Characterizing and Forecasting Individual Weight Changes in Term Neonates

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Objectives To develop a mathematical, semimechanistic model characterizing physiological weight changes in term neonates, identify and quantify key maternal and neonatal factors influencing weight changes, and provide an online tool to forecast individual weight changes during the first week of life.

Study design Longitudinal weight data from 1335 healthy term neonates exclusively breastfed up to 1 week of life were available. A semimechanistic model was developed to characterize weight changes applying nonlinear mixed-effects modeling. Covariate testing was performed by applying a standard stepwise forward selection-backward deletion approach. The developed model was externally evaluated on 300 additional neonates collected in the same center.

Results Weight changes during first week of life were described as a function of a changing net balance between time-dependent rates of weight gain and weight loss. Males had higher birth weights (WT0) than females. Gestational age had a positive effect on WT0 and weight gain rate, whereas mother's age had a positive effect on WT0 and a negative effect on weight gain rate. The developed model showed good predictive performance when externally validated (bias = 0.011%, precision = 0.52%) and was able to accurately forecast individual weight changes up to 1 week with only 3 initial weight measurements (bias = −0.74%, precision = 1.54%).

Conclusions This semimechanistic model characterizes weight changes in healthy breastfed neonates during first week of life. We provide a user-friendly online tool allowing caregivers to forecast and monitor individual weight changes. We plan to validate this model with data from other centers and expand it with data from preterm neonates. *(J Pediatr 2016;173:101-7)*.

As part of normal physiology, newborns lose body fluid and fat during the first days of life.[1] Once food intake outweighs the initial loss of fluid and fat, the nadir of weight loss is achieved and weight gain follows.[2,3] Multiple maternal and neonatal factors influence weight changes during the first week of life. In a subgroup of newborns, an imbalance of fluid and fat loss and weight gain results in an excessive weight loss, usually defined as ≥10% of birth weight, which increases the risk for serious clinical complications such as exaggerated jaundice and hypernatremia.[4,5] In past years, hospital stays of mother-infant dyads shortened significantly, resulting in an increase of newborn readmissions mainly because of jaundice, dehydration, and feeding difficulties.[6,7] Therefore the American Academy of Pediatrics announced recently that a shortened hospital stay of less than 48 hours after delivery for healthy term newborns may be accommodated but that it is not appropriate for every mother and newborn.[8]

To identify newborns at increased risk for excessive weight loss, a first-day weight loss ≥5% was identified as a warning sign,[9,10] and weight loss charts were established for breastfed newborns.[11-13] To account for important confounders, such charts were published for newborns delivered vaginally and for those born by cesarean delivery.[12] However, the impact of other possible confounders such as sex remains unclear.[11,14-16] Weight loss charts are a good first step to guide caregivers and may set the frame for further research identifying the percent weight loss at which intervention (eg, formula feeding) should be initiated to prevent clinical complications,[17] but they do not allow for individual forecasting of weight changes in neonates.

IIV	Interindividual variability	$Kout_{PNA}$	Shape of time-Kout positive relationship
Kin	Time-dependent rate of weight gain	MAE	Mean absolute prediction error
Kin_{Base}	Basal rate of weight gain	MPE	Mean prediction error
Kin_{PNA}	Shape of the time-dependent weight gain curve	PNA	Postnatal age
Kout	Time-dependent rate constant of weight loss	T50	Time at which Kout is equal to 50% of $Kout_{max}$
$Kout_{max}$	Maximum rate of weight loss constant	TLag	Delay before the start of the weight gain
$Kout_{Base}$	Basal increase of Kout	VPC	Visual predictive check
		WT0	Birth weight

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Individual prediction can be obtained with the use of pharmacometrics, an emerging science of developing and applying mathematical and statistical methods for characterizing, understanding, and predicting pharmacokinetics of medicines, biomarkers, and clinical responses over time.[18,19] Introduced by Sheiner et al[20] in the 1970s, the population approach, or nonlinear mixed-effects modeling, is based on a simultaneous analysis of all data from a study population while taking into account that different observations are derived from different individuals. Such analyses permit us to estimate average population parameters, characterize intersubject and intrasubject variability, and identify and quantify key factors that influence parameters and their variability.

