-6, and tumor necrosis factor- α , play an essential role in parturition [5]. IL-6 is a cytokine with a wide range of biological activities, produced by B cells, T cells, and macrophages [6]. Studies in the field of inflammation, labor onset, and the impact of various cytokines in parturition have considered a unique role for IL-6 in the labor process and birth [7-12]. IL-6 is the primary cytokine that increases in response to term labor in the absence of infection in the fetal blood circulation [13]. IL-6 and other inflammatory cytokines help the normal physiological process of labor [14-17], such as stimulating the synthesis of prostaglandins [14-18], inducing the contraction of the uterine myometrium [18], and the dilatation of cervix [14, 15]). Studies have shown that the strength and frequency of uterine contractions are associated with IL-6 [19-21]. Also, studies have shown that IL-6 increases in labor activities [3, 21, 22]. The results of these studies indicate that IL-6 plays a crucial role in the labor process. Several studies have been conducted to evaluate the levels of IL-6 in normal vaginal birth and cesarean section [5, 9, 11, 14, 23-26]. In most of these studies, the level of IL-6 has been higher in the vaginal group than cesarean. Most studies have revealed the role of IL-6 in infection and chorioamnionitis, term and pre-term birth, type of epidural analgesia [18], vaginal birth, and cesarean section. However, there is no study about the impact of cytokines, particularly IL-6, in labor induction. Just one study has reported that IL-6 is produced profoundly by cord blood cells of normal spontaneous term labor than infants born by induction of labor ($P < 0.001$) [24]. Different studies have evaluated the cord blood samples in order to investigate cytokines in labor events and the status of infants. According to the critical role of IL-6 in labor and this fact that selective induction changes the physiology of normal birth [27]. Blood samples from the umbilical cord reflect the status of the mother and fetus and the effects of IL-6 on neonatal outcomes and maintaining neonatal immune response [5, 12, 14, 28-30], we designed this study aimed to determine and

Table 1. IL - 6 test performance characteristics

Assay range	7.8-500 pg./ml
Standard curve points	500, 250, 125, 62.5, 31.25, 15.62, 7.8 and 0 pg./ml
Intra-assay-precision	< 9.4%
Inter-assay-precision	< 8.6%
Inter-lot-precision	< 12%
Cross-reactivity	No cross reactivity was observed with the following recombinant human proteins: IL-1 α , IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, TNF α , TARC
Specificity	Recognizes both natural and recombinant human IL-6.
Sensitivity	< 7 pg./ml.

compare the IL-6 levels in selectively induced pregnancy terminations, compared with spontaneous vaginal birth, with comparing neonatal outcomes in two groups.

METHODS

This cross-sectional study was conducted on patients referred to Shahid Motahari hospital's maternity ward in 2013. Informed consent forms were completed by all study subjects. This research has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

Sample Size and Sampling Method

The eligible subjects were recruited based on a convenient sampling method and were evaluated within each group. The inclusion criteria were: not taking medication (e.g., steroids, antibiotics) and were not smokers, alcoholics, or drug abusers. The pregnant women with alive and healthy fetuses without complications, including chorioamnionitis, preeclampsia, gestational diabetes, placental abruption, and intrauterine growth restriction call Singleton. Rupture of the membranes (ROM) occurred in less than 18 hours in both groups. Mothers with chronic medical conditions, symptoms of infection (e.g., fever or leukocytosis) and have received types of regional anesthesia (pudendal block, Para cervical, spinal, and epidural) and anesthetic gases (N₂O) during labor were excluded from the study. Vaginal birth is performed without tools (forceps and vacuum) with the normal placenta and umbilical cord. Two studied groups were: (1) Women whose labor did not occur naturally and were induced by using oxytocin infusion, (2) women who had a spontaneous vaginal birth.

Blood Sampling Collection

Blood samples were drawn from the doubly clamped umbilical cord at birth (2 - 3 cc). The blood was collected in pyrogen-free tubes and was immediately centrifuged after clotting at 4°C for 5 minutes at 3800 RPM, and the supernatant serum was kept at -20°C until assessment. They were analyzed within three months of the collection by an enzyme-linked immunosorbent (ELISA) technique (AviBion interleukin six kits of organism company, Finland). The sensitivity and specificity characteristics of the IL - 6 kits has shown in Table 1.

