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Maternal BMI, 25-Hydroxyvitamin D serum level and Cervical Length Measurements: Markers for Preterm Delivery

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ABSTRACT

Background: Preterm delivery is the delivery between 20th - 37th weeks of gestation.

Aim of the work:to study the maternal BMI, 25-Hydroxyvitamin D (25(OH)D) serum level, and uterine cervical length (CL) as predicting factors for PTD.

Patients and methods: A prospective study included 188 pregnant women recruited during 20th - 24th weeks of gestation. The maternal BMI was calculated, the serum level of 25(OH)D was measured, and the uterine CL was measured via transabdominal and transvaginal ultrasound. All women followed until delivery time and then were divided into 2 groups; group1 (n=54) women who delivered preterm, and group2 (n=134) women who delivered at term.

Results: BMI results showed statistical significance between women who delivered preterm and those who delivered at term (29.7±1.7 vs. 23.6±2.2 kg/m2, P<0.001). Serum 25(OH)D showed no significant difference between the studied groups. CL was significantly shorter in women who delivered preterm than other group (32.39±5.93 vs. 44.42±4.17 mm, P<0.001). At 25 mm as a cut-off value for CL, the sensitivity, specificity, PPV, and NPV were 90.7%, 78.4%, 62.8%, and 95.5%, respectively. Women with BMI >25kg/m2 had significantly longer cervix than those who had BMI <25kg/m2. Regarding the effect of CL on the mode of delivery, 65.4% of women with CL <25 mm delivered vaginally.

Conclusion: Maternal BMI has a significant relation with PTD. Measuring the CL during 20th - 24th weeks helps to predict preterm delivery and the mood of delivery. There is an association between BMI and cervical length. However, no associations were detected between serum 25(OH)D level and PTD.

Keywords:*BMI; 25-Hydroxyvitamin D; Cervical Length; Preterm Delivery.*

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INTRODUCTION

Preterm delivery (PTD), which was regarded as the main health problem worldwide, represents one of the leading morbidity and mortality factors .[1]It is defined as delivery between the 20th - 37th weeks of gestation and accounts for 2/3 of the first-year mortality rate and 50% of the neonatal mortality rate in developed countries .[1, 2, 3]

Numerous biological and biochemical factors had been applied for diagnosing and predicting spontaneous PTD. Since stopping the PTD process was associated with less success, today's modern researches are now focusing on the prevention of PTD. The first step to be taken for preventing PTD is its prediction. Therefore, one of the main goals is the early diagnosis of women at risk, as well as providing the necessary treatment in the neonatal ICU.[4]

High BMI in pregnant women was found to have several pregnancy-related complications, e.g., PTD .[5]Studies have shown that obese women could have physiological, endocrinal environments that differ from their control peers, and this might affect cervical length (CL) .[6] Both obesity and cervical insufficiency are regarded as chief leading causes of morbidity in pregnancy. Recent studies revealed an association between obesity and longer CL .[7]It has been reported that, before and during early pregnancy, BMI was found to be associated with PTD, although its distinctive role is still undetermined .[8]

Vitamin D, a pleiotropic fat-soluble nutrient and prohormone, is produced by the skin due to exposure to ultraviolet rays from sunlight. However, diet is a poor source of vitamin D .[9]Moreover, it has both classic functions (e.g., calcium absorption, metabolism, bone health) and non-classic actions that may affect other various aspects of health. The main circulating form of vitamin D is 25-hydroxy vitamin D (25(OH)D), which represents the best measure of vitamin D status .[10]Serum vitamin D level in pregnant women is of great concern for pregnancy outcomes. Although some studies had found that vitamin D deficiency increases the risk of gestational diabetes, preeclampsia, decreased fertility, increased disease activity, placental insufficiency, threatened PTD, cesarean section, and low birth weight, yet other studies found no significant associations with these outcomes. To date, no consensus exists regarding optimal vitamin D levels in pregnancy .[9,11]Since infections were known to increase the risk for PTD, vitamin D could play an important role in the maintenance of pregnancy, as well as the prevention of infection and inflammation-induced PTD .[12]

It has been reported that vitamin D deficiency regulates the levels of inflammatory factors, which in turn increase the levels of uterine contraction hormones (e.g., prostaglandin) and thus causes PTD .[13]Moreover, the magnitude of change in CL during uterine contraction is a good predictor for the consequent progression of labor. Consequently, vitamin D level might explain the changes observed in CL during the progression of labor.

