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Serum Melatonin as a Biomarker for Assessment of Late-term and Postterm Pregnancies in Women without Spontaneous Onset of Labor

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ABSTRACT

We conducted a prospective study to assess serum melatonin as a biomarker to predict the development of late-term and postterm pregnancies and spontaneous beginning of labor in women with term pregnancies. Population of this prospective study included pregnant women with late-term and postterm pregnancies and term pregnancies as controls. In these study groups, serum melatonin concentrations were measured in women with or without labor and their perinatal data were collected. In the postterm pregnancies without labor, the lowest median melatonin concentrations were measured ($p<0.05$). In the late-term and postterm pregnancies with and without labor, the median serum melatonin concentrations were significantly lower than term ones ($p<0.05$). In the term pregnancies with labor, the highest median melatonin concentration was measured ($p<0.05$). A serum melatonin concentration ≤ 34 pg/mL as a cut-off value determines late-term and postterm pregnancy with a sensitivity of 80.4 % and a specificity of 81.4 %. A serum melatonin concentration > 29.35 pg/mL as a cut-off value determines presence of labor with a sensitivity of 82.1 % and a specificity of 55.0 %. In women with term pregnancies, with the measurement of serum melatonin, it is possible to predict the development of late-term and postterm pregnancies and whether these pregnancies undergo spontaneous labor. With further studies, these findings need to be supported before their routine clinical use.

Introduction

Although precise mechanisms regulating the increase in melatonin are not fully known in humans, the peak serum melatonin concentration at night lowers slightly during first half of pregnancy, then increases after 24 weeks of pregnancy, reaching its maximum by the end of pregnancy, and later returns to the pre-pregnancy value within 2 days of the postpartum period [1–5]. In myometrial tissue, melatonin acts in accordance with oxytocin, and at the end contributes to the increase of oxytocin sensitivity, which leads to spontaneous uterine contractility and finally labor and delivery. In humans, placental melatonin secretion may directly contribute to increasing maternal plasma melatonin. It is thought to promote uterine contractions necessary for labor as mentioned above [1, 6, 7].

When pregnancy exceeds 294 days (42 completed weeks) from the first day of a regularly occurring last menstrual period (LMP), it is defined as post-term. In addition, late-term pregnancy is defined as a period in between 41 + 0 and 41 + 6 weeks and days. If gestational age is not certain based on menstrual dating, ultrasonography is performed in the first trimester or first half of the pregnancy to determine the most accurate dating with an acceptable variation of ± 7 days [8–10]. Postterm pregnancy increases maternal and fetal risks, including abnormal fetal growth, oligohydramnios, meconium-stained amniotic fluid, non-reassuring fetal monitoring, fetal and neonatal death, the need for neonatal intensive care (NICU), dystocia, cesarean or operative vaginal delivery, and perineal lacerations. In late-term pregnancies, antenatal surveillance is recommended with non-stress testing and modified or full biophysical profile tests to reduce the rate of cesarean delivery and perinatal morbidity and mortality [10]. The prevalence of postterm pregnancies varies in different parts of the world from 0.33 to 8.1% in the United States and European countries, partly owing to different management modalities in term pregnancies and beyond. The prevalence of late-term births is 6.25% [8, 11, 12]. Among etiologic factors of postterm pregnancy, the most common cause is inaccurate gestational age dating, but in the rest, the cause is unknown [13].

