Chapter

New Technologies to Dating Pregnancy at Birth

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Abstract

The chapter provides a vision of new methods of pregnancy dating at birth to overcome the high costs of existing approaches or lack of access to the existing technologies. The authors have presented a literature review on recent scientific reports exploring novel technologies, such as those based on the newborn's skin maturity assessment as machine learning models based on clinical data. The effortlessness of new approaches based on simplified clinical systems contrasting with molecular genetics and newborns screening analytes is discussed, even in scientific validation. Without the intention of an exhaustive or systematic review, we searched databases for reports concerning postnatal gestational age, prediction or estimate, novel approach, low and medium-income countries since 2015. Therefore, the authors did not compromise to offer a comprehensive picture of all postnatal gestational age methods. On the other hand, prematurity identification at birth remains a challenge in many birth settings, mainly in a scenario with scarce resources. Although postnatal pregnancy dating methods have strengths and disadvantages, this information is critical to recognize the risk of the newborn during the first hours of life, justifying technological investments.

Keywords: gestational age, infant, premature, skin physiological phenomena, artificial intelligence, equipment, and supplies

1. Introduction

The estimate of antenatal age faces the lacking of certainty of the day in the female cycle on which conception occurred and the dependence of early prenatal care access with crown-rump-length ultrasound measure [1]. While maternal-child worldwide policies do not provide a broad spectrum of technological options to obtain a reliable gestational age, the last menstrual period (LMP) remains the most extensive reference for pregnancy dating in many low and medium-income countries [2, 3]. However, a reliable last menstrual period (LMP) depends on sure of dates, regular cycles, absence of bleeding, or use of hormonal contraceptives in the last months before the date. In such a scenario, uncertainties related to memory bias, irregular menstrual cycles, breastfeeding, or failure of contraceptives have deprived many pregnant women and their babies of trustable gestational age [4]. The consequences

are not restricted to antenatal care since prematurity identification at birth remains a challenge for neonatal care. Most of the preterm birth occurs in settings with limited resources to achieve a trustworthy chronology of gestation and, at the same time, neonatal due care. Preterm births and their complications are the leading cause of death of children under 5 years [5]. Most preterm births occur in the late preterm period, making decision-making difficult about what interventions and levels of assistance are needed [6]. Thus, gestational age is critical information to make timely decisions and provide appropriate neonatal support.

1.1 Disclosure agreement

The chapter provides a vision of new methods of pregnancy dating at birth to overcome the high costs of existing approaches or lack of access to the existing technologies, presenting recent scientific reports without an exhaustive or systematic review of the literature. We searched databases for reports concerning postnatal gestational age, prediction or estimate, novel approach, low and medium-income countries since 2015. Therefore, the authors did not compromise to offer a comprehensive picture of all postnatal gestational age methods. The authors have been working on solutions for gestational age prediction for scenarios with low resources and a scarcity of health facilities.

2. Technologies based on the newborn skin maturity

The skin barrier, formed during gestation, is essential for neonatal survival. It is not by coincidence that this essential protection exists since the limit of the viability of preterm infants means around 24 weeks [7]. However, the competence of the skin barrier against the loss of body heat and water ad infections depends on a process of maturity along the time. The analysis of the newborn's skin has shown a potential relation of the structure of this tissue with the chronology of gestation, reflecting the temporal process of skin maturation [8]. Part of the due care delivered to preterm newborns is a skin immaturity compensation as an incubator or a radiant warmer and environment humidity. It is not news that there are critical clinical connections between the competence of the skin barrier with the neonatal survival [9].

Markers of pregnancy dating from the newborn's skin are available by invasive and noninvasive technicians.

