HEALTHY BIRTH, GROWTH & DEVELOPMENT

Mechanistic Maternal-Fetal Growth Energy Budget Model

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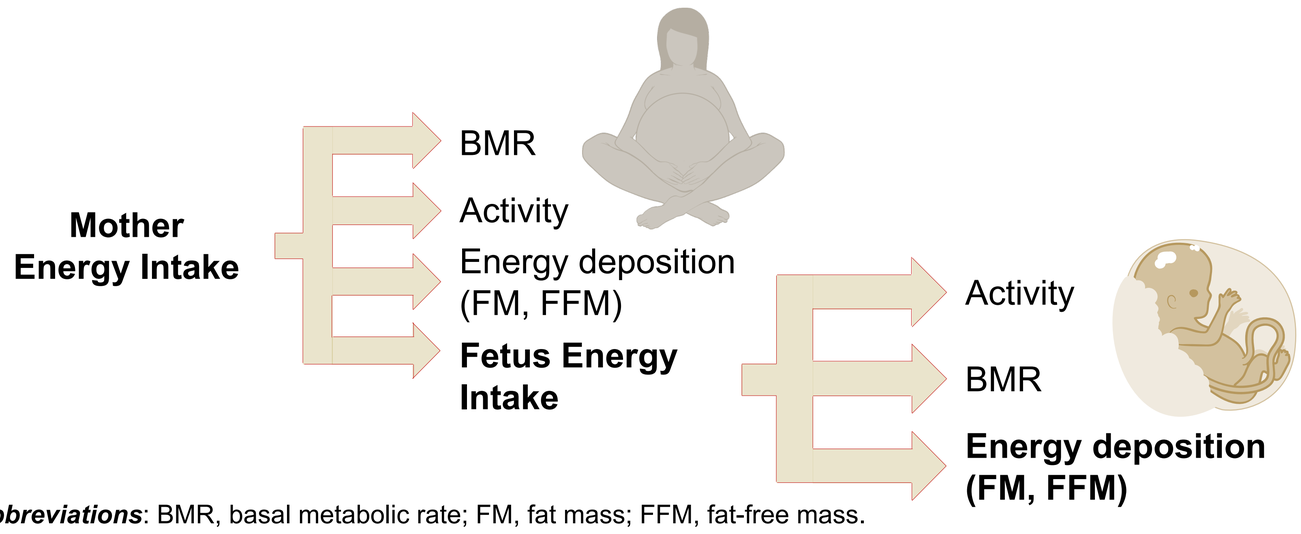
Objectives

The objectives of this study were:

- To develop a growth model of fetal weight based on fetal energy expenditure within a population approach modeling framework.
- To quantify required uniform flow of nutrients to the fetus and mammary glands.
- To quantify the effect of nutrient flow on maternal energy metabolism.



Abbreviations: BMR, basal metabolic rate; FM, fat mass; FFM, fat-free mass.

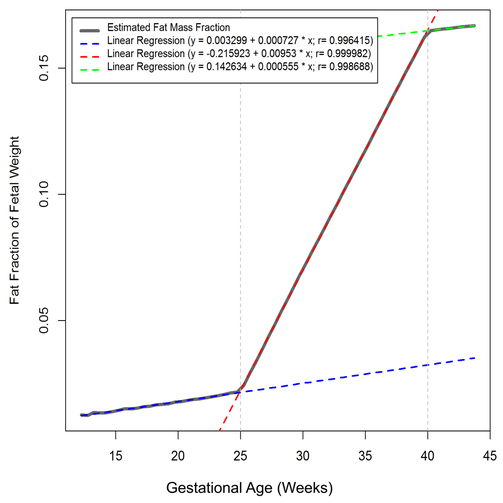


Figure 1. Literature-based estimates[3-9] and piecewise equation predictions of fat mass fraction as a function of gestational age

