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Preterm Labor Predictors: Maternal Characteristics, Ultrasound Findings, Biomarker, and Artificial Intelligence

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ABSTRACT

The identification of risk factors for preterm labor is an important predictor. The risk factors for preterm labor can be maternal characteristics, namely maternal obstetric history, maternal body mass index and weight gain, multiple pregnancy, maternal infections, periodontal disease, maternal vitamin D deficiency, and lifestyle. Nowadays, various accurate diagnostic methods have been developed to diagnose preterm labor, namely ultrasound (cervical length, cervical consistency, uterocervical angle, and fetal adrenal gland) and biomarkers (IL-6 and IL-8 in cervicovaginal fluid, Placental Alpha Microglobulin-1 (PAMG-1), and Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1), Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PGF), Soluble VEGF Receptor-1 (sFlt-1), High Mobility Group Box-1 (HMGB1), and calponin. Artificial Intelligence was developed to predict preterm labor, namely in the form of ultrasound software which is capable of detecting cervical funneling processes ranging from resembling the T, Y, V, and U-shaped. This software is expected to be easily used by general practitioners and obstetricians and gynecologists, especially those who work in rural areas.

Keywords: Preterm labor, Ultrasound, Artificial intelligence

1. INTRODUCTION

Preterm labor is a labor that occurs at gestational age less than 245 days after conception or menstrual period, at or after 20 weeks gestational age and before 37 weeks (259 days) gestational age from the first day of last menstrual period.[1,2] Several etiologies of preterm labor are identified, namely multiple pregnancy, intrauterine infection, bleeding, placental infarction, premature cervical dilatation, cervical insufficiency, hydramnios, uterine fundal abnormalities, and fetal anomalies. In addition, several maternal causes include infection, autoimmune disease, and gestational hypertension.[1,2]

In 2010, there were 15 million preterm births worldwide, with a prevalence of 5-18% of live births.[3,4] In 2015, the number of preterm births in the United States was 9.62% among 3,977,745 births. Based on data from the World Health Organization (WHO) in 2018, Indonesia ranks 9th for preterm labor (15.5 per 100 live births).[3] Preterm labor is the leading cause of death among children under 5 years old, which are responsible for around 1 million deaths in 2015.[3,5] As many as 28% of neonatal deaths unrelated to malformations are caused by preterm labor.[6] Preterm infants are also more risky for short-term and long-term complications (Figure 1).

Some complications that can occur, namely neurocognitive deficits, pulmonary dysfunction namely respiratory distress and bronchopulmonary dysplasia, ophthalmological disorders and hearing impairment.[4,5,7]

Figure 1. Preterm Baby.
Cited from: Parkinson C. Kangaroo care key for premature babies. BBC News Website.

Because of the high prevalence and complications due to preterm labor in Indonesia, preventive strategies are needed through the identification of maternal risk factors and accurate diagnostic methods to predict preterm labor.[8,9] Through these steps, doctors have enough time to provide antenatal corticosteroid therapy, prophylaxis for group B Streptococcus infections, magnesium sulfate for neuroprotection and referral of patients to more capable health facilities.[3,4,8] In addition, through preventive strategies, it can reduce social and economic burdens through reducing the length of stay.[4]

Historically, preterm labor could be detected through anamnesis and physical examination namely external examinations (Figure 2a) and internal examinations where the examiner was kneeling down and the patient was standing (Figure 2b). Later on, there has been an evolution in technique that makes it easier for examinations in which the patient is lying on his back in a lithotomy position.

