Maternal Blood Biomarkers of Placentation to Predict Low-Birth-Weight Newborns: A Meta-Analysis

Eita Goto, MD, MPH

Department of Medicine and Public Health, Nagoya Medical Science Research Institute, Nagoya, Japan

Abstract

Objective: The development of methods for pre-delivery prediction of low-birth-weight newborns would be clinically advantageous because low birth weight contributes to a high infant mortality rate. This study was performed to examine whether maternal blood biomarkers of placentation can be used to predict low-birth-weight newborns.

Methods: Ten databases, including PubMed/Medline, were searched. Any English language study that provided all of the true- and false-positive and true- and false-negative results of this prediction was included in the analysis. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies. Bivariate diagnostic meta-analysis was performed to construct hierarchical summary receiver operating characteristic curves.

Results: Based on relatively good quality studies, alpha fetoprotein (AFP), human chorionic gonadotropin (hCG), and pregnancy-associated plasma protein A (PAPP-A) ($n = 73$, 19, and 7, respectively) showed low sensitivity and specificity and low diagnostic odds ratio. The informational usability was categorized as "no exclusion or confirmation" (i.e., positive likelihood ratio <10 and negative likelihood ratio >0.1). The diagnostic accuracy of AFP and hCG or PAPP-A was categorized as low (i.e., $0.5 \leq$ area under the curve ≤ 0.7) or could not be categorized (i.e., area under the curve <0.5).

Conclusion: There is no evidence that maternal blood levels of AFP, hCG, or PAPP-A used as a single predictor are useful to predict low-birth-weight newborns.

Résumé

Objectif : L'élaboration de méthodes permettant de prédire, avant l'accouchement, qu'un bébé aura un poids insuffisant à la naissance présenterait des avantages cliniques, car un poids insuffisant est associé à un taux élevé de mortalité infantile. Cette étude avait pour but d'évaluer si l'analyse de biomarqueurs de placentation dans le sang maternel pouvait être utilisée à cette fin.

Méthodologie : Dix bases de données ont été interrogées, dont PubMed/Medline. Nous avons retenu les études de langue anglaise mentionnant tous les taux de vrais et de faux positifs ainsi que de vrais et de faux négatifs associés à ces prédictions. La qualité des études a été évaluée au moyen de la Quality Assessment of Diagnostic Accuracy Studies. Une méta-analyse bivariée des diagnostics a été réalisée pour établir des courbes ROC sommatives hiérarchiques (HSROC).

Résultats : Selon des études de relativement bonne qualité, l'alpha-fœtoprotéine (AFP), la gonadotrophine chorionique humaine (hCG) et la protéine plasmatique placentaire A (PAPP-A) ($n = 73$, 19 et 7, respectivement) auraient une sensibilité, une spécificité et un rapport de cote de diagnostic faibles. L'utilité des données étudiées se trouvait dans la catégorie « pas d'exclusion, ni de confirmation » (c.-à-d. un rapport de vraisemblance positif <10 et un rapport de vraisemblance négatif $>0,1$). La précision diagnostique de l'AFP et de la hCG ou de la PAPP-A était basse ($0,5 \leq$ aire sous la courbe $\leq 0,7$) ou ne pouvait être classée (aire sous la courbe $<0,5$).

Conclusion : Rien n'indique que les taux d'AFP, de hCG ou de la PAPP-A présents dans le sang maternel sont utiles pour prédire, à eux seuls, un poids insuffisant à la naissance.

J Obstet Gynaecol Can 2017;■(■):1–10

https://doi.org/10.1016/j.jogc.2017.03.099

Key Words: Biomarkers, low birth weight, meta-analysis, newborn, pregnancy, sensitivity, specificity

Corresponding Author: Dr. Eita Goto, Department of Medicine and Public Health, Nagoya Medical Science Research Institute, Nagoya, Japan. egoto1@nifty.com

Competing interests: None declared.