One of the diagnostic tools used to predict PTD is the vaginal ultrasound that is a proper method for a morphologic evaluation of the cervix and measuring its details with high validity .[14] Moreover, CL measurements play a major role in the prediction of labor .[15] Although standard measurements for uterine CL with increasing gestational age are not available yet, several studies have provided reference ranges (measured by TVUS) in large populations of women with singleton pregnancies .[16] An inverse relation between the uterine CL during pregnancy and the frequency of PTD has been reported .[17]

PATIENTS AND METHODS

This study was conducted at the Centre of Excellency clinics, National Research Centre, and Al Hussien University Hospital antenatal care clinic, Egypt, during the period between Jan 2020 to Dec 2020. Two hundred pregnant women attending the outpatient clinic for their routine antenatal care were enrolled in this study and underwent follow-up till delivery. The fulfilled inclusion criteria of the participant women were: age range (20-35 years), BMI (20-32 kg/m^2), gestational age (20-24) weeks, primigravida, and singleton pregnancy. The exclusion criteria were being smokers, having congenital anomalies of uterus and cervix (assessed by ultrasonography), multiple pregnancies, placental abnormalities, past history of cervical operations, and the presence of cervical abnormalities.

This prospective study was approved by the Ethics Committee of Al-Azhar University, Cairo, Egypt (approval number is 00000430). Written informed consent was obtained from every participant woman after explaining the aim of the study and the steps of the ultrasound examination. The study was carried out on 200 pregnant women who continued antenatal follow-up until delivery. They were divided into 2 groups; group (1) includes women who had preterm delivery: (n=54), and group (2) includes Women who had term delivery: (n=134).

Gestational age was calculated from the first day of the last menstrual period. For all participants, maternal BMI was calculated, serum 25(OH)D level was evaluated, and CL was measured at the 20th week of gestation. Until the delivery time, follow-up of all women was done to record those who will deliver term or preterm, as well as to record the gestational age at which labor occurred. Spontaneous PTD was defined as the onset of labor before 37th weeks. All participants were subjected to full history taking, complete general and gynecological examination. BMI (kg/m^2) was calculated as follows: body weight (kg) divided by height in meter square (m^2) [18].

Serum 25(OH)D was quantitatively assessed using 3 ml maternal venous blood sample; collected, at the non-fasting condition, during the 20th week of gestation. Serum 25(OH)D concentration was measured using enzyme-linked immunosorbent assay (ELISA) [19], (IDS Diagnostics Ltd, Boldon, Tyne and Wear, UK), following the instructions written on the kit.

Routine ultrasound examination was done at 20th weeks. Transabdominal ultrasound (TAUS) was used to assess both fetal growth and fetal wellbeing [fetal biometry (BPD, FL, AC), estimated gestational age, placenta (site and maturity), liquor (amount and turbidity)] and CL. Transvaginal ultrasound (TVUS) was used to assess CL. The ultrasound equipment used was TOSHIBA ECCOSEE machine (made in Japan, 1998), equipped with both a transabdominal 3.5 MHz curvilinear probe and a high-resolution transvaginal 6.5 MHz probe. All cases were examined by the same sonographer.

Statistical analysis: Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 20.0, Inc., Chicago, Illinois, USA. Quantitative data were expressed as mean ± standard deviation (SD), while qualitative data were expressed as frequency and percentage.

RESULTS

Among the two hundred participating women enrolled in the study, 188 candidates continued antenatal follow-up, while only 12 candidates didn't, and hence they were excluded from our study. The enrolled women in the study (n=188) were divided into 2 groups; group 1 (n=54) included women who delivered preterm babies, and group 2 (n=134) included women who delivered at term. Comparison between the 2 groups regarding the patient's age revealed no statistically significant difference (27.64±4.44 vs.. 26.18±3.95, P=0.126).

Table (1) showed a comparison between both groups regarding BMI, 25(OH)D, and CL assessed by transvaginal ultrasound (TVUS). BMI results revealed a statistically significant difference between women who delivered preterm and those who delivered at term (29.7±1.7 vs. 23.6± 2.2 kg/m^2, respectively, P <0.001). About 63% of women who delivered preterm had BMI>25kg/m^{2,} and 37% of the same group had BMI <25kg/m^2. Whereas only 42% of women in the term group and 58% had

BMI>25kg/m^2.On the contrary, serum 25(OH)D levels showed no statistically significant differences (28±12 vs. 29±13 nmol/L, respectively, P=0.614). Regarding the CL, measured transvaginally (TVUS), it was significantly shorter in women who delivered preterm, compared to that in those who delivered at term (32.39±5.93 vs. 44.42±4.17 mm, respectively, P <0.001). It worth noting that when we measured the CL by transabdominal ultrasound (TAUS), we got the same significant values between both groups (34.87±4.53 vs. 42.70±3.29 mm, respectively, P <0.001). After that, we classified women according to their CL, that measured by TVUS, into women with short CL (<25 mm) and women with long CL (>25 mm). Among women with short CL (n=78), 49 women delivered preterm and 29 women delivered at term, while in women with the long CL (n=110), only 5 women delivered preterm and 105 delivered at term.

