**Personalized Prediction of Weight Changes and Effect of Formula Milk in Neonates**

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**Background & Objectives**

- In newborns, **physiological weight loss** during the first days of life is followed by weight gain.
- **Excessive weight loss** (>8%) should be avoided as it increases morbidity whereas too early intervention complicates breastfeeding.
- **Model published** in the Journal of Pediatrics, describing physiological weight changes, is limited to healthy term neonates exclusively breastfed.

**Objectives of this work were to:**

- Expand the existing model in different neonatal populations: late preterm and term neonates, neonates who are exclusively breastfed, exclusively formula fed or breastfed and supplemented with formula milk +/- pumped breast milk;
- Describe effects of formula milk feeding on neonatal weight changes during the first week of life;
- Identify and quantify maternal and neonatal factors influencing weight changes;
- Early forecast individual weight changes and effects of formula milk up to 1 week of life.

**Methods**

- **Data:**
  - Longitudinal weight data from 3638 neonates up to 1 week of life
  - Heterogeneous population of newborns: term, late preterm, exclusively breastfed, exclusively formula fed, breastfed with additional formula milk with or without pumped breast milk
  - Key neonatal and maternal characteristics:

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (min - max) / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3400 [1980 - 5580]</td>
</tr>
<tr>
<td>Gestational age (GA) (weeks)</td>
<td>39.9 [34.4 - 42.4]</td>
</tr>
<tr>
<td>Gender</td>
<td>Female / Male</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>Cesarean section / vaginal delivery</td>
</tr>
<tr>
<td>Parity</td>
<td>1st child / 2+ children</td>
</tr>
<tr>
<td>Mother’s age (years)</td>
<td>32 [15 - 51]</td>
</tr>
</tbody>
</table>

- Random data-splitting: N=2425 neonates for model expansion; N=1213 neonates for advanced evaluation

- Model expansion:
  - Expansion of the existing model by adding an effect of supplemental feeding: K-PD model, direct/indirect dose effect on additional weight gain using different mathematical functions, such as linear and Emax
  - Non-linear mixed effect modeling using Nonmem 7.3

**Results**

**Model:**

Physiological weight change is a function of the net balance between weight gain rate $K_{in}(t)$ and weight loss rate constant $K_{out}(t)$:

$$\frac{d\text{Weight}}{dt} = K_{in}(t) + K_{in, Add,FM} \times \text{Dose FM} + K_{in, Add, PM} \times \text{Dose PM} - K_{out}(t) \times \text{Weight}(t)$$

- **$K_{in}(t)$:**
  - starts to increase 2 days after vaginal delivery and 3 days after cesarean section ($T_{lag}$)
  - 2 components: $K_{in base}$ independent of time; $K_{in, PNA}$ dependent on postnatal age (PNA)
- **$K_{out}(t)$:**
  - decreases with decreasing magnitude of fluid loss
- **Supplemental feeding:**
  - Additional weight gain ($K_{in, Add, FM}$) dependent on dose of supplemental formula milk ($\text{Dose FM}$)
  - Additional weight gain ($K_{in, Add, PM}$) dependent on dose of pumped breast milk ($\text{Dose PM}$)

**Covariates:**

Simulations (median, 10th and 90th percentiles) of postnatal weight changes:

- **Best case scenario:**
  - Term: GA=42 weeks
  - Male
  - Exclusively breastfed
  - Vaginally delivered
  - Mother’s age: 25 years
  - Parity: 2 children

- **Worst case scenario:**
  - Pre-term: GA=34 weeks
  - Female
  - Breastfed with supplemental formula and pumped breast milk
  - Elective cesarean section
  - Mother's age: 45 years
  - Parity: 1st child

**Clinical Application:**

- Early forecast of individual weight changes up to 1 week, based on:
  - Individual weight observations up to 3 days of life
  - Final model
  - Covariates: GA, gender, delivery mode, type of feeding, mother's age, parity

**Model Evaluation:**

Visual Predictive Check

- Simulated CI (95%) of the 10th and 90th percentiles
- Simulated CI (95%) of the median
- Observed percentiles (10th and 90th) and median

The model was also validated on the 1213 neonates not used for model expansion.

**Forecasted values** were with acceptable precision and without bias:

- MPE (Mean Percentage Error) = 0.15 %
- RMSE (Root Mean Squared Error) = 61.7 g
- MAPE (Mean Absolute Percentage Error) = 1.43 %

**Conclusion**

- First model that describes weight changes and effects of formula and pumped breast milk feeding during the first week of life in late preterm and term neonates
- **Next steps:** (i) to develop a user-friendly online tool to support caregivers on decision making including the use of supplemental feeding, and further personalize and optimize care of neonates; (ii) to expand the model in sick and very preterm neonates.