2.1 Invasive assessment: Histology

Microscopic images analysis is the basis of invasive approaches. The measurement of skin thickness is an important parameter that indirectly reflects the state of neonatal maturity and how prepared the newborn will be in the period of adaptation to the external environment [10]. Structural patterns that are strongly related to fetal age are easy to recognize as potential markers of skin maturation [10]. Structural patterns are strongly related to fetal age, are easy to recognize as potential markers of skin maturation [10]. **Figure 1** shows the skin of stillbirths from biopsies over the plantar surface of the sole at different gestational ages. The epidermis is the outermost layer, organized by stratified pavement epithelial tissue sublayers, which is keratinized in its external bound. Fetal epidermal thickness presents a clinical significance for the diagnosis of fetal prematurity [11, 12]. However, using measures with imaging software support, the

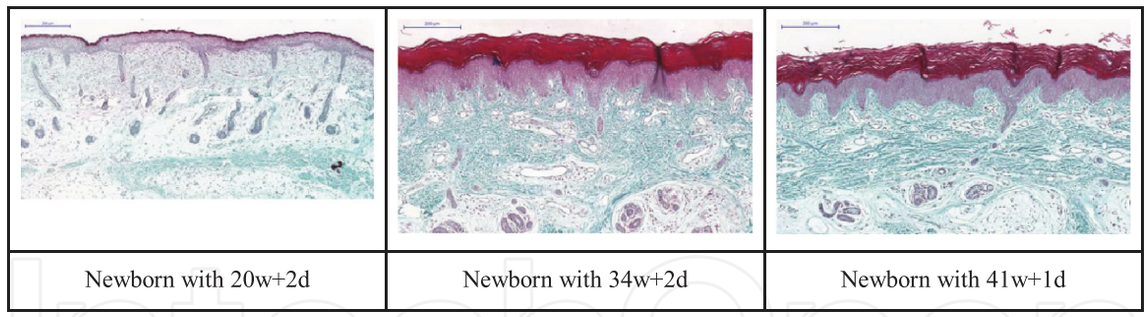

Figure 1.
Histological images of the skin over the sole of the foot. Note: Gomori trichrome staining, scale: 200 μm. Source: The authors.

composite formed by the thickness of the epidermis, dermis, and the area of sebaceous glands achieved an excellent correlation with gestational age ($r = 0.99$, $p < 0.001$) in dead concepts ranging from 20.3 to 41.6 weeks of gestation [11]. Meantime, the histological study of this tissue met limitations due to its invasive acquisition of materials from a human being for ethical issues [13]. Despite this, invasive postmortem studies can provide a basis for noninvasive approaches for alive newborns, at the same time provide information to support necropsies.

2.2 Noninvasive assessment of skin

Noninvasive assessment of skin maturity to predict gestational age is possible just as an overview impression or analyzing medical images. Moreover, a new technology reported gestational age correlation with optical properties of the newborn skin at birth [14]. An ongoing multicentric study has been conducted to validate this technology based on this proof of concept [15].

The skin characteristics have been used in several clinical scores for decades. Visible modifications during clinical ectoscopy of newborns have demonstrated that the skin of extremely premature has little or no visible pigmentation, being markedly erythematous, putting these and other characteristics of the skin as potential markers of the chronology of pregnancy, as provided by maturity scores [16, 17]. External characteristics of the newborn involving edema and skin opacity, lanugo, ear form, and firmness are antecedents in assessing gestational age at birth [18]. Besides, the composite anthropometric measurements, external characteristics, neurological tests, postnatal examination of epiphyseal center, and ulnar nerve motor conduction velocity are described, with 95% of the infants correctly estimated within ±3 weeks [19].

The melanin index is an optical skin parameter related to the melanin content in the tissue, accessible with bio-optical models [20], even in newborns [21]. The quantification of changes in skin reflection according to pigment distribution and concentration has been associated with gestational age, by using the melanin index [22] and the skin reflection by spectrophotometry [23]. Noninvasive approaches grounded on optics have the potential for characterization of the skin maturity, in addition to or in replacement of biopsy analysis. The advantages over histological techniques are keeping the original tissue morphology and providing *in vivo* tissue analysis, in real time.