Table (2) shows the sensitivity, specificity, and both positive and negative predictive values of the transvaginally measured CL in both groups. At 25 mm as a cut-off value for CL, the sensitivity was 90.7%, the specificity was 78.4%, the positive predictive value was 62.8%, and the negative predictive value was 95.5%. We then subdivided all women according to BMI into women with BMI < 25 kg/m2 (n=98) and women with BMI > 25 kg/m2 (n=90). The association between BMI and CL revealed a statistically significant relation (P<0.001). Women with BMI >25kg/m2 had significantly longer cervix when compared with those who had BMI <25kg/m^2, as shown in table (3). The relation between CL and mode of delivery was studied in table (4). A statistically significant difference (P=0.014) was observed in the mode of delivery in relation to the variably measured CL in both studied groups.

	Preterm delivery (n=54)	Term delivery (n=134)	P-value
BMI (kg/m^2) Mean±SD	29.7±1.7	23.6±2.2	<0.001*
< 25 kg/m^2 (n=98) > 25 kg/m^2 (n=90)	20 (37%) 34 (63%)	78 (58%) 56 (42%)	0.009*
25(OH)D nmol/L Mean±SD	28±12	29±13	0.614
C.L. in mm (by TVUS) Mean±SD	32.39±5.93	44.42±4.17	<0.001*
C.L.< 25mm (n=78) C.L.> 25mm (n=110)	49 (62.82%) 5 (4.55%)	29 (37.18%) 105 (95.45%)	<0.001*

* Significant P-value

Table 1: Comparison between both groups regarding BMI, 25(OH)D, and cervical length (C.L.) assessed by transvaginal ultrasound (TVUS).

C.L. in mm (by TVUS)	Sensitivity %	Specificity %	PPV %	NPV %
C.L.< 25mm (n=78) C.L.> 25mm (n=110)	90.7%	78.4%	62.8%	95.5%

Table 2: Sensitivity, specificity, PPV(+ve predictive value), and NPV (-ve predictive value) of transvaginal measuring cervical length (C.L.) in all cases.

C.L. in mm (by TVUS)	BMI < 25 kg/m^2(n=98)	BMI > 25 kg/m^2(n=90)	P-value
C.L.< 25 mm(n=78) C.L.> 25 mm(n=110)	72 (67.29%) 26 (32.10%)	35 (32.71%) 55 (67.90%)	<0.001*

* Significant P-value

Table 3: Association between body mass index (BMI) and cervical length (C.L.)

C.L. in mm (by TVUS)	Vaginal delivery (n=103)	Cesarean delivery (n=85)	P-value
C.L.< 25 mm(n=78) C.L.> 25 mm(n=110)	51 (65.38%) 52 (47.27%)	27 (34.62%) 58 (52.73%)	0.014*

* Significant P-value

Table 4: Relation between cervical length (C.L.)and mode of delivery

DISCUSSION

The risks of PTD were extensively reported. This had led many authors to search for a reliable method to predict the occurrence of PTD. This study was conducted in outpatient hospital clinics and enrolled 200 participant women. Maternal BMI was calculated, serum 25(OH)D was measured at 20th week. Women were examined using both transvaginal and transabdominal ultrasound in order to measure the CL, as well as to assess the pregnancy status. Our aim was to study maternal BMI, serum level of 25(OH)D, and CL measurement as factors associated with the occurrence of PTD. Out of the 200 selected women, only 12 cases were excluded as they didn't continue follow-up.

In our study, participant women were selected to be 20-35 years old. There was no statistical difference between groups that excluded the effect of different ages on pregnancy outcomes.Regarding BMI, our study revealed a statistically significant difference between the two studied groups (29.7±1.7, 23.6± 2.2 respectively, P<0.05). We concluded that overweight and obese women (BMI>25kg/m^2) experienced PTD more than those with BMI <25kg/m^2. However, the association between pre-pregnancy obesity (BMI > 25kg/m^2) and PTD is still debatable and questionable. Liu, et al. (2019) studied the association between maternal pre-pregnancy obesity and PTD and found a significant correlation between them .[20] However, they correlated their results to age; on the contrary, we had chosen candidates with an insignificant age difference in our work. Eick et al. (2019) studied a group of pregnant women from Puerto Rico, North America, and found that pre-pregnancy BMI was associated with increased PTD .[21] Similarly, in Sweden, Cnattingiuset et al. (2013) concluded that maternal overweight and obesity during pregnancy were associated with higher risks of PTD .[22] However, our results disagreed with those concluded by Ibrahim et al. (2019), who found that BMI showed no statistically significant difference between the preterm and term groups. This might be due to their small sample size .[3]

In this study, the gestational age range of selected women was 20-24 weeks. This age range represented a usual period for performing their second-trimester anomaly scan. This was reported by McIntosh et al. (2016), who stated that most clinical guidelines recommended performing CL screening between 16-24 weeks of gestation for asymptomatic women with a history of preterm labor. Moreover, the CL should not be regularly measured before 16 weeks of gestation, as the predictive accuracy of CL assessment, at 1st and early 2nd trimester, for PTD is low, particularly in asymptomatic women without a history of PTD .[23] Goya et al. (2012) showed that routine CL screening is not recommended after 24 weeks of gestation in asymptomatic women .[24] The majority of studies exploring different interventions aimed to prevent PTD (e.g., cervical cerclage, vaginal progesterone) had most frequently used 24 weeks of gestation as the maximum bound for screening and initiation of therapies or interventions. They concluded that early identification of a short cervix in asymptomatic women could be beneficial, as it helped administration of corticosteroids and magnesium sulfate, admission to a high-risk ward, and transfer to a tertiary center .[24]