Although the mechanisms that promote delivery and birth in normal pregnancies are not yet fully understood, a seasonal and daily periodicity of human birth has been identified [14]. Melatonin would seem to be an important factor in controlling birth time and it may be one of the determining factors for postterm pregnancies. Measurement of serum melatonin concentration in late-term and postterm pregnancies can lead to the development of a biomarker to predict and diagnose postterm pregnancy. A discussion should take place with the patient as to the options for management of late-term and postterm pregnancies, given the modalities for cervical ripening and labor induction and risks of continued pregnancy. If a decision is reached for expectant management, weekly antepartum surveillance with amniotic fluid assessment and non-stress tests are indicated. For the management of late-term and postterm pregnancies, novel biomarkers could be useful to predict and diagnose women requiring labor induction. We hypothesized that late-term and postterm pregnancies with or without spontaneous labor would be associated with altered serum melatonin levels compared to term pregnancy with or without spontaneous labor. To test this hypothesis, we prospectively recruited a large cohort of women with term and late-term and postterm pregnancies with and without labor to measure serum melatonin concentrations to analyze them with their perinatal data. The aim of this study was to assess serum melatonin as a biomarker to predict the development of late-term and postterm pregnancies and the spontaneous beginning of labor in women with term pregnancies.

Methods

Study design

The population of this prospective study was composed of consecutive pregnant women receiving antenatal care who applied to the obstetric service of Samsung Training and Research Hospital in Samsun, Turkey. Women with late-term and postterm pregnancies were eligible for participation if they were aged 18 or more, understood oral and written information, and had a singleton pregnancy with a fetus in cephalic presentation beyond 40 weeks + 6 days of pregnancy according to ultrasound-based dating in the first or early second trimester or for pregnancies after assisted reproduction according to the day of oocyte retrieval. Exclusion criteria were previous caesarean delivery or other uterine surgery, pregestational and insulin-dependent gestational diabetes, hypertensive disorder of pregnancy, known oligohydramnios (amniotic fluid index < 50 mm or deepest vertical pocket < 20 mm) or small-for-gestational-age fetus, diagnosed fetal malformation, contraindication for vaginal delivery, and any other maternal condition affecting the progress of the pregnancy to 42 weeks or beyond.

Antepartum testing has been widely accepted in postterm pregnancies, even though there is no evidence that it decreases perinatal mortality [15]. Because of ethical concerns, it is unlikely that any studies of postterm pregnancies would include a group of patients who did not undergo antepartum fetal monitoring. American College of Obstetricians and Gynecologists (ACOG) guidelines state that it is "reasonable to initiate antenatal surveillance of postterm pregnancies between 41 and 42 weeks" gestation [16]. The testing options vary and may include a biophysical profile (BPP), determination of amniotic fluid index (AFI), non-stress test (NST), or a combination of these [16].

The Human Research Ethics Committee of the University of Health Sciences approved the research protocol (process KAEK 2020/5/9 dated 2020). All procedures were in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Blood samples for melatonin measurement

Blood samples were collected, in a fasting state, from 22:00 to 6:00 a.m. on admission of the patients. Serum samples were stored at −80 ℃ until use. Serum melatonin measurements were performed by ELISA.

Sample size determination

According to the formula, the sample size equals $[2(Z\alpha + Z1\text{-}\beta)^2]\ \delta^2/\Delta^2$ to estimate the minimum number of samples required in each experimental subgroup to obtain an alpha error of 5% ($Z\alpha$ is equal to 1.96 for two-tailed test because the results could be bidirectional for an alpha error of 5%), 90% power ($Z1\text{-}\beta$ is equal to 1.2816 for 90% power) to detect approximately double exchange rate transcriptional expression between groups (Δ is equal to 10 as the expected effect size for this study) and standard deviation levels (δ) of 25 (δ as the expected standard deviation according to findings of study mentioned above) [17]. After finding a sample size of 66 and accepting a 10% drop-out rate, to complete the study 72 patients per arm would be required to be able present with any degree of confidence whether a difference exists between the term, late-term, and postterm pregnancies.