An innovative multiband photometer was developed to assess gestational age at birth analyzing the skin transparency (**Figure 2**). This reflective test automatically processes the light, scattered by the skin against the device, when a small optoelectronic light emitter/receiver sensor touches the newborn's skin. A feasibility

Figure 2.
The application of the multiband photometer for predict gestational age prediction in simulated newborn-doll application. Source: The authors.

study provided a mathematical model to predict gestational age based on the skin reflectance adjusted to clinical variables (R2 = 0.828, $p < 0.001$) [14]. A multicenter clinical trial evaluated the accuracy of this technology to detect preterm newborns, adding machine learning models to adjust birth weight and antenatal corticosteroid therapy for fetal maturation. For prematurity discrimination, the area under the receiver operating characteristic curve (AUROC) was 0.986 (95% CI: 0.977 to 0.994). Considering 7 days of error range, this device correctly detected 98.7% of gestational ages, preprint report of the author [10.21203/rs.3.rs-1,216,628/v2]. A new ongoing study to evaluate the device's ability to detect prematurity or small for gestational age, or both conditions simultaneously and predict short-term pulmonary complications in a cohort of low-birth-weight newborns has been conducted [24].

Another opportunity is assessing the skin of a newborn with dermatologic ultrasound equipment. The morphology of the skin can be observed *in vivo* with high-frequency ultrasonography. The microstructure of human skin is visualized in three layers and the skin thickness has a high correlation with that verified in histology from skin biopsies in adults ($r = 0.96$, $p < 0.0001$) [25]. Regarding the newborn's skin, Petersen et al. associated prematurity with the dermal and subcutaneous fat thickness obtained by ultrasonography on the plantar surface with the skinfold measure to support the nutritional evaluation in the neonatal period, analyzing echograms [26]. Vitral et al. analyzed 436 images of the skin in 222 newborns and reported a relationship between gestational age at birth to neonatal skin layer thickness obtained by ultrasound. Epidermal skin thickness on the forearm correlated with the gestational length, in the natural logarithm function ($r = 0.610$, $p < 0.001$). This parameter was not influenced by the standard of fetal growth as intrauterine growth restriction [27]. **Figure 3** shows three high-frequency ultrasonography images of the skin over the forearm of newborns of different gestational ages. A detailed protocol of the skin assessment with high-frequency ultrasound is available at dx.doi.org/10.17504/protocols.io.nfgdbjw.

Dermatologic ultrasound devices with high-frequency probe are portable and more economically accessible than conventional ultrasound. However, they are specific to skin evaluation and demand training [28].