Neonatal outcomes: After labor, the checklists related to newborns were completed and the neonate's situations, hospitalization, and diseases were followed via phone calls after the mother's discharge. In this research, the neonatal outcomes were assessed through the following variables: the first and fifth minute Apgar scores, use of mechanical ventilation, occurrence of neonatal jaundice, hospitalization in neonatal unit and neonatal intensive care unit, and the occurrence of any neonatal disease up to one month after birth.

Data analysis: In order to summarize and describe the samples according to the variable type, frequency tables or mean and standard deviation were used. Before performing any analysis, normality of quantitative variables in the model was checked by the Kolmogorov-Smirnov test. To investigate IL - 6 in two groups, the Mann-Whitney test was used. In order to compare the pregnancy and infancy outcomes in the two groups, the chi-square test, t - test, Mann-Whitney test and repeated measurement analyses were used. To determine the relationship between IL-6 with other variables, the Spearman correlation coefficient was used. For data analysis, the SPSS software version 22 was used.

RESULTS

In the present study, 40 participants were assessed in each group. The clinical characteristics of the study population in each groups are demonstrated in Table 2. According to Table 2, there were no significant difference between groups regarding the clinical

characteristics, except that participants in the induced labor group underwent more vaginal examination than the spontaneous labor group ($P < 0.05$). In this study, none of the infants required resuscitation or NICU hospitalization in neonatal unit. Approximately 97.5% of infants were breastfed in the induced birth group. Only one of the newborns in the induced birth group had jaundice and underwent phototherapy for 8 hours at home. None of the infants were hospitalized because of jaundice or treatment with phototherapy or transfusion at the hospital. There were no reports in regard neonatal deaths until one month after birth. The rate of history of neonatal death was 2.5% in the induced labor group. The gestational age in spontaneous birth, based on LMP, was 37 - 41.3 weeks and based on sonography was 37.1 - 41.6 weeks, before 12 weeks of gestational age. In the induced labor group, the range of gestational age, based on LMP, was 37.1 - 41.7 weeks and based on sonography (before 12 weeks of gestational age), was 37 - 41.4 weeks.

Laboratory results: Mean and standard deviation of IL - 6 in the spontaneous and induced labor groups was 250.20 ± 39.36 pg/ml and 240.97 ± 39.06 pg/ml respectively. Although mean IL - 6 was higher in the spontaneous labor group, it was not statistically significant ($P = 0.847$). The levels of IL - 6 in different subgroups, based on gender (male / female) and being nulliparous and multiparous showed no significant difference in the IL-6 levels in these groups ($P = 0.828, 0.74, 0.74$).

Table 2. Clinical characteristics of patients referred to maternity ward of Motahari Hospital, Orumieh, Iran, in 2013

Variables	Induced Labor (n = 40) ^a	Spontaneous Labor, (n = 40) ^a	(P Value)
Maternal age, y	25.55 ± 5.68	25.8 ± 5.99	0.85
Nulliparous, multiparous	56.9, 44.59	36.73, 56.41	0.263
Gestational age in sonography before 12 weeks, week	39.1 ± 1.37	39.32 ± 0.97	0.41
Gestational age with LMP, week	39.31 ± 1.29	39.07 ± 1.40	0.58
Duration of the first stage of labor, min	197.25 ± 17.78	184.03 ± 13.53	0.62
Duration of the second stage of labor, min	41.875 ± 3.89	27.07 ± 4.97	0.1
Duration of ROM, min	311.51 ± 44.08	236.00 ± 38.40	0.16
Number of vaginal examinations	4.4 ± 1.61	3.47 ± 1.86	0.008
Episiotomy, yes, no	56.9, 31.82	43.10, 68.18	0.04
Birth weight, g	3287.00 ± 347.60	3261.5 ± 400.66	0.76
Neonate's sex, male, female	52.38, 47.37	47.62, 52.63	0.64

^aData are presented as Mean ± SD or N. %.

Table 3. The mean of the first and fifth minute apgar scores in two groups

Groups, Apgar, scores	Spontaneous labor, N = 40	Induced labor, N = 40	P-value
The first minute Apgar score			P < 0.001
Mean	8.92	8.65	
SD	0.34	0.66	
The fifth minute Apgar score			
Mean	9.92	9.70	
SD	0.51	0.34	
P-value	P = 0.021		

Neonatal characteristics and outcomes: Mean and standard deviation of the first minute Apgar in the spontaneous and induced labor groups was 8.92 ± 0.34 and 8.65 ± 0.66 respectively, and the fifth minute Apgar scores was 9.92 ± 0.34 and 9.70 ± 0.51 respectively.