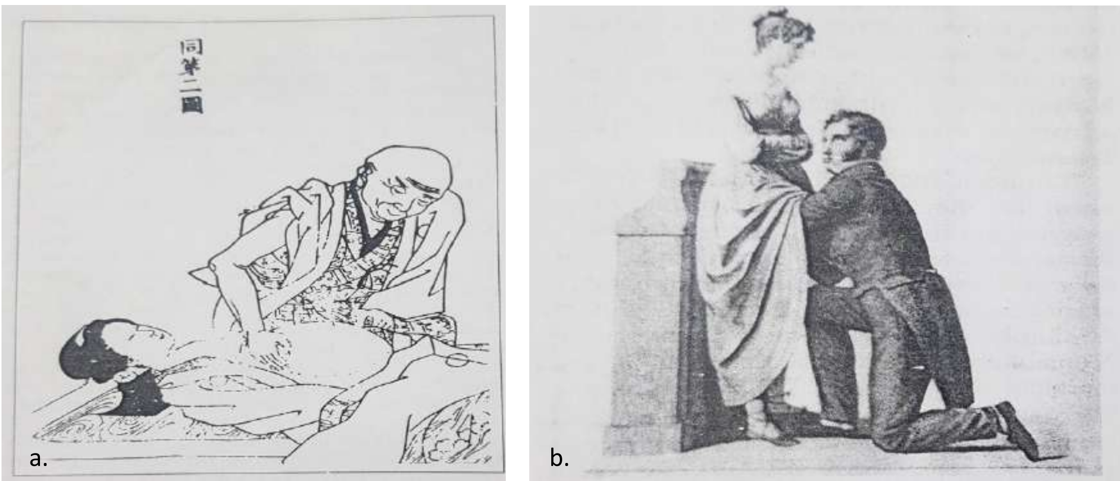

Figure 2. (a) Pieces of wood from the 18th century in Japanese textbooks based on French illustration 1668. (b) Illustration of Jacques Pierre Maygrier's Atlas - Nouvelles Demonstrations d 'Accouche-ments, Paris, Bechet (1822).

The identification of risk factors is one of the important preventive strategies. The risk factors for preterm labor can be maternal characteristics, namely maternal obstetric history, maternal body mass index and weight gain, multiple pregnancy, maternal infections, periodontal disease, and maternal vitamin D deficiency, lifestyle (smoking, drug abuse, stress, and physical violence).[5,9] Along with the times, various accurate diagnostic methods have been developed to diagnose preterm labor.[6] Several diagnostic methods through ultrasound (US) which can be used are cervical length, cervical consistency, uterocervical angle, fetal adrenal gland through transvaginal ultrasound.[9-10]

Cervical length is a good predictor of the risk of preterm labor in pregnancy. Measurement of cervical length can also be used to identify increased risk of preterm labor in asymptomatic women at < 24 weeks gestational age who have other risk factors for preterm labor (Figure 3).[9] There are various threshold of cervical length in 24 weeks gestational age which is at risk for preterm labor namely 25 mm (10th percentile), with a sensitivity of 37.3% and specificity of 92.2%, 38 mm at 23 weeks gestational age, and 35 mm at 24 weeks gestational age [9,11] A meta-analysis showed that if the cervical length can be known then the risk of preterm labor before 37 weeks gestational age will be reduced.[11] In addition, preterm labor can be measured through the Cervical Consistency Index (CCI), formulated as (AP1/AP) x 100, measuring anteroposterior cervical diameter before (AP) and after (AP1) which is a more effective method than measuring cervical length to predict preterm labor.[11]

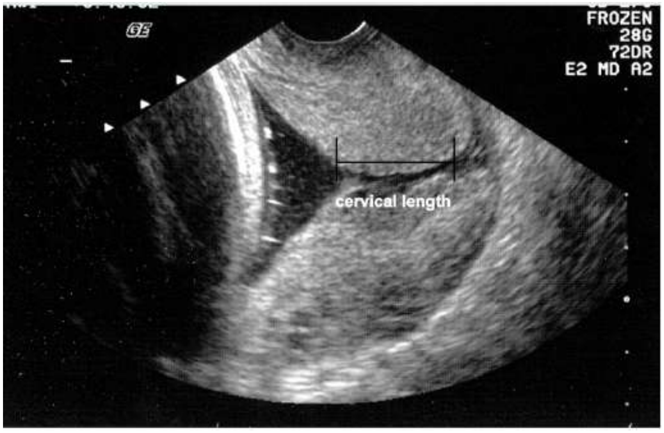

Figure 3. Measuring cervical length.