In our study, both transabdominal and transvaginal ultrasounds were used to assess the CL measurement. The advantages of using ultrasound for the assessment of the CL were: being standardized, objective imaging often done by an independent person, and with measurements documented and achieved for re-assessment. However, the main subjectivity of digital assessment by a clinician was its ability to measure the portiovaginalis only, but not the whole CL, lack of documentary proof, as well as it could not be achieved for re-assessment. Also, Berghella and Saccone (2019) had shown that the CL was more accurate than cervical dilatation .[25]

Regarding CL measurement in our study, it was assessed by TVUS, and then women were classified into 2 categories: CL<25 mm, and CL >25 mm. Our results revealed a statistically significant difference, which explained and clarified the relationship between the CL and the occurrence of PTD with a cut-off point <25 mm. Moreover, the CL in the preterm group was shorter than those in the term group, with a statistically significant difference (32.39±5.93 mm vs. 44.42±4.17 mm when measured transvaginally and 34.87±4.53 mm vs. 42.70±3.29 mm when measured transabdominally).Lamiaa et al. (2021) observed a significant positive correlation between CL and PTD, and hence CL measurement can be used for predicting PTD .[26]Raval, et al. (2020) studied 150 antenatal women and found that the CL (measured by TVUS between 16-24 weeks of gestation) was 25 mm in about 24% with PTD .[27] Similarly, Jafari et al. (2015) found that the mean of uterine CL during the 2nd trimester was 38.28 ± 5.13 mm .[28] In contrast to our study, Kwasan et al. (2017) showed that the cut-off value of CL, in the prediction of preterm labor, was 30 mm with a sensitivity of 93.3% and specificity of 82.0%. This finding can be attributed to the small sample size used in their study .[29]

In our study, the comparison of CL (by TAUS and TVUS) in preterm and term groups had revealed that, although both techniques were efficient in detecting/identifying CL, TVUS was easier than TAUS avoiding difficulty resulting from the thickness of the abdominal wall and fetal parts. It was observed that, by using transvaginal ultrasound, the sensitivity (90.7%) observed at cut-off = 25 mm, specificity was (78%), the positive predictive value was 62.8%, and the negative predictive value was 95.5%.

In agreement with our study, Navathe et al. (2019) declared that the common methods for the sonographic assessment of CL include transvaginal (TVUS) and transabdominal (TAUS). They also concluded that the CL measured by TVUS is associated with better prediction of a PTD than other approaches, and hence it is considered the gold standard for CL measurement. They believed that the assessment of CL with TVUS is less influenced by obesity, cervix position, and shadowing from the fetal presenting part. However, it worth noting that many studies claimed the efficacy of treatment of women with a short cervix was used by TVUS to assess CL .[30] Similarly, Raval et al. (2020) confirmed that TVUS was the most effective, useful, better, safe, accurate, less expensive, objective, and acceptable technique that was used for CL assessment in all antenatal women and also for predicting preterm labor when assessed between 16-24 weeks of gestational age .[27] Likewise, Hernandez-Andrade et al. (2012) and Friedman et al. (2013) concluded that TVUS is the superior and accurate method for CL assessment compared to TAUS .[31, 32] Their results were in accordance with ours.

In our work, we tried to clarify the association between BMI (<25, >25 kg/m^2) and transvaginal measurements of CL. We observed that women with BMI >25kg/m^2 had significant long cervix when compared with those who had BMI <25kg/m^2. Although obese women had a significant incidence of PTD, we observed that they had a significant long cervix. This could explain the presence of other factors related to obesity rather than CL triggering PTD.Kandeel et al. (2014) studied 100 Egyptian pregnant women with singleton pregnancies at 20-22 weeks' gestation. They concluded that both overweight and obese women had a longer CL than their normal-weight counterparts. They also found that short CL (< 15 mm at 22-24 weeks of gestation) was associated with a higher risk of PTD. However, short cervix in women with low BMI was not an inevitable predictor for PTD unless associated with other risk factors. In their study, they depended on a cut-off value of 15 mm while our cut-off value was 25 mm .[33]