There was a significant difference between groups based on the mean of the first and fifth Apgar scores. The spontaneous labor group had a higher first and fifth Apgar scores compared to the induced labor group ($P = 0.00$). In the repeated measures analysis, the mean of the

fifth minute Apgar score was significantly higher than the first minute Apgar score ($P = 0.021$). (Table 3).

To determine the correlation between cord blood level of IL - 6 with each pregnancy and neonatal outcomes, the Spearman correlation was recruited and none of the variables showed a significant correlation with cord blood interleukin - 6. The level of IL - 6 showed a

positive correlation with birth weight, maternal age, number of vaginal examinations, duration of the first stage labor, ROM duration, and a negative correlation with the first and fifth minute Apgar score, parity, gestational age based on LMP, gestational age based on ultrasound (before 12 weeks) and duration of the second stage of labor (Table 4).

Table 4. The relationship between il-6 levels and different variables in two groups (spontaneous and induced labor) in patients referring to Shahid Motahari Hospital's maternity ward in 2013

Variable	Spearman Correlation Coefficients	P-value
Maternal age, y	R = 0.005	P = 0.967
Parity, No	R = - 0.2	P = 0.864
Number of abortions, No	R = - 0.115	P = 0.311
Number of vaginal examinations, No	R = 0.118	P = 0.297
Gestational age based on LMP, week	R = - 0.092	P = 0.577
Gestational age by sonography before 12 weeks, week	R = - 0.110	P = 0.339
Duration of the first stage of labor, min	R = 0.012	P = 0.941
Duration of the second stage of labor, min	R = - 0.084	P = 0.548
Duration of ROM, min	R = 0.125	P = 0.31
The first minute Apgar score	R = - 0.065	P = 0.565
The fifth minute Apgar score	R = - 0.076	P = 0.504
Birth weight	R = 0.044	P = 0.696

DISCUSSION

Our results indicate that induced and spontaneous birth had no effect on the level of IL-6 in the umbilical cord blood, but the birth method had just a significant effect on the Apgar score. Induction of labor is associated with adverse birth outcomes. IL-6 levels also had no significant relationship with different demographic, obstetric, and infantile variables. Labor Initiation and birth is a physiological process that often begins spontaneously, but the process is poorly defined in human pregnancy [2]. It is stated that the production of prostaglandins in myometrium during labor should be considered as the most efficient mechanism for active contractions [31]. The main increase in prostaglandins in amnion occurs after labor starts and it is believed that this increase is a result of an inflammatory response that sends the message of events leading to active labor [7, 10, 31-35]. During this inflammatory response, a complete set of cytokines is produced that either increases production of uterotonins (mainly prostaglandin) or contracts the myometrium by putting a direct effect on it. These cytokines include tumor necrosis factor-alpha and interleukins 1, 6, 8, and 12 [31]. Increasing cytokines and prostaglandins also influences the process of cervical ripening, the loss of myometrium relaxation, and myometrium irritability [3, 36]. It is assumed that IL-6, as well as other inflammatory cytokines, plays a role in events related to birth by reacting with prostaglandin symptom pathways [37].

It seems that IL-6 should be secreted and regulated through a natural and physiologic process, while various interventions in labor have kept the labor process away from its physiologic process, including decisions on starting labor away from its normal time or inducing labor. Labor induction in developed countries is

performed in more than 20% of pregnancies [38] and it is stated that the rate of elective induction of labor without obstetric or medical indications has increased more in recent years [27]. Induction of labor is considered to be the most common cause of obstetric interventions, which can unfortunately be associated with adverse consequences for mothers and newborns [39].

In this study, although the mean level of IL - 6 was greater in the spontaneous birth than the induced labor group, the amount of IL - 6 was not significantly different between the two groups ($P = 0.868$). Steinborn assessed the levels of IL - 6 and reported a higher IL - 6, secreted by cells cultured from cord blood, in spontaneous birth than induced labor at term ($P < 0.001$). Also in this study, IL - 6 in cesarean birth and induced labor were not significantly different ($P = 0.908$) [24]. The results of the present study were contrary to the results of Steinborn's study. It seems that culturing umbilical cord blood cells can affect IL - 6 levels. In this study, only IL - 6 levels were measured in umbilical cord blood without cell culture. In fact, according to the results of Steinborn's study, spontaneous term labor is associated with the activation of fetal myelomonocytic cells.