Statistical Analysis

After the normality test, continuous variables were described by the median (interquartile range (IQR): 1st quartile–3rd quartile). Categorical variables were described by numbers and percentages. The Kruskal–Wallis test with post hoc Mann–Whitney and chi-square tests were used as appropriate. Receiver operating characteristic (ROC) analysis was performed to examine the predictive value of serum melatonin concentrations to determine statuses of postterm pregnancy and labor. All statistical tests were two-tailed with the significance level set at 5%. Significance values have been adjusted by the Bonferroni correction for multiple pair-wise comparisons. The analyses were conducted using IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

A total of 362 pregnant women who completed the study protocol were as stratified into four groups according to their gestational age and labor status: term pregnancy without labor (n = 111), term pregnancy with labor (n = 72), late-term and postterm pregnancies without labor (n = 100), late-term and postterm pregnancies with labor (n = 79). The main baseline characteristics for the study groups are shown in ▶ **Table 1**. There was no significant difference among the study groups regarding the age, gravidity, parity, and BMI ($p > 0.05$).

▶ **Table 2** present the selected clinical characteristics of the study groups. There were no significant differences between the term pregnant women with and without labor regarding the median gestational age at admission ($p > 0.05$). Of the term pregnant women without labor, the median gestational age at delivery was significantly higher than that of the term pregnant women with labor ($P < 0.05$). There were no significant differences between the late-term and postterm women with and without labor regarding

▶ **Table 1** Baseline characteristics of women with term pregnancy with or without labor and late-term and postterm pregnancies with or without labor.

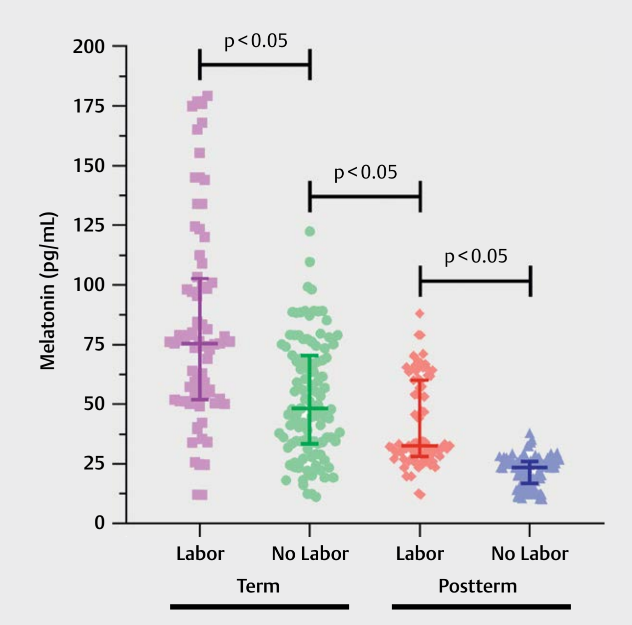
	Term pregnancy		Late-term and postterm pregnancies	
	Without labor (n = 111)	**With labor (n = 72)**	**Without labor (n = 100)**	**With labor (n = 79)**
Age (y)	26 (22–28)	25.5 (23–29)	27 (22–31)	25 (22–29)
Gravidity	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–2)
Parity	1 (0–1.5)	1 (0–2)	1 (0–2)	1 (0–1)
BMI (kg/m^2)	24 (23.1–26.6)	24.4 (23–27.5)	23 (23–27.9)	25.2 (23.3–28)

Data are expressed as median with interquartile range (25–75 %) and analyzed with Kruskal–Wallis test. No significant differences are present among the study groups regarding these variables ($p > 0.05$).