Kandil et al. (2017) and Venkatesh and Manuck (2020) found a significant association between maternal BMI and second-trimester CL and concluded that overweight and obese women had longer CL compared to normal-weight women .[34,35] This difference in the mean CL in different populations can be attributed to racial differences and different sample sizes.Recent studies concluded that obese women (BMI > 30 kg/m^2) had longer CL and a lower risk of PTD .[7,36] The increased CL in obese women could be attributed to possessing different physiological and endocrinal environments .[6,37]Hawzheen and Srwa (2019) found that women with higher BMI (BMI ≥25) had normal CL and a lower risk of PTD (32.1%, p = 0.001). On the other hand, none of the obese or normal-weight women had short cervix. Whereas, women with BMI < 18.5 mostly have short cervix and 89.5% PTD rate (p < 0.001) .[38]

Vitamin D regulation of the inflammatory markers and the contractile-associated factors (in human uterine myometrial smooth muscle (UtSM) showed that vitamin D reduces inflammation-induced cytokines, which increases the levels of contractile-associated proteins, and thus initiates PTD .[39] This idea allowed us to study the correlation between vitamin D serum level and PTD. When studying 25(OH)D, our findings showed that the mean serum 25(OH)D in PTD and term groups were 28±12 and 29±13, respectively, with P value >0.05. This indicated that 25(OH)D levels, during the 2nd trimester, had insignificant relation, with a limited role in predicting preterm labor. We suggested that other factors might be involved in the pathogenesis of PTD rather than vitamin D. Similarly,Zhou et al. (2014), Flood-Nichols et al. (2015), Rodriguez et al. (2015), and Yang et al. (2016) found no statistically significant difference in maternal vitamin D levels between the PTD and term groups .[40-42, 13] Grant (2011) reported that sufficient vitamin D levels during pregnancy might decrease the risk of PTD via diminishing placental colonization caused by bacterial vaginosis species .[43]Shakir et al. (2019) observed an association between serum vitamin D levels in pregnant women and PTD .[44] Similarly, Gernand et al. (2015) studied 2798 pregnant women with singleton pregnancies and found no associations between maternal vitamin D level and the risk of PTD .[45] Also, Tabatabaei et al. (2017) studied 2456 pregnant women with singleton pregnancies and concluded that vitamin D deficiency is associated with an insignificant higher risk of PTD .[46]

In contrast, Woo et al. (2019) found that vitamin D deficiency is associated with increased risk for PTD .[47] This was confirmed by other studies, e.g., McDonnell et al. (2017), who found that women with 25(OH)D ≥40 ng/mL had a 62% lower risk of PTD compared to those with <20 ng/mL (p<0.0001) .[48] Qin et al. (2016) did a meta-analysis on 10 studies that included 10,098 pregnant women and emphasized a marked association between maternal serum vitamin D deficiency (< 20 ng/mL) and a significantly higher risk of PTD .[49] Also, Ibrahim et al. (2019) and Fernando et al. (2020) found a significant correlation between vitamin D deficiency during pregnancy and PTD, where serum vitamin D was significantly lower in the preterm compared to the term deliveries .[3,9] This association between vitamin D deficiency and PTD, which has attracted much public health attention, is still controversial .[11] These conflicts might be due to different racial factors.

Studies reported a statistically significant difference between the mode of delivery and the uterine CL. Women with CL < 25 mm are more expected to have a vaginal delivery, while those with CL > 25 mm had a greater number of cesarean delivery. CL among patients who delivered vaginally was significantly shorter than those delivered by CS. This was in agreement with the study of Thangaraj et al. (2018), who found that CL < 30 mm (measured between 20-24 weeks of gestation) associated with PTD and favored vaginal birth whereas, CL > 40 mm associated with postdated pregnancy and increased incidence of CD .[50] Also, Thanh et al. (2019) reported that the prevalence of women with PTD delivered by CS was 31.0% and 36.7%, as reported in the WHO Global Survey and WHO Multi-country Survey, respectively .[51] This very recent study concluded that CL, among patients who delivered vaginally, was significantly shorter than those delivered by CS (P< 0.001). However, Ibrahim et al. (2019), in their study, showed that in the preterm group, a statistically significant difference was observed between vaginal and CS deliveries, where vaginal deliveries were much less. Whereas CS was more in the same group (p= 0.004) [3]. This difference might be related to their small number of participants (n= 80) in comparison to our studied participants

The main limitation of this study was the relatively small sample size. The negative findings may be influenced by such a small sample size, and it is possible that these findings would not be replicated in a larger cohort study.

CONCLUSION

For the prediction of PTD, maternal BMI could be considered a marker for the prediction. However, no associations were detected between serum 25(OH)D level and PTD. Cervical length measurement by ultrasonography could be considered an accurate, non-invasive, cheap tool for predicting the occurrence of PTD. Transabdominal and transvaginal ultrasound could be used with success, although TVUS approach was easier and avoided difficulty resulting from the thickness of the abdominal wall. Women with cut-off CL <25 mm were more liable for PTD. Cervical length assessment by TVUS, between 20-24 weeks, help to predict mode of delivery. Future studies should correlate BMI, vitamin D level, and cervical length and their significance in predicting PTD.