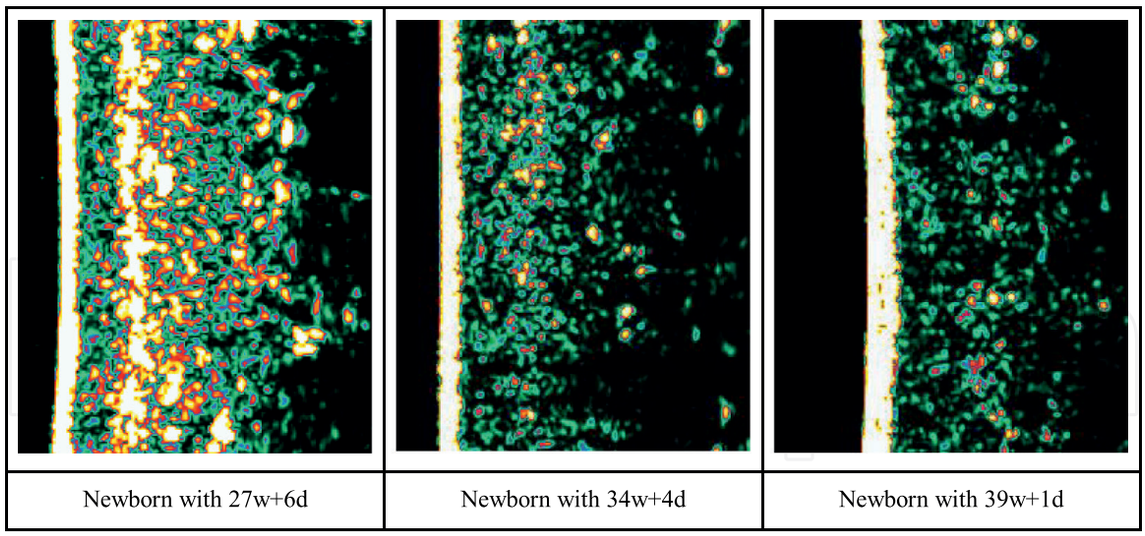

Figure 3.
High-frequency ultrasonography image of the skin over the forearm. Note: Epidermis corresponds to the white layer at the left side, resolution: 356- × 276-pixel. Source: The authors.

3. New approaches based on clinical characteristics

Novel methods based on clinical features for establishing an infant's gestational age have emerged that may be able to overcome some of the existing limitations.

3.1 The foot length

Measuring the postnatal foot length of the newborn is an alternative method for preterm newborn discrimination. Such an approach requires minimal training, is fast, and requires minimal handling. In addition, it causes wisp distress to premature infants or ill infants. Therefore, health professionals can use it with different levels of skills, making it applicable for a low-resource setting [29]. Using a plastic ruler, tape, or paper footprint, the accuracy of this measure for preterm newborns discrimination reached 76.9% sensitivity and 53.9% specificity [30]. The high inter-and intra-observer agreement is an advantage of this approach [31].

Furthermore, to underground this method, the foot length is an alternative for gestational age estimation during intrauterine life. It matters when other existent markers are unreliable, such as when the fetal is hydrocephalus, anencephaly, or limb dysplasia [31]. However, the strong correlation of fetal foot length with the chronology of gestational age, correlation coefficient $r = 0.960$, ($p < 0.001$), became from narrow results by small samples [32]. Limitations for this method are the influence of fetal growth, as foot measurements incorporate bone and soft tissue. Soft tissue stores of subcutaneous fat are decreased in small for gestational age infants and may be increased in large for gestational age infants, interfering with the accuracy of the test [31].

A recent study compared clinical examinations for gestational dating with a mask to the ultrasound-based gestational age at birth. Different approaches for pregnancy dating at birth are LMP, New Ballard (NBS), foot length, anterior lens assessments and anthropometric measures (including BW and birth length and mid-upper arm, abdominal and head circumferences measures at the time of assessment), and an

End-of-Bed gestational age assessment based on a brief nonstructured examination. Unfortunately, none of the methods studied could confidently predict the gestational age of individual babies within 1 week [33].

3.2 Simplified clinical score methods

End-of-Bed gestational age assessment itself concerns a simplified clinical score for newborn maturity. The development and tests were conducted in South Africa. Such non-structure evaluation presented lower bias in inter-observer agreement. However, it presented 2 weeks difference compared to reference early ultrasound [33].

Another approach based on clinical assessment is score methods, such as simplified gestational age score (SGAS). It was developed by using the most predictive items from the 12-item from NBS, 21-item Dubowitz score (DWS), and 11-item Meharban Singh (MS) and validated against the best obstetrics estimate in low-birth-weight newborns in India. The NBS, DWS, and MS were reduced to four, five, and six items, respectively, and all of them reduced total scores were not significantly different from the total score's estimate of gestational ($p > 0.05$). Such promising results and ease-to-use approach conducted to an adaptation to a mobile application, the T-SGAS, include a simple score associated with simple technology, using an app with combinations of references standards [34].