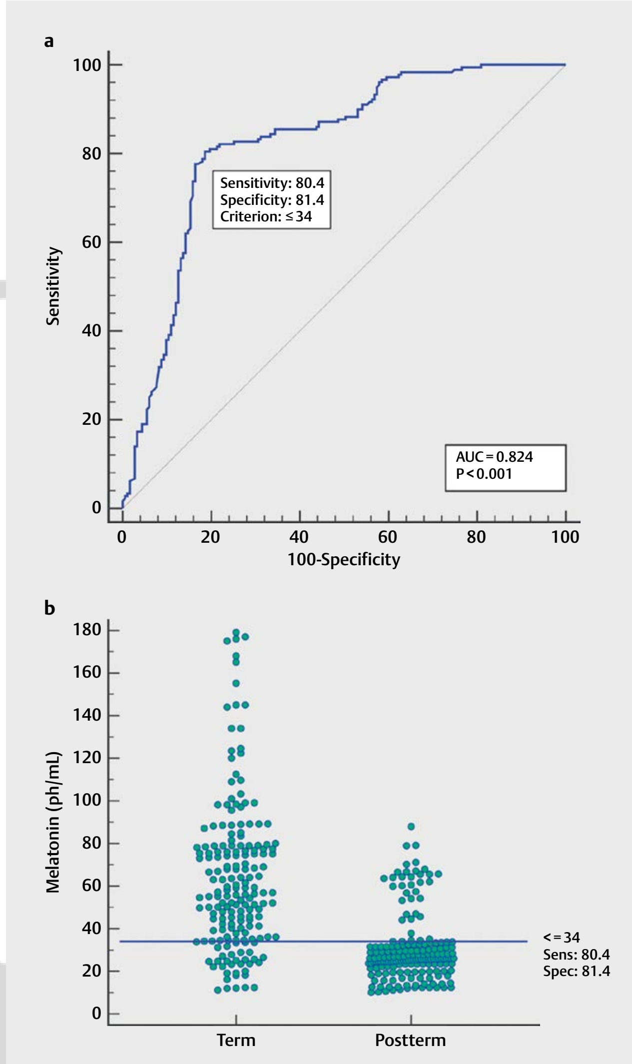
▶ **Table 2** Selected clinical characteristics of women with term pregnancy with or without labor and late-term and postterm pregnancies with or without labor.

	Term pregnancy		Late-term and postterm pregnancies	
	Without labor (n = 111)	**With labor (n = 72)**	**Without labor (n = 100)**	**With labor (n = 79)**
Gestational age (w)				
at admission	39 (38–40)	39 (38–40)	42 (41–42)	42 (41–42)
at delivery	40 (39–41)[a]	39 (38–40)	42 (41–42)	42 (41–42)
Mode of delivery (n, %)				
Vaginal	102 (91.9 %)	57 (79.2 %)	64 (64 %)	54 (68.4 %)
Cesarean	9 (8.1 %)	15 (20.8 %)	36 (36 %)	25 (31.6 %)
Apgar score				
1 min	8 (7–8)	9 (8–9)[b]	8 (7–9)	9 (8–9)[c]
5 min	9 (9–10)	10 (9–10)	9 (8–9)	10 (9–10)
Birth weight (g)	3600 (3210–3900)[d]	3375 (3125–3587)	3450 (3070–3765)	3370 (3070–3730)
Meconium-stained amniotic fluid (n, %)	11 (9.9 %)	8 (11.1 %)	20 (20 %)	12 (15.2 %)
NICU admission (n, %)	10 (9 %)	6 (8.3 %)	10 (10 %)	7 (8.9 %)
Mechanic ventilation (n, %)	4 (3.6 %)	3 (4.3 %)	7 (7.0 %)	4 (5.1 %)

Data are expressed as median with interquartile range (25–75 %) and number (percentage) as appropriate and analyzed with chi-square and Kruskal–Wallis test as appropriate. No significant difference is present among the study groups regarding the rates of cesarean delivery, meconium-stained amniotic fluid, NICU admission, and mechanic ventilation ($p > 0.05$). [a]$P < 0.05$ compared to term with labor. [b,c]$P < 0.05$ compared to term and late-term and postterm without labor. [d]$P < 0.05$ compared to other groups.



▸ **Fig. 1** Melatonin levels of term (Term) and late-term and postterm (Postterm) pregnant women with and without labor. The data are expressed as median with interquartile range. The Kruskal–Wallis test with post hoc Mann–Whitney test revealed there were significant differences among all the study groups ($p<0.05$).