REFERENCES

1. Reicher L, Fouks Y, Yogev Y. Cervical Assessment for Predicting Preterm Birth-Cervical Length and Beyond. *J Clin Med*. 2021;10(4):627. Published 2021 Feb 7. doi:10.3390/jcm100406 27
2. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res ClinObstetGynaecol.* 2018 Oct;52:3-12. doi: 10.1016/j.bpobgyn.2018.04.003.
3. Ibrahim M, Rehab M, Marwa E. Association of vitamin D deficiency in pregnancy and risk of preterm labor. *Evidence Based Women s Health Journal* 2019, 9(1):383-389. DOI:10.21608/ EBWHJ.2019.28643.
4. Conde-Agudelo A, Romero R, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Erez O, Pacora P, Nicolaides KH. Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix: updated indirect comparison meta-analysis. *Am J Obstet Gynecol.* 2018 Jul;219(1):10-25. doi: 10.1016/j.ajog.2018.03.028.
5. Faucher MA, Hastings-Tolsma M, Song JJ, Willoughby DS, Bader SG. Gestational weight gain and preterm birth in obese women: a systematic review and meta-analysis. *BJOG*. 2016 Jan; 123(2):199-206. doi: 10.1111/1471-0528.13797. Erratum in: BJOG. 2016 Mar;123(4): 648.
6. Van der Ven AJ, Van Os MA, Kleinrouweler CE, de Groot CJ, Haak MC, Mol BW, Pajkrt E, Kazemier BM. Is cervical length associated with maternal characteristics.*Eur J ObstetGynecolReprod Biol*. 2015 May;188:12-6. doi: 10.1016/j.ejogrb.2015.02.032.
7. Venkatesh KK, Cantonwine DE, Zera C, Arjona M, Smith NA, Robinson JN, McElrath TF. Is There an Association between Body Mass Index and Cervical Length? Implications for Obesity and Cervical Length Management in Pregnancy. *Am J Perinatol*. 2017 May;34(6):568-75. doi: 10.1055/s-0036-1594242.
8. Torloni MR, Betrán AP, Daher S, Widmer M, Dolan SM, Menon R, Bergel E, Allen T, Merialdi M. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. *J Matern Fetal Neonatal Med.* 2009 Nov;22(11):957-70. doi: 10.3109/1476705090 3042561.
9. Fernando M, Ellery SJ, Marquina C, Lim S, Naderpoor N, Mousa A. Vitamin D-Binding Protein in Pregnancy and Reproductive Health. Review. *Nutrients*. 2020 20;12(5):1489. doi:10.3390/ nu12051 489.
10. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. *PaediatrPerinatEpidemiol*. 2012 Jul;26Suppl 1(0 1):75-90. doi: 10.1111/j.1365-3016.2012.01283.x.
11. Cyprian F, Lefkou E, Varoudi K, Girardi G. Immunomodulatory Effects of Vitamin D in Pregnancy and Beyond. Review. *Front Immunol*. 2019 Nov 22;10:2739. doi: 10.3389/fimmu. 2019.02739.
12. Thota C, Laknaur A, Farmer T, Ladson G, Al-Hendy A, Ismail N. Vitamin D regulates contractile profile in human uterine myometrial cells via NF-κB pathway. *Am J Obstet Gynecol*. 2014 Apr;210(4):347.e1-347.e10. doi: 10.1016/j.ajog.2013.11.027.
13. Yang, L., Pan, S., Zhou, Y., Wang, X., Qin, A., Huang, Y., and Sun, S. (2016). The Correlation between Serum Vitamin D Deficiency and Preterm Birth. Medical science monitor: *international medical journal of experimental and clinical research*, 22, 4401–5. https://doi.org/10.12659/ msm.898117.
14. Kashanian M, Eshraghi N, Rahimi M, Sheikhansari N, Javanmanesh F. Efficacy comparison of titrated oral solution of misoprostol and intravenous oxytocin on labor induction in women with full-term pregnancy. *J ObstetGynaecol*. 2020 Jan;40(1):20-4. doi: 10.1080/01443615.2019. 1587598.
15. Taha OT, Elprince M, Atwa KA, Elgedawy AM, Ahmed AA, Khamees RE. Antenatal cervical length measurement as a predictor of successful vaginal birth. *BMC Pregnancy Childbirth*. 2020 Mar 30;20(1):191. doi: 10.1186/s12884-020-02878-z.
16. Slager J, Lynne S. Assessment of cervical Length and the relationship between short cervix and preterm birth. *J Midwifery Womens Health*. 2012 Jul;57Suppl 1:S4-11. doi: 10.1111/j.1542-2011.2012.00209.x.
17. Di Tommaso M, Berghella V. Cervical length for the prediction and prevention of preterm birth. *Expert Rev Obstet Gynecol*. 2013;8(4):345-555. doi.org/10.1586/17474108.2013. 811932.
18. Weir CB, Jan A. BMI Classification Percentile and Cut Off Points. [Updated 2021 May 9]. In: *StatPearls*[Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541070/)
19. Enko D, Kriegshäuser G, Stolba R, Worf E, Halwachs-Baumann G. Method evaluation study of a new generation of vitamin D assays. *Biochem Med* (Zagreb). 2015 Jun 5;25(2):203-12. doi: 10.11613/BM.2015.020.
20. Liu B, Xu G, Sun Y, Du Y, Gao R, Snetselaar LG, Santillan MK, Bao W. Association between maternal pre-pregnancy obesity and preterm birth according to maternal age and race or ethnicity: a population-based study. *Lancet Diabetes Endocrinol*. 2019 Sep;7(9):707-14. doi: 10.1016/S2213-8587(19)30193-7.