The uterocervical angle is a new ultrasound finding that is defined as a triangular segment measured between the lower uterine segment and the cervical canal. This angle is measured using a line starting from the cervical canal between the internal and external ostium and a second line that tracks the internal segment of the anterior uterine wall (3 cm from the internal ostium) (Figure 4).[12,13] Based on a research by Bafali O, et al. (2018), the intersection point of the uteroservical angle was 80.5° and has a sensitivity of 75%, selectivity of 58%, a positive predictive value of 53%, and a negative predictive value of 77%.[13] Meanwhile, the research of Eser A., et al. (2018) showed that the optimal intersection point of the anterior cervicovaginal angle was 97° and the cervical length was 27 mm.[14]

Figure 4. Transvaginal ultrasound measurements from the anterior uterocervical angle (UCA). UCA is formed by intersecting lines drawn from the internal ostium to the external ostium and parallel to the second line with the lower aspect of the anterior uterine wall, passing through the internal cervical ostium. (A) UCA> 110 degrees, CL 33 mm; (B) UCA <110 degrees, CL 32 mm.

Cited from: Knight JC, Tenbrink E, Onslow M, Patil AS. Uterocervical angle measurement improves prediction of preterm birth in twin gestation. Am J Perinatol. 2018; 35: 648-54.

Another important predictor of preterm labor is the measurement of the central zone of the fetal adrenal gland which is effective in predicting preterm labor with the same accuracy as cervical length measurement (Figure 5).[10,15] Based on research from Sage YH, et al. (2015), preterm labor was more common in women who had smaller adrenal volumes than those who did not (0.32 cm^3/kg vs 0.53 cm^3/kg, $p = 0.06$).[15] Meanwhile, the OM Turan study. et al. (2011) showed that enlargement of the fetal zone greater than 49.5% was the single best predictor for preterm labor (sensitivity = 100% and specificity = 89%).[10]

In addition to ultrasound findings, biological markers are also continuously researched and developed in order to obtain sensitive and specific markers with high accuracy enabling to predict preterm labor.[8,11] Some biological markers that have been frequently used are IL-6 and IL-8 in cervicovaginal fluid, Placental Alpha Microglobulin-1 (PAMG-1), and Insulin-Like Growth Factor Binding Protein-1 (IGFBP-1). In amniotic fluid, increased Vascular Endothelial Growth Factor (VEGF), Placental Growth Factor (PGF), and decreased Soluble VEGF Receptor-1 (sFlt-1) at 16−19 weeks gestational age can indicate angiogenesis and inflammation. Those are predictive factors for preterm labor.[11]