▸ **Fig. 2** An ROC curve of serum melatonin for the diagnosis of late-term and postterm (Postterm) pregnancy. The area under the curve value is 0.824 ($p<0.001$). **a** Serum melatonin concentration ≤ 34 pg/mL as a cut-off value determines late-term and postterm pregnancy with a sensitivity of 80.4 % and a specificity of 81.4 %. **b** Scatter dot plot of serum melatonin concentrations of women with term (Term) and late-term and postterm pregnancies. The horizontal line represents the serum melatonin concentration ≤ 34 pg/mL as a cut-off value calculated by ROC curve analysis.

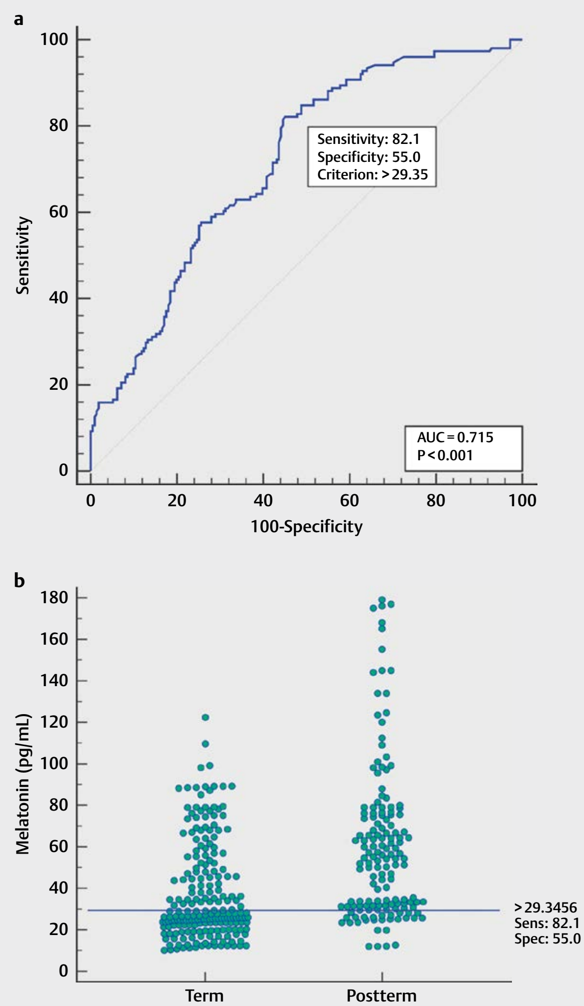
the median gestational age at admission and at delivery ($p>0.05$). There were no significant differences between the term and late-term and postterm women with and without labor regarding the rate of cesarean delivery ($p>0.05$). Of the newborns of the term and late-term and postterm women with labor, the median Apgar scores at 1 and 5 min were significantly higher than those of the newborns of the term and late-term and postterm women without labor ($P<0.05$). The median birth weight of newborns of the term women without labor was significantly higher than those of newborns of the women in the other study groups ($p<0.05$), and the median birth weight of newborns of pregnant women in the other study groups were found to be comparable ($p>0.05$). The rates of meconium-stained amniotic fluid, NICU admission, and mechanic ventilation in the study groups were found to be similar ($p>0.05$).

The median concentrations of serum melatonin measured in term, late-term, and postterm women with and without labor are presented in ▸ **Fig. 1**. As seen on the presentation, the statuses of late-term and postterm pregnancies and labor significantly affected the melatonin concentrations ($p<0.05$). In the late-term and postterm pregnancies, we measured the lowest median melatonin concentrations ($p<0.05$). In the late-term and postterm pregnancies with and without labor, the median serum melatonin concentrations were significantly lower than those of the term pregnancies with and without labor ($p<0.05$). In the term pregnancies with labor, we measured the highest median melatonin concentrations ($p<0.05$).