21. Eick SM, Welton M, Cordero JF. Relationship between Prepregnancy Overweight, Obesity, and Preterm Birth in Puerto Rico. *Matern Child Health J*. 2019 Jul;23(7):925-33. doi: 10.1007/s 10995-018-02719-8.

22. Cnattingius S, Villamor E, Johansson S, EdstedtBonamy AK, Persson M, Wikström AK, Granath F. Maternal obesity and risk of preterm delivery. *JAMA*. 2013 Jun 12;309(22):2362-70. doi: 10.1001/jama.2013.6295.

23. McIntosh J, Feltovich H, Berghella V, Manuck T., Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, The role of routine cervical length screening in selected high- and low-risk women for preterm birth prevention. *Am J Obstet Gynecol*. 2016 Sep;215(3):B2-7. doi: 10.1016/j.ajog.2016.04.027.

24. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, Juan M, Rodríguez A, Muñoz B, Santacruz B, Bello-Muñoz JC, Llurba E, Higueras T, Cabero L, Carreras E; Pesario Cervical paraEvitarPrematuridad (PECEP) Trial Group. Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. *Lancet*. 2012 May 12;379(9828): 1800-6. doi: 10.1016/S0140-6736(12)60030-0.

25. Berghella V, Saccone G. Cervical assessment by ultrasound for preventing preterm delivery. *Cochrane Database Syst Rev*. 2019 Sep 25;9(9):CD007235. doi: 10.1002/14651858. CD007235. pub4.

26. Lamiaa M. Youssry, Doaa M. Effat, Nesreen H. Zaid. Role of calponin 1 and cervical length measurement in predicting preterm labor. *Sci J Al-Azhar Med Fac, Girls*. 2021 5(1):235-241.

27. Raval B, Sisodiya V, Yadava P, Mehta S, Patel S, Dadhania B. Measurement of cervical Length using transvaginalsonography for prediction of preterm labor. *Int J of ReprodContracepObstetGynecol*; (2020). 9(11):4471-4476. DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog202 0479 5.

28. Jafari-Dehkordi E, Adibi A, Sirus M. Reference range of the weekly uterine cervical length at 8 to 38 weeks of gestation in the center of Iran. *Adv Biomed* Res. 2015 May 29;4:115. doi: 10.4103/2277-9175.157839.

29. Kwasan S, Paisarntuntiwong R, Charoenchainont P. Cervical length measurement by transvaginalsonography in preterm pregnant women for prediction of preterm birth. *J Med Assoc Thai*. 2005 Oct;88Suppl 2:S48-55.

30. Navathe R, Saccone G, Villani M, Knapp J, Cruz Y, Boelig R, Roman A, Berghella V. Decrease in the incidence of threatened preterm labor after implementation of transvaginal ultrasound cervical length universal screening. *J Matern Fetal Neonatal Med*. 2019 Jun;32(11):1853-1858. doi: 10.1080/147670 58.2017.1421166.

31. Hernandez-Andrade E, Romero R, Ahn H, Hussein Y, Yeo L, Korzeniewski SJ, Chaiworapongsa T, Hassan SS. Transabdominal evaluation of uterine cervical length during pregnancy fails to identify a substantial number of women with a short cervix. *J Matern Fetal Neonatal Med*. 2012 Sep;25(9):1682-9. doi: 10.3109/14767058.2012.657278.

32. Friedman AM, Srinivas SK, Parry S, Elovitz MA, Wang E, Schwartz N. Can transabdominal ultrasound be used as a screening test for short cervical length.*Am J Obstet Gynecol*. 2013 Mar;208(3):190.e1-7. doi: 10.1016/j.ajog.2012.12.021.

33. Kandeel MS, Sanad ZF, Sayyed TM, ElyazidElmenawy SA. The effect of body mass index on cervical characteristics and on the length of gestation in low-risk pregnancies. *Menoufia Med J* 2014;27(3):518-523.

34. Kandil M, Sanad Z, Sayyed T, Ellakwa H. Body mass index is linked to cervical length and duration of pregnancy: An observational study in low risk pregnancy. *J ObstetGynaecol*. 2017 Jan;37(1):33-7. doi: 10.1080/01443615.2016.1205555.