A cross-sectional validation study evaluated the accuracy of the mobile version of T-SGAS to ascertain postnatal gestational age within 24 hours of birth. A total of 8591 live singleton births whose gestational age by LMP and ultrasound was within 1 week of each other were enrolled. T-SGAS consisted of photographs that were the best fit for each score of the following four items: newborn's posture (score 0 to +4), skin (score − 1 to +5), breast (score − 1 to +4), and genitals (score − 1 to +4). The mobile app then auto-calculated the total score and classified the newborn's gestational age category. Such test showed strong inter-observer agreement (concordance correlation coefficient 0.77 (95% CI 0.76–0.78) and Fleiss' kappa was 0.76 (95% CI 0.76–0.78). ROC curves showed that the predictive accuracy of T-SGAS varied between 74% (LMP or USG) to 79% (LMP and USG). The simplicity of use by nurse-midwives has pointed it to be a helpful tool in resource-limited settings [34].

However, clinical maturity scores have presented lower values for small for gestational age infants and underestimated gestational age considering physical characteristics. Neurological evaluation is less affected by intrauterine growth and nutrition. Besides, they can be affected by infectious, metabolic, and other clinical conditions [35].

3.3 Cerebral maturity

Under visual or spectral analysis, the maturational electroencephalography (EEG) patterns of the newborn are associated with low development scores in small-for-gestational-age and low-birth-weight. This approach can reveal the delayed brain function development and not necessarily the gestational age [36].

4. Learning models for gestational age prediction at birth

Computer science has advanced detecting patterns by processing datasets through layered mathematical models, fostering skills and competencies of professionals to

support the best healthcare decisions [37]. Machine learning models brought opportunities for data science to improve prediction models for pregnancy dating. Keeping the attention on postnatal gestational age estimative, a sort of reports associated variables to discriminate better preterm from term newborns.

A multicountry prospective study developed machine learning models to predict postnatal gestational age, gathering anthropometry, neuromuscular/physical signs, and feeding maturity variables. The most precise algorithm included infant sex, five anthropometric measurements, three physical and one neurological sign, and LMP, correctly classifying 91% of infants as preterm or term [38].

Another report on machine learning models relied on a set of options, including birth weight, LMP, and NBS, to estimate gestational age as a continuous outcome. The advantage is using variables accessible to health workers in resource-limited settings at the time of delivery, even without medical records. The correct classification of predictive models combining variables varied from 83.6% to 94.0% concerning NBS with LMP composite in parts or totally [39].

5. Newborn screening analytes to predict gestational age

Newborn screening programs are available worldwide with broad coverage, even using different protocols. Metabolic screening profiles have the potential for preventing severe health problems of newborns detecting different conditions at birth [40]. However, the newborn bloodspot screening commonly used to identify inborn errors of metabolism or other inherited disorders offers new opportunities to provide accurate estimates of gestational age [41].

There is considerable potential value in using metabolic markers to measure gestational age after birth. The newborn fetal/adult hemoglobin ratio provides gestational age estimative. Wilson et al., 2017 proposed a model for postnatal gestational age estimation utilizing newborn hemoglobin levels and metabolic analyte data derived from newborn blood spot samples. Models, including birth weight, hemoglobin, TSH, and 17-OHP levels, accurately estimated gestational age to ±2 weeks in 95·3% of the cohort and discriminated ≤34 versus >34 (c-statistic, 0·98) [42]. While models utilizing a full panel of newborn screening analytes accurately estimate gestational age, hemoglobin-based models are promising in discriminating ≥34 versus <34 weeks' gestational age, even where full mass spectrometry screening is not accessible [42].

Metabolites markers mirror metabolic processes during the first hour of life. There are many opportunities to assess newborn maturity using screening programs samples. The retrospective evaluation of the newborn screening dataset with infants from the different maternal origins in Ontario revealed distinct performance for gestational age prediction based on screening algorithm. It means that refining by development can predict gestational age better, and validation is necessary across the ethnicities [43]. Database from Iowa Newborn Screening Program considered 88 metabolites, and the models predicted gestational age within 1 week for 78% of neonates, with an area under the curve of 0.899 (95% confidence interval 0.895–0.903) in differentiating that born preterm (<37 weeks] from term (≥37 weeks) [44].