▸ **Fig. 2** and **3** show the ROC analysis for the determination of a cut-off value for serum melatonin concentration to determine the status of late-term and postterm pregnancies and labor, respectively. A serum melatonin concentration ≤ 34 pg/mL as a cut-off value determined postterm pregnancy with a sensitivity of 80.4 % and a specificity of 81.4 %. A serum melatonin concentration > 29.35 pg/mL as a cut-off value determined the presence of labor with a sensitivity of 82.1 % and a specificity of 55.0 %.

Discussion

To better understand the participation of melatonin in the labor process of late-term and postterm pregnancies, we explored serum melatonin concentrations in pregnant women with or without labor. In the study groups including pregnant women with term



▶ **Fig. 3** **a** ROC curve of serum melatonin for the diagnosis of labor in term (Term) and late-term and postterm (Postterm) pregnancies. The area under the curve value is 0.715 ($p<0.001$). Serum melatonin concentration > 29.35 pg/mL as a cut-off value determines the presence of labor with a sensitivity of 82.1 % and a specificity of 55.0 %. **b** Scatter dot plot of serum melatonin concentrations of women with term and late-term and postterm pregnancies. The horizontal line represents the serum melatonin concentration > 29.35 pg/mL as a cut-off value calculated by ROC curve analysis.

and late-term and postterm pregnancies with and without labor, overall, the basic characteristics were considerably similar. We found that according to the presence of term and labor characteristics, serum melatonin concentrations increased. For the determination of a postterm pregnancy, a serum melatonin concentration ≤ 34 pg/mL as a cut-off value provided a sensitivity of 80.4 % and a specificity of 81.4 %. For the determination of a postterm pregnancy, a serum melatonin concentration > 29.35 pg/mL as a cut-off value provided a sensitivity of 82.1 % and a specificity of 55.0 %. Overall, these findings support the value of melatonin as a biomarker for clinical evaluation of women with late-term and postterm pregnancies.

Postterm pregnancies, although less common in the era of ultrasound dating, are associated with perinatal morbidity and mortality. Several antenatal care units prefer routine induction of labor at 41 weeks in women with low-risk singleton gestations to prevent progression to postterm pregnancy and increasing perinatal risks. Induction of labor in late-term pregnancy has the potential to prevent these complications; however, both mothers and obstetricians alike are concerned about risks associated with the induction of labor leading to increased cesarean delivery rates. However, there is a strong body of evidence that demonstrates that a policy of induction of labor at 41 weeks in late-term mothers could be beneficial with potential improvement in perinatal outcome and a reduction in maternal complications [18, 19].

In infants born postterm as well as in the late term, several key morbidities are encountered, including meconium-related respiratory problems, neonatal academia, low Apgar scores, and macrosomia-related neonatal problems including birth injury. Approximately 20 % of postterm fetuses have fetal dysmaturity syndrome, which describes infants with characteristics of chronic intrauterine growth restriction from uteroplacental insufficiency [20]. These pregnancies are at increased risk of umbilical cord compression from oligohydramnios, non-reassuring fetal antepartum or intrapartum assessment, intrauterine passage of meconium, and short-term neonatal complications (such as hypoglycemia, seizures, and respiratory insufficiency) [21]. The maternal risks of postterm pregnancy also need to be appreciated. These include an increase in labor dystocia, an increase in severe perineal injury (3rd and 4th degree perineal lacerations) related to macrosomia and operative vaginal delivery, and a doubling in the rate of cesarean delivery that is also associated with higher risks of complications such as endometritis, hemorrhage, and thromboembolic disease [21].

Considering these fetal, neonatal, and maternal morbidity and mortalities and current knowledge collected with melatonin-related research in pregnant women, melatonin has a potential to be used as a therapeutic agent or as a biomarker to predict and diagnose labor in pregnant women. Synergistic actions of melatonin on oxytocin-induced contractility may be of clinical relevance in that it could provide a means to lower the oxytocin dose used in the induction of labor and thus reduce the contraindications associated with oxytocin induction of labor. This could be a research topic to develop novel treatment modalities to be used in late-term and postterm pregnancies to improve obstetric outcomes.