35. Venkatesh KK, Manuck TA. Maternal body mass index and cervical length among women with a history of spontaneous preterm birth†. *J Matern Fetal Neonatal Med.* 2020 Mar;33(5):825-30. doi: 10.1080/14767058.2018.1505856.

36. Palatnik A, Miller ES, Son M, Kominiarek MA. Association among Maternal Obesity, Cervical Length, and Preterm Birth. *Am J Perinatol*. 2017 Apr;34(5):471-479. doi: 10.1055/s-0036-1593350.

37. Carlhäll S, Källén K, Blomberg M. Maternal body mass index and duration of labor. E*ur J ObstetGynecolReprodBiol*, (2013) 171(1): 49-53.

38. Hawzheen Q Jalal, Srwa Khalid Ismail. Is There an Association Between Body Mass Index and Cervical Length?.*Curr Res Diabetes Obes J*. 2019; 12(1):12-7. DOI:10.19080/CRDOJ.2019. 11.555829.

39. White, John H. Vitamin D signaling, infectious diseases, and regulation of innate immunity. *Infect Immun*. 2008; 76(9):3837-3843.

40. Zhou J. Su L, Liu M, Liu Y, Cao X, Wang Z, Xiao H. Associations between 25-hydroxyvitamin D levels and pregnancy outcomes: a prospective observational study in southern China. *Eur J ClinNutr*. 2014 Aug;68(8):925-30. doi: 10.1038/ejcn.2014.99.

41. Flood-Nichols SK, Tinnemore D, Huang RR, Napolitano PG, Ippolito DL. Vitamin D deficiency in early pregnancy. *PLoS One*. 2015;10(4):e0123763. Published 2015 Apr 21. doi:10.1371/ journal.pone.0123763.

42. Rodriguez A, García-Esteban R, Basterretxea M, Lertxundi A, Rodríguez-Bernal C, Iñiguez C, Rodriguez-Dehli C, Tardón A, Espada M, Sunyer J, Morales E. Associations of maternal circulating 25-hydroxyvitamin D3 concentration with pregnancy and birth outcomes. *BJOG*. 2015 Nov;122(12):1695-704. doi: 10.1111/1471-0528.13074.

43. Grant WB. Adequate vitamin D during pregnancy reduces the risk of premature birth by reducing placental colonization by bacterial vaginosis species.

mBio. 2011 Mar 29;2(2): e00022-11. doi: 10.1128/mBio.00022-11.

44. Shakir N, All-Hilli AS, Saffa AH. Early pregnancy vitamin D deficiency and risk of preterm birth. *Ann Trop Med and Public Health*; 2019. 22(4): 20-7. SPe146. DOI: 10.36295/ASRO. 2019. 22043

45. Gernand AD, Klebanoff MA, Simhan HN, Bodnar LM. Maternal vitamin D status, prolonged labor, cesarean delivery and instrumental delivery in an era with a low cesarean rate. *J Perinatol*. 2015 Jan;35(1):23-8. doi: 10.1038/jp.2014.139.

46. Tabatabaei N, Auger N, Herba CM, Wei S, Allard C, Fink GD, Fraser WD. Maternal Vitamin D Insufficiency Early in Pregnancy Is Associated with Increased Risk of Preterm Birth in Ethnic Minority Women in Canada. *J Nutr*. 2017 Jun;147(6):1145-1151. doi: 10.3945/jn.116.241216.

47. Woo J, Giurgescu C, Wagner CL. Evidence of an Association Between Vitamin D Deficiency and Preterm Birth and Preeclampsia: A Critical Review. *J Midwifery Womens Health*. 2019 Sep;64(5):613-629. doi: 10.1111/jmwh.13014.

48. McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, Baggerly LL, Ebeling MD, Rittenberg CS, Goodier CG, Mateus Niño JF, Wineland RJ, Newman RB, Hollis BW, Wagner CL. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. *PLoS One*. 2017 Jul 24;12(7): e0180483. doi: 10.1371/journal.pone.0180483.

49. Qin L-L, Lu F-G, Yang S-H, Xu H-L, Luo B-A. Does Maternal Vitamin D Deficiency Increase the Risk of Preterm Birth: A Meta-Analysis of Observational Studies. *Nutrients*. 2016; 8(5):301. doi: 10.3390/nu8050301.

50. Thangaraj JS, Habeebullah S, Samal SK, Amal SS. Mid-Pregnancy Ultrasonographic Cervical Length Measurement (A Predictor of Mode and Timing of Delivery): An Observational Study. *J Family Reprod Health*. 2018 Mar;12(1):23-6.

51. Thanh BYL, Lumbiganon P, Pattanittum P, Laopaiboon M, Vogel JP, Oladapo OT, Pileggi-Castro C, Mori R, Jayaratne K, Qureshi Z, Souza J. Mode of delivery and pregnancy outcomes in preterm birth: a secondary analysis of the WHO Global and Multi-country Surveys. *Sci Rep*. 2019 Oct 29;9(1):15556. doi: 10.1038/s41598-019-52015-w.