In Steinborn's study, labor was induced due to medical conditions (gestational diabetes, premature ROM, prolonged pregnancy or fetal distresses) that might have an effect on the amount of IL - 6. However, in the present study, cases with gestational diabetes, PROM, and fetal distresses were excluded, as they would have an impact on the amount of IL - 6. Regarding the starting process of labor, it has been stated in William's Obstetrics and Gynecology textbook that the human fetus might also send the necessary message through a kind of blood agent that acts on placenta. The more

likely pathway is that the uterus must be ready for labor before applying the optimum effect of an uterotonic. Oxytocin appears not to be the beginner of the birth process, but is probably one of several factors responsible for ensuring the effectiveness of an active labor. There is little evidence considering the role of oxytocin during childbirth [31].

Studies show that oxytocin alone cannot trigger labor, including Robertson's study that was conducted on mice showing that IL-6 stimulates uterine contractions through stimulation of oxytocin receptor expression. In this study, the delay in birth of mice with a mutated IL-6 gene was modified by exogenous cytokines. Studies have also shown that labor proceeds naturally in the absence of oxytocin in clinical disorders of the pituitary gland [4]. Considering these findings that the induction of labor is merely induced with oxytocin infusion and triggers labor, the role of IL - 6 in labor induction is significant.

Similar to oxytocin, prostaglandins (produced in the myometrium tissue) may have an important role in the efficiency of myometrium contractions in the active phase of labor and the main increase in prostaglandins in amnion occurs after labor starts. It is thought that cytokines produced in the fore bag greatly increases the amount of prostaglandins produced in amnion. In the cervix, these cytokines trigger leukocyte infiltration and cervical ripening [31]. These findings demonstrate the major role of cytokines in triggering labor and the minor role of oxytocin and prostaglandin. According to the issues raised in William's textbook, it appears that the presence of cytokines (including IL - 6) is necessary to trigger labor, but in the present study, the presence of cytokines in the group that were induced with oxytocin was not different from IL-6 levels of umbilical cord blood in the spontaneous labor group. But regarding the fact that all mothers were term, regarding gestational age, IL-6 is possibly secreted sufficiently at this time and the type of starting labor could have no effect on it. On the other hand, if there was a possibility to assess IL-6 before the labor onset, different results might be obtained in this study.

In addition, regarding the fact that studies have stated that enduring physical activity and exercise may increase the secretion of IL - 6 from stimulated monocytes in blood stream and normal labor is associated with more physical effort and stimulations [14, 16, 18, 40], it seems that this lack of difference in the level of IL - 6 in the cord blood in the two birth groups may be due to the physical activity of the groups during labor that might have affected the level of IL-6 in the cord blood.

It can also be stated that lack of IL - 6 may be compensated in induced labors; labor would proceed normally and if there is a deficiency for the inflammatory process and IL-6 production, required for start and continuation of labor in the induced labor group, this deficiency would be compensated by uterine

contractions during labor. In this study, if the mother's level of IL-6 was measured before labor in both groups and was then compared with levels of interleukin-6 of cord blood or the mother's serum, a better outcome would be obtained. Possibly, a closer look at the field of interleukin-6 and other inflammatory markers would be useful at different ages in different birth situations and labor induction methods.

Previous studies, alike the present study, have also not observed a significant relationship between IL-6 and the length of labor [12, 25, 41]; it seems that this issue indicates that labor itself is not inflammatory. In addition, many studies [14, 16, 18, 40] state that physical activity leads to an increased secretion of IL - 6, and it is expected that the length of labor and hence more physical activity increases the amount of IL - 6. However, such an outcome has not been reported. In the present study, no association was observed between IL - 6 and gestational age. In Herrera's study as gestation advances IL - 6 levels increases [3] and in other study IL - 6 decreased significantly with increasing gestational age [42]. Also in Mankowitz's study cytokine levels including IL-6 were not influenced by the gestational age of the pregnancy [7].