To overcome the main limitations of weight loss charts, this study performed a multimodal approach targeting the following goals: (1) to develop a semimechanistic model that characterizes physiological weight loss and weight gain during the first week of life in healthy term neonates exclusively breastfed; (2) to identify and quantify effects of maternal and neonatal factors on weight changes; (3) to forecast individual weight changes during the first week of life; and (4) to provide a user-friendly online monitoring tool to support pediatricians, neonatologists, midwifes, and other caregivers.

Methods

A retrospective, single-center study of prospectively recorded maternal and neonatal data from healthy term newborns exclusively breastfed was performed at the University Hospital of Basel and approved by the local ethics committee (EKZN 2015-050). Two complete birth years (2009 and 2010) including 4128 term neonates were screened. To describe natural weight changes, newborns were excluded if they received any formula feeding at any time during individual study participation and if they were transferred to a neonatal ward. For mathematical modeling purpose, neonates without initial weight loss and with only 1 observation were excluded. Finally, only singleton neonates were included. A total of 300 additional healthy term newborns exclusively breastfed (external dataset) were collected in the same center from an additional birth year (2011) for external evaluation of the developed model.

A semimechanistic model, defined as a compartmental model with minimal physiological components, was built to describe longitudinal weight data from neonates during their first week of life. Physiological weight changes during the first week of life were described with a turnover model, characterizing weight change as a function of a changing net balance between rates of weight gain (input rate) and weight loss (output rate) (**Figure 1**).[21] If the input rate is greater than the output rate, the net balance is positive and body weight increases. On the other hand, if the input rate is smaller than the output rate, body weight decreases. As input and output rates change over time, they were described with time-dependent mathematical functions.

Previous studies showed that the rate of weight gain (input rate) increases 2 days after vaginal delivery, whereas it increases 3 days after cesarean delivery.[2,3] As a result of initial loss of fluid and fat, the rate of weight loss (output rate) is maximal at birth and decreases during the first 2-3 days of life before increasing with increasing input rate. To define structural components of the semimechanistic model, different time-dependent mathematical functions were tested for the rates of weight gain and weight loss: linear, exponential, saturable Emax (sigmoid functions plateauing at maximum weight gain or weight loss rates), and different combinations of these functions (plots illustrating evaluated mathematical functions in **Figure 2**; available at www.jpeds.com).

To estimate population average parameters and their intersubject and intrasubject variability, a population analysis was performed using a nonlinear mixed-effects modeling approach, analyzing data from all individuals simultaneously (**Appendix 1**; available at www.jpeds.com).[20] Once structural and statistical components of the model were developed, maternal and neonatal characteristics, called covariates in modeling analysis, were tested applying a standard stepwise forward selection-backward deletion approach. The goal of such tests was to identify covariate effects that explain (at least in part) intersubject variability of model parameters.

Evaluation of the final model was performed by applying rigorous statistical criteria and methods. First, prespecified criteria such as maximization of the likelihood, precision of parameter estimation (relative SEs), and classical goodness-of-fit plots, such as predicted vs observed weight changes were used to evaluate models.[22] Second, the model's predictive performance was tested using the visual predictive check (VPC) method.[22,23] To obtain VPC, 100 simulations of the data were performed with parameters estimates from the final model. Simulated 10th, median, and 90th percentiles and their 95% CIs were compared with observed values. Third, the final model was applied to predict individual weight changes in neonates of the external dataset (ie, data not used in the model development process). Classical goodness-of-fit plots and VPC were generated based on this external dataset. Further, the predictive performance of the final model was numerically externally evaluated by calculating mean prediction error (MPE) to assess prediction bias and mean absolute prediction error (MAE) to estimate prediction accuracy (**Appendix 2**; available at www.jpeds.com).

From the external dataset, the 3 initial weight observations (birth weight and 2 additional time points) for each neonate were retained. The final model and its parameter estimates were applied to these data to forecast individual weight changes up to 1 week of life. The maximum a posteriori Bayesian method was used (**Appendix 1**) to predict