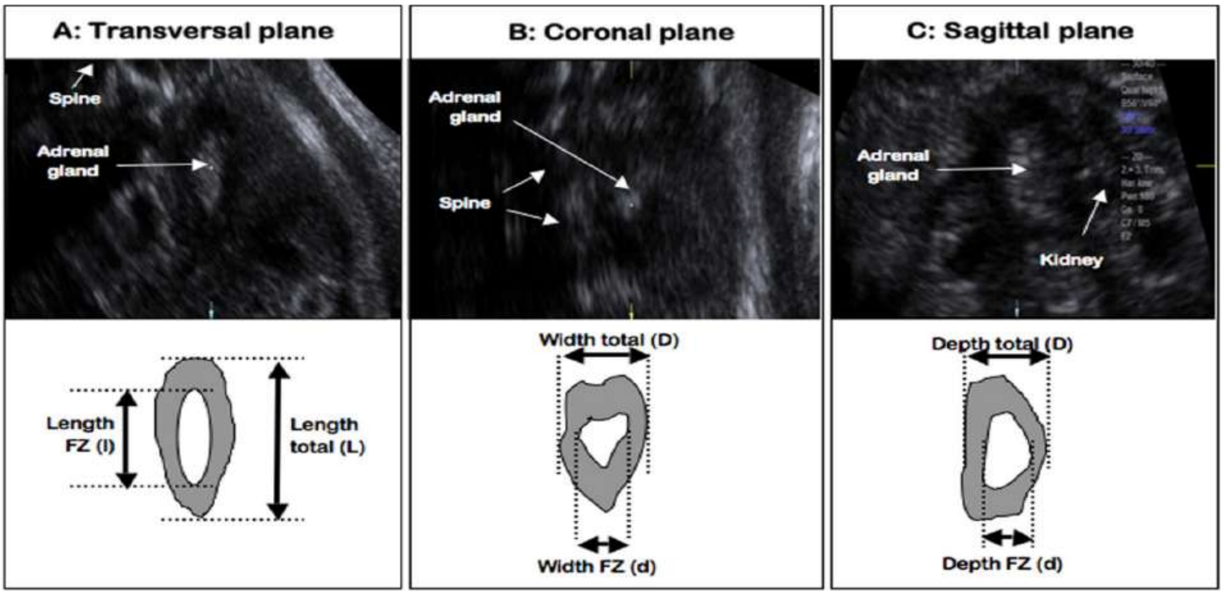

Figure 5. (A) Transversal ultrasound images. (B) Coronal, and (C) Sagittal and schematic appearance of the adrenal glands and fetal zones are shown. The adrenal glands, kidneys, and vertebrae are marked with arrows.
Cited from: Turan OM, Turan S, Funai EF, et al. Ultrasound measurement of fetal adrenal gland enlargement: an accurate predictor of preterm birth. Am J Obstet Gynecol 2011;204:311.e1-10.

Fetal Fibronectin (fFN) is one of the important tests to detect preterm labor.[16] It is found in amniotic fluid, placental tissue, cervicovaginal secretions, and extra-cellular basal decidua components adjacent to the placental intervillous space.[16,17] Fetal fibronectin level of 50 ng/mL is positive in 22 until 36 weeks gestational age and level less than 50 ng/mL is negative.[16,17] The latest systematic review showed that the sensitivity of the fFN qualitative test is probably highest to predict preterm labor within 7−10 days of test.[16] Based on reports from the International Federation of Gynecology and Obstetrics (FIGO, 2019), the fFN threshold of 10 ng/mL has a high sensitivity and negative predictive value to determine women who will undergo preterm labor.[16]

Another marker is Placental Alpha Microglobulin-1 (PAMG-1) which is a protein produced from decidual cells and found in high concentrations in amniotic fluid during pregnancy.[6,8,18] Its concentration in the amniotic fluid is greater 1000 times than that found in normal vaginal fluid or maternal blood.[8] Research by Lee et al. regarding PAMG-1 for ROM detection noted that in 20 of 23 cases where PAMG-1 was positive and the standard clinical assessments (ie, nitrazine, fern test and pooling) were negative, the patient eventually experienced a rupture of membrane.[6] Later, for all preterm patients in this group who showed signs and symptoms of labor, labor would occurr within 7 days.[6] Based on a report from FIGO (2019), PAMG-1 had the highest effectiveness in determining women at risk of preterm labor.[16]

Based on research from Cekmez Y. et al. (2017), in predicting primary outcomes (delivery within 7 days), the sensitivity of PAMG-1 and fFN were 73.3−80% and 50−73.6%, respectively and the specificity of PAMG-1 and fFN was 92.9−95% and 72−94.3%. The positive predictive value of PAMG-1 and fFN was 71−76% and 29−82.3%. Meanwhile, the negative predictive value of PAMG-1 and fFN was 92.9−98% and 87−90.9%.[4,6,8] Detection of PAMG-1 in cervical secretions can predict preterm labor within 7 days and detection of fFN is also successful for this.[6,8]