Received on December 23, 2016

Accepted on March 8, 2017

INTRODUCTION

Low birth weight (i.e., <2500 g), which includes preterm neonates, SGA, and a combination of both,[1] has been shown to contribute to high rates of infant mortality and morbidity, poor growth in childhood, and increased incidences of adult diseases in later life.[2] SGA is also a mix of being constitutionally small due to genetic traits and intrauterine growth retardation. Therefore, the etiology of low birth weight is complex. The risk factors for low birth weight include poor nutritional status; low weight gain during pregnancy; multiple pregnancies; fetal anomalies; anemia; placental problems, such as placenta previa and abruptio placentae; incompetent cervix; infection;

preeclampsia; progesterone deficiency; smoking; and alcohol and other substance abuse.[3] These multiple origins are believed to necessitate preventive interventions in selected women (e.g., progesterone therapy for women at risk of preterm delivery, antiplatelet agents before 16 weeks of gestation for women at risk of preeclampsia, and balanced protein−energy supplementation).[1] Nevertheless, early access to prenatal care for all women, especially those who deliver low-birth-weight newborns regardless of the origin, is critical to improve health outcomes in infancy, childhood, and across the whole life[1,2] and probably most importantly to reduce infant deaths as the largest cause of deaths in the first year of life, which has been reported to be perinatal death (e.g., infection).[4] Newborn chest or arm circumference has been shown to be useful in identifying low-birth-weight newborns in developing countries,[5] but it is clinically more advantageous to predict low-birth-weight newborns prior to pregnancy. However, maternal anthropometric measurements, symphysis-fundal height, and ultrasonography have not been shown to be useful for predicting low birth weight in developing or developed countries.[6−8] On the other hand, maternal blood biomarkers of placentation, such as those used in Down syndrome screening (i.e., alpha fetoprotein, beta human chorionic gonadotropin, pregnancy-associated plasma protein A, unconjugated estriol, and inhibin-A), may be useful for this purpose.

For this study, bivariate diagnostic meta-analysis was performed and hierarchical summary receiver operating characteristic curves were constructed[9] to evaluate whether maternal blood biomarkers of placentation are useful for the prediction of low-birth-weight newborns.

MATERIAL AND METHODS

Primary Outcomes and Inclusion Criteria

The primary outcomes of this study were as follows: sensitivity and specificity, positive and negative likelihood ratios, and DOR for predicting low-birth-weight newborns using maternal blood biomarkers of placentation. Low birth weight was defined as birth weight <2500 g. Any English language study that provided all of the true- and false-positive and true- and false-negative results of this prediction was included. Studies were included if all of the missing results could be calculated from other data. The objectives of the included studies were not limited to evaluation of this prediction.

Search Strategies, Study Selection, and Data Extraction

The PubMed/Medline database was searched using the terms described in the Online Supplementary Methods (September 21, 2016). There was no limitation regarding publication date. Articles that were determined to be unrelated by scanning the titles and abstracts and by retrieving the full texts were excluded. Those remaining were potentially eligible articles. The PubMed Related Citations, shown by clicking "See all…" on the right side of the PubMed screens displaying potentially eligible articles, and the bibliographic references of potentially eligible articles were also investigated. The following nine other databases were searched: CINAHL; PsycINFO; Wiley Online Library; ProQuest Central (e.g., ProQuest Health and Medical Complete and ProQuest Nursing & Allied Health Source); ProQuest Dissertations & Theses Global; the entire Cochrane Library (e.g., CENTRAL); Web of Science; Google Scholar; and Sage Publications Online. The articles in which studies did not provide all of the true- and false-positive and true- and false-negative results and review articles that did not provide primary data were excluded. The remaining articles were finally eligible for the analysis. Duplicated data were integrated. This process was periodically repeated.

Study Quality Assessment

Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies, a tool designed to assess study quality of diagnostic meta-analysis, which consists of 14 question items.[10] After five assessments, the most frequent responses were considered to be the most appropriate responses. For statistical analysis, a value of "1" was assigned to a "yes" response to each question item, whereas a value of "0" was assigned to a "no" or "unclear" response. The QUADAS score (0−14) was defined as the total number of "yes" responses for each study.

Statistical Analysis

Outlier detection was performed by model checking using (1) the spike plot of Cook's distance for each study and (2) the scatter plot of the standardized residuals of healthy (x axis) and diseased (y axis) populations for each

ABBREVIATIONS

AFP	alpha fetoprotein
AUC	area under the curve
DOR	diagnostic odds ratio
GA	gestational age
hCG	human chorionic gonadotropin
HSROC	hierarchical summary receiver operating characteristic
LR	likelihood ratio
PAPP-A	pregnancy-associated plasma protein A
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
SG	small-for-gestational-age