Melatonin, a monoamine hormone secreted by the pineal gland, is a major molecular messenger of the nocturnal phase of the day. As a ligand, it is effective by means of 2 G-protein coupled receptors, melatonin receptors 1 and 2. Human myometrium is a target for melatonin and expresses both melatonin receptors. Crosstalk between oxytocin and melatonin pathways is important in myometrial contractions. Melatonin potentiates in vitro norepinephrine-induced contractility in a dose-dependent manner in human myometrial strips [4, 5, 22–27]. Rahman et al. [28] investigated whether it is possible that light exposure could modulate uterine contractions by altering melatonin levels that were measured in saliva. Their data supported that ocular light exposure modulated melatonin concentrations, and in accordance with that change, uterine contractions increased. Studies of the timing of initiation of spontaneous labor show a peak between 12:00 am and 05:00 am.

Both term and preterm human parturition have been reported by several groups to occur most frequently during the late night and early morning hours, i. e., between 10:00 pm and 8:00 am. This peak in labor onset coincides with peak serum melatonin levels in humans [8, 25].

In the literature, there are studies investigating clinical variables related to postterm pregnancy to ease prediction and diagnosis of postterm pregnancy and to decrease postterm pregnancy-related adverse outcomes. Torricelli et al. [13] assessed maternal clinical characteristics, ultrasound cervical length measurement, and serum estrogens E3 and E2 and their ratios as potential variables influencing the response to the induction of labor in nulliparous women with postterm pregnancies. They suggested that the combined use of ultrasonographic cervical length and a novel biochemical marker like the E3-to-E2 ratio could be a good predictor of successful induction of labor. Kosinska-Kaczynska et al. [29] evaluated insulin-like growth factor binding protein-1 (IGFBP-1) in cervical secretion in term and postterm pregnancies can predict spontaneous onset of labor or successful vaginal delivery in pregnant women with induced labor. They found that the phosphorylated IGFBP-1 test may be a predictor of spontaneous onset of labor and successful vaginal delivery in postterm pregnancies. They suggested that the phosphorylated IGFBP-1 test may be the most objective method compared to the Bishop score and ultrasound cervix assessment. In a similar study, Vallikkannu et al. [30] evaluated cervical IGFBP-1 and its value as a predictor of successful labor induction in term pregnancies compared with the Bishop score and transvaginal ultrasound (TVUS) cervical length. Their findings supported the usability of IGFBP-1 as a predictive test for successful labor induction.

As a limitation, basing on the theoretical premises, serial measurements of melatonin in the study groups would increase its predictive values in pregnant women with late-term and postterm pregnancies. A serum melatonin test could be performed before successful labor induction with different modalities including prostaglandins, oxytocin, and mechanical methods. Additional studies are required to elucidate the clinical relevance of the change in serum melatonin concentrations as assessed in women with late-term and postterm pregnancies. Adding melatonin or its agonists alone, before or with labor induction with oxytocin, may enhance uterine stimulation and shorten labor [8]. At the same time, existing data indicate the need to keep balanced light conditions in obstetric services to maintain normal endogenous production of melatonin as well as to restrict the use of melatonin-suppressing drugs.

According to the findings of this prospective study, measuring serum melatonin level in term pregnant women may have value as a predictive biomarker as to whether late-term and postterm pregnancies will occur. In addition, the serum melatonin level can also predict the status of labor although it provides a lower specificity. As a supplementary test, serum melatonin levels could bring additional information to determine follow-up and labor management in women with late-term and postterm pregnancies.

Author’s Contributions

NY: protocol/project development, data collection and analysis, manuscript writing and editing. CSC: protocol/project development, data analysis, manuscript writing and editing. SC: protocol/project development, data collection, manuscript writing and editing. AC: data analysis, manuscript writing and editing. All authors contributed to the study conception and design. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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