Meanwhile, there are 2 other markers that are important enough to predict preterm labor, namely calponin and High Mobility Group Box-1 (HMGB-1). Research by Perlitz Y. et al. (2014) showed that if calponin levels increased in patients who were in labor, they suspected that HMGB-1 was a marker of possible preterm labor. Their hypothesis was that calponin could be excreted from the uterine smooth muscle that contracted into maternal serum, as a result of damage to uterine smooth muscle fibers during active labor. This was based on observing an increase in CPK (creatine phosphokinase) levels as a result of striated muscle damage during heavy physical activity.[19,20] Based on the research of Taema MI et al. (2018), the optimal cutoff point for calponin is ≥ 2.4 ng/mL (sensitivity 78.90%, specificity 71.10%, positive predictive value 71.80%, and negative predictive value 78.30%).[21]

Other biological markers can be a series of intracellular proteins that can be associated with damage (also known as alarmin) which are released as a result of the host response towards microbial pathogens. One of these alarms is High Mobility Group Box-1 (HMGB1) in amniotic fluid, characterized as an important endogenous mediator of cellular injury in the regulation of inflammation (chorioamnionitis) caused by preterm labor.[22–26] Study by Baumbusch MA., et. al. (2016) showed that HMGB1 was increased in patients with intraamniotic infections which play a role in causing preterm labor.[24]

Meanwhile, the development of artificial intelligence (AI) can also help develop methods to diagnose preterm labor. Technology modifies the environment and the environment then produces further opportunities and new obstacles for the technology. In the end, the goal of artificial intelligence will be achieved, because it already exists in the human brain. However, a federation of 'narrow' and 'targeted' machine learning systems are able to deal with core information processing problems throughout the health system by increasing the ability of decision makers, and thereby setting new standards of effectiveness and efficiency in clinical operations and management of a disease. This is a significant opportunity for health system transformation because the costs of increasing decision-making capacity throughout the health system are unlikely to be high. There is no other approach that offers potential impacts without an equivalent cost scale.[27]

One of the most common benefits of AI in health care is computer-aided diagnosis (CAD) which has been widely studied in many fields including prostate, breast, and cardiac imaging.[28-30] Many AI applications are used to develop and implement protocols, thereby shortening imaging time, optimizing staffs, and reducing costs.[31] Computer-aided diagnosis has also become a tool in helping doctors make decisions about patient care.[32] It has even been studied to identify placenta accreta spectrum disorder and cervical length, cervical funneling, and sludge to predict preterm labor in patients with short cervix.[33-34] For an obstetricians and gynaecologists (OB/GYN), ultrasound is routinely used everywhere for almost every reproductive age women in this modern world. Thus, OB/GYN play an important role in using and developing AI through ultrasound.

One of the AIs needs to be developed is ultrasound software which is able to detect cervical funneling processes, starting from the T, Y, V, and U-shaped (Figure 6). The author hopes to create effective and efficient software so that it can be easily used by general practitioners and OB/GYN, especially those who work in rural areas. In this case, doctors are responsible for identifying the right landmarks in the chosen field, and after being asked, the machine will label and measure the desired biometry. If it is true, this can save time. Conversely, if the image quality is poor, due to fetal position or maternal obesity for example, mistakes can occur. One study compared 100 manual biometry measurements with 100 automatic measurements and showed a time savings approximately 20 seconds and seven steps for each 20 minutes anatomical survey.[35]

Thus, it is expected that the rate of preterm labor detection can be increased and immediate management such as cervical cerclage can be carried out immediately by an OB/GYN. In addition, they can immediately refer preterm labor cases which must be referred immediately. The expected output is the decrease of preterm labor prevalence and complications.