In Arad's study, there was a relationship between high levels of IL - 6 and low gestational age (44). In the study by Unal, there was no correlation between gestational age and cytokines levels (IL-1, 6 and tumor necrosis factor-alpha) [2]. In most studies, there was no association between IL-6 and gestational age. The possible reason for lack of correlation between IL-6 levels in this study and similar studies can be the specific pregnancy age range and lack of considering pre-term; so if a study could assess a wider ranged gestational age, different results might be obtained.

In this study, the first and fifth minute Apgar score were assessed to evaluate an infant's outcome, Although the infantile the first and fifth minute Apgar scores were less in the induced labor, IL - 6 was not associated with the first and fifth minute Apgar scores. It was concluded that labor induction leads to a decrease in the first and fifth minute Apgar scores and it seems that reduced interventions (including induction) are effective in improving neonatal outcomes. In Arad's study, high levels of IL - 6 were significantly associated with lower Apgar scores of the first minute [43]. In Claudio Chiesa's study there was a negative correlation between cord bloods IL - 6 levels with the Apgar scores [22]. In another study higher cord blood concentrations of IL - 6 was associated with lower Apgar scores 1 min and 5 min [9]. In this study, no relationship was observed between IL - 6 levels and Apgar score. However, studies showed the relationship and importance of cytokines including IL - 6 with neonatal outcomes [14, 16, 18, 40]. It seems that these findings are due to the following: 1) no specific neonatal disease has been reported, 2) term

pregnancies without complication was considered, and 3) infants' Apgar score was more than 7.

Goetzl's study, as well as the present study, showed no relationship between the number of vaginal examinations and duration of ROM with maternal serum levels of interleukin - 6 [41]. It seems that the increasing number of vaginal examinations and PROM increases the risk of infection and thus the amount of IL - 6; interleukin-6 is associated with PROM and the number of vaginal examinations, but given that patients with durations of ROM more than 18 hours were excluded, no relationship was found in the present study. In the present study, the amount of vaginal examination and episiotomy was more in the group of induced labor, which indicates that labor induction, considered an intervention in normal labor, requires more interventions in labor, which indicates that induced birth are high risk.

In this study, no significant correlation was observed between IL-6 levels and birth order or parity. According to Arad's study, infants of nulliparous women had a higher level of IL-6 than infants born to multiparous women [43]. There was an association between infant's serum IL-6 and parity in Macaubas's study [9]. The results of studies seem to show that parity influences IL-6 levels, but such a result was not obtained in the present study and it seems that conclusions on this issue requires more investigations.

LIMITATIONS AND IMPLICATIONS

Small sample size, Not measuring IL-6 before and after labor, Not sampling mother's serum IL-6, and just measuring one cytokine, were our study limitations. The immunobiological role of inflammatory cytokines in parturition and the onset of spontaneous labor at term, especially without exogenic motivation, remain unspecified. Current study was a different view helping future studies to investigate other aspects of post term pregnancy and supporting physiological parturition.

CONCLUSIONS

In summary, IL - 6, which plays a role in the inflammatory response that is necessary to initiate labor, was not significantly different in induced and spontaneous birth. IL - 6 levels also had no significant relationship with different demographic, obstetric, and infantile variables. The results of this study may have clinical implications. Better insight in the physiological

role of intrauterine inflammation may eventually result in strategies to intervene in normal labor and Delivery, including induction of labor in post term pregnancies. We have considered the potential physiological role of intrauterine inflammation for both the onset of spontaneous labor at term and the induction of labor.

it seems that a better perspective would be obtained on the role of intra-uterine inflammation resulting from investigations on the strategies related to interventions in labor and normal birth, including labor induction and post-term birth, and not only assessing term and pre-term pregnancies. Ultimately, it is recommended that performing further studies for assessing this issue with a larger sample size, measuring before and after labor, sampling mother's serum and umbilical cord blood, and measuring different cytokines will be necessary. If current study would found positive relationship between IL-6 and mode of delivery, it would provide insight in the pivotal role of intrauterine inflammation in normal parturition.

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Author Contribution

Sahebazamani and Torkzahrani designed the study. Sahebazamani and Behroozilak collected the data. Shahsavari performed the data analysis. Sahebazamani wrote the paper.

Ethical Consideration

Informed consent forms were completed by all study subjects. This research has been approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

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Conflict of Interest

Authors declare no conflict of interests and Financial Disclosure.

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