

A Novel Approach to Predict Glomerular Filtration Rate from Pre-birth to Geriatrics

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PURPOSE

Glomerular filtration rate (GFR) is an important marker of renal function. Published models estimate GFR based on the clearance of endogenous (creatinine) or exogenous (e.g. mannitol, iohexol, inulin) compounds. Amongst these substrates, inulin clearance is the gold standard measure of GFR as transporter mediated active secretion may confound other markers. The current inulin-based models of GFR focus on clearance in older children or they combine inulin data with other probes.

The aim of the current study is to develop an ontogeny function for GFR maturation, using inulin clearance following intravenous (iv) infusion, to determine age-related changes from pre-birth to geriatrics. In order to distinguish the GFR changes associated with post-menstrual age (PMA) from those of postnatal age (PNA), we have utilised gestational age at birth (GA_B) and PNA as the covariates in the model. This may have clinical application in defining the appropriate dose for renally excreted drugs administered to infants with the same PMA but different PNA, and vice versa.

METHOD(S)

Individual clearance values of iv inulin were collected from the literature covering the whole age range from premature neonates to geriatrics. Where individual values were not available, bootstrapping was carried out to generate individual values based on the reported mean and standard deviation for the number of subjects in that study. Bootstrapping was carried out on inulin clearance values, age and where necessary body weight and height (if units of GFR were ml/min/1.73m²) to calculate body surface area. A variety of models were assessed in Phoenix 7.0.0.2535 to obtain the best-fit to the clinical data. An ontogeny model consisting of two age-related parameters, PNA and GA_B , was selected as the best-fit model for GFR values relative to mean adult inulin clearance. Performance of the new GFR model was validated using gentamicin and vancomycin clearance data sets.

RESULT(S)

The ontogeny model shows an increase in relative GFR from birth to 1 day old full-term and pre-term neonates indicating the pattern of GFR development pre-birth. During neonatal life GFR increased as a function of both GA_B and PNA taking into account the impact of birth and reached half of adulthood activity at about 2 years. GFR declined in the elderly from about 63 years as a function of age (Figure 1). More than 80% of predicted vancomycin clearance (CL) and all of predicted gentamicin CL were within two-folds of the observed data in all age groups (Figure 2). The difference in GFR between preterm and full-term neonates seems to be less than 10% from about 52 weeks of postmenstrual age (PMA), regardless of GA_B (Figure 3).

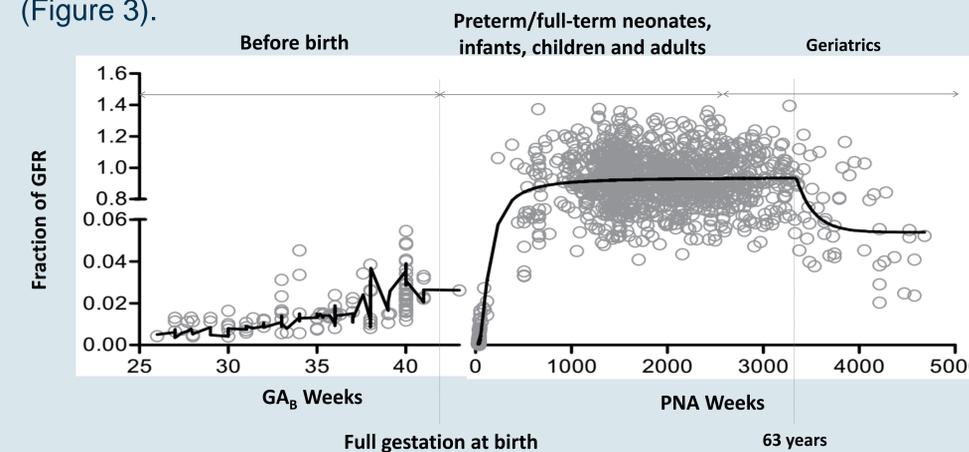


Figure 1. Fraction of GFR values as the ratio of GFR at each age relative to mean adult reference value (circles). The best-fit models to the observed ratios are presented by the solid line.

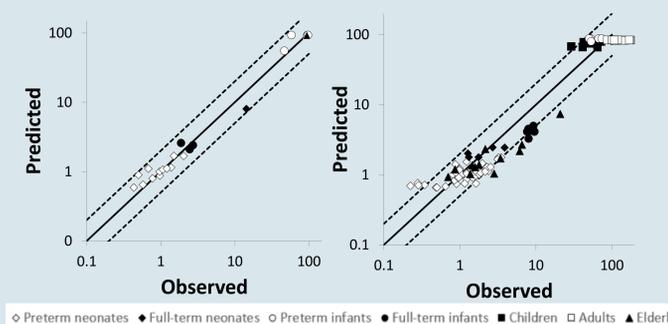


Figure 2. Predicted and observed clearance values for vancomycin (right) and gentamicin (left).

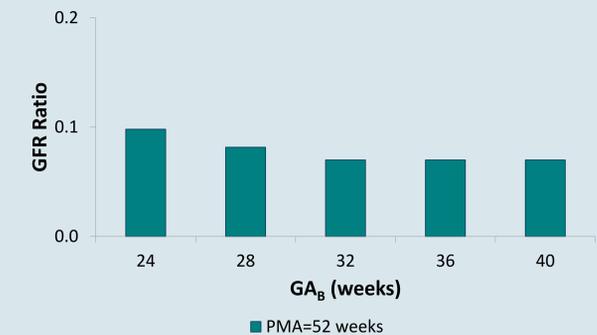


Figure 3. Neonatal GFR relative to adults for subjects at 52 PMA weeks but born at different GA_B weeks.

CONCLUSION(S)

When implementing GFR in preterm PBPK models, it is important to consider both PNA and GA_B , separately and not just PMA alone.

The model is capable of differentiating between preterm and full-term neonates at certain PMA that are born at different GA_B .

This model can determine the age at which the difference in GFR between preterm and full-term neonates diminishes.

GFR increases *in utero* from 27 weeks of pregnancy until birth.

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