The advantages of this approach are drawn blood samples with minimum invasive for the newborn maturity evaluation, using cord blood and heel prick samples at birth. A predictive model including clinical data (infant sex, multiple births (yes/no), birth weight), screening analytes, and pairwise interactions had high accuracy in

discriminating preterm from term newborns: AUROC 0.945 (95% CI 0.890, 0.999) for heel prick profiles and AUC 0.894 (95% CI 0.853, 0.935) for cord blood profiles [45].

Data from Newborn Screening Ontario (NSO) allowed for developing an algorithm capable of accurately estimating gestational age. Model performance was evaluated across multiple birth categories, such as ≥37, between 33 and 36, between 28 and 32, ≤27 weeks' gestation, ≤34, and < 37 weeks' gestational age. The algorithms estimated gestational age to be within 1.07 weeks of ultrasound-validated gestational age overall and correctly estimated gestational age to within 2 weeks for 94% of the infants. The validity in different ethnic populations showed outstanding performance although some variation in accuracy of gestational age estimation, 1.05 weeks among nonimmigrant mothers and 0.98 to 1.15 weeks among immigrant mothers. Moreover, aiming at low-income settings, the model was refined to facilitate its implementation where technological and resource requirements could be an issue. The ratio of fetal-to-adult Hb combined with clinical factors, such as sex and birth weight demonstrated better estimated gestational age than clinical covariates alone [46].

6. Molecular genetics in gestational age estimation

Gene expression has the potential to predict age-associated physiological changes. DNA methylation (DNAm) is associated with chronological age over long time scales and plays an essential role in development and growth. The mechanisms that drive changes in the aging methylome are not well understood; however, the quantitative measurements of methylome states may identify factors involved with slowed or accelerated aging rates [47].

DNAm of neonatal cord blood and blood spot samples has proven to accurately estimate gestational age at birth, from 24 to 44 weeks of gestation. The median absolute difference between DNAm gestational age and estimated clinical gestational age was 1.24 weeks, and the correlation coefficient was r = 0.99. It is a convenient molecular marker in that both exams are routinely performed to monitor neonatal health. Although DNAm demonstrated a remarkable correlation to estimated clinical gestational age, concerns whether gestational age acceleration is truly a measure of maturity versus a reflection of the relative accuracy of DNAm gestational age remains. Accurate classification systems that reflect both developmental time and maturity may improve the ability to predict neonatal risk [48].

Concerning studies of DNAm association to birth weight and chronological age, using cord blood, methylation at 224 CpG sites was found to be associated with gestational age and 23 CpG sites with birth weight [49]. There was a strong positive association between birth weight and development and a negative relationship between methylation and development in 12 of the 14 phenotypes. Of the 14 associations, eight involved methylations at cg15783941 (NFIX), and five were found in two CpG sites in the LTA gene [49].

7. Final considerations

The length of pregnancy has been estimated worldwide with the gestational age calculation at birth, using different available technologies. In childbirth settings, health professionals need gestational age assessment to make timely decisions to deliver newborn care and obtain vital statistics for public policies planning. Indeed, gestational

age is a covariate in many studies and systems of the newborn's classification. All current methods have strengths and weaknesses, challenging recent technological advancements [49]. Prematurity identification remains a challenge in many birth settings, mainly in a scenario with scarce resources. There are promising novel approaches in different stages of development to provide a more easily obtainable and reliable gestational age. Developing new approaches under the vision of low-cost technologies are required to achieve birth settings in low and medium-income countries where pregnancy dating is more frequently unknown or absent.

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Conflict of interest

Authors declare two patents deposit on behalf of the Universidade Federal de Minas Gerais and Fundação de Amparo a Pesquisa de Minas Gerais, Brazil, http://www.fapemig.br/en/, nonprofit institutions. The first author, ZSNR is one of the inventors for both BR1020170235688, and BR1020200215736.

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