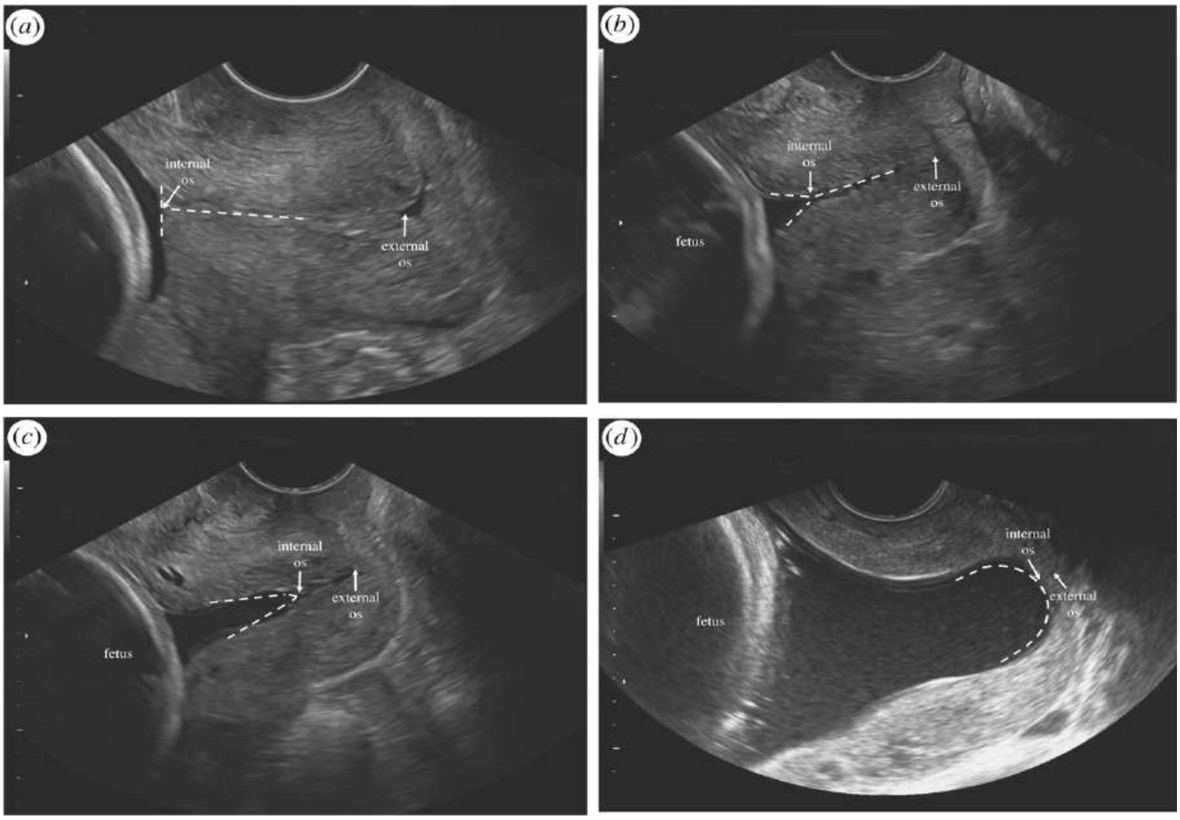

Figure 6. Cervical funnelling, (a) T-shaped, (b) Y-shaped, (c) V-shaped, and (d) U-shaped. Cited from: Feltovich H. Labour and delivery: A clinician's perspective on a biomechanics problem. Interface Focus. 2019;9: 1-7.

As explained above, there are various risk factors, ultrasound findings, biomarkers of preterm labor, and artificial intelligence software. To improve the accuracy of preterm labor predictors and prevent morbidity and mortality in both mother and fetus, research about preterm labor predictors is needed including maternal characteristics, ultrasound findings, and biomarkers. We hope that they could increase our knowledge, especially regarding biomedical science.

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