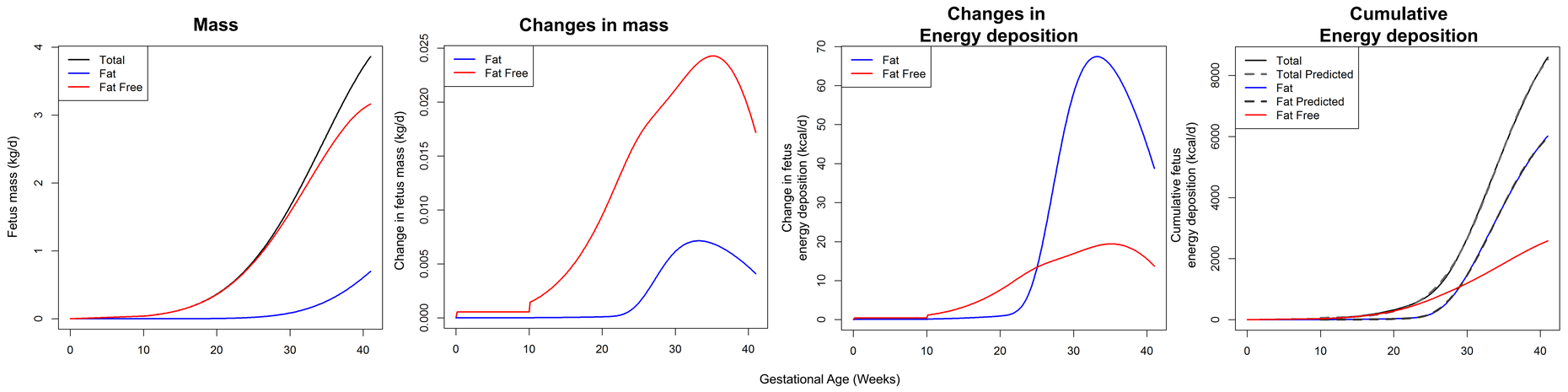
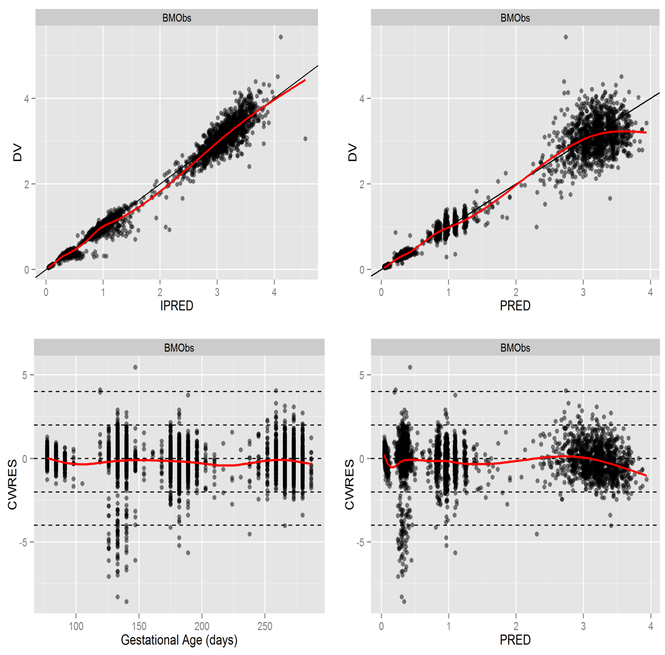


Figure 2. Derivation of energy deposition vs gestational age curve in a reference fetus and predictions of cumulative energy deposition in fat and total



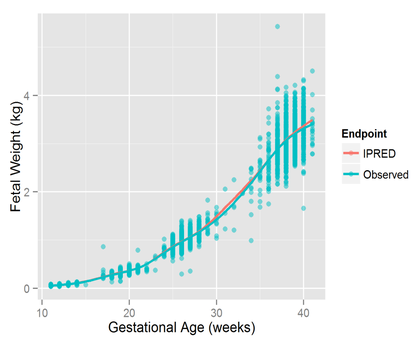


Figure 3. Goodness of fit of the population model for fetal growth in 1161 subjects from the GUSTO Study

Abbreviations: CWRES, conditional weighted residual; DV, Observation; IPRED, individual prediction; PRED, population prediction.

Methods

- Daily energy deposition in a reference fetus was estimated by back-calculating the necessary calories based on a published reference fetal mass growth equation.[1]
- Published energy densities of fat mass (FM) and fat-free mass (FFM) changes[2] and calculated FM and FFM based on published data[3-9] were used as energy sinks.
- Exponential, power, polynomial and Gompertz models were fitted to the cumulative energy deposition-gestational age (GA) curve and fraction of cumulative energy deposition in fat (FMnrgF).
- The literature-based reference energy deposition curve was tested externally against ultrasound-based fetal and birth-weight data from 1161 subjects[10] using a nonlinear mixed effects model estimating between-subject variability (BSV) on relevant parameters (FOCE-ELS engine in Phoenix NLME, v1.3, Certara, Princeton, NJ).
- Maternal daily energy intake was estimated based on age, weight, and height.[2]
- Fetus sex and maternal daily energy intake were a priori included in the model as covariates.

Phoenix Modeling language code

```
deriv(A1 = a*b*MAXNRG * exp(a*exp(b*t)+b*t))
# Fetus energy deposition
NRGdepot = A1 # Fetus energy deposition

FMnrg = NRGdepot*FMnrgF # Energy deposited
in fat mass
FFMnrg = NRGdepot*FFMnrgF # Energy
deposited in fat free mass

deltaFM = deltaFMnrg/(rhodeltaF*1000) #
Change in fat mass in kg
deltaFFM = deltaFFMnrg/(rhodeltaL*1000) #
Change in fat Free mass in kg

# Fetus mass in kg
BM = (FM+FFM)

error(BMEps = 0.104074)
observe(BMObs = BM*(1+
BMEps),doafter={prevNRGdepot=NRGdepot;
prevFMnrg=FMnrg;prevFFMnrg=FFMnrg})

FMnrgF = 1.2820611*exp(-9.3140914*exp(-
3.8176080*FMF^0.2796103)))
a = tva*exp(dasex1*(SEXCD==1))*
    (EEkcal/2192)^daEI*
    (daperiod1*(period==1)+(period==2)+(period
    ==3))*exp(na))
b = tvb*exp(dbsex1*(SEXCD==1))
     *(EEkcal/2192)^dbEI*
     (dbperiod1*(period==1)+(period==2)+(period
     ==3))*exp(nb))
MAXNRG =
    tvMAXNRG*exp(dMAXNRGsex1*(SEXCD==
    1)) * (EEkcal/2192)^dMAXNRGEI*
    (dMAXNRGperiod1*(period==1)+(period==2)
    +(period==3)))

ranef(diag(na,nb)=c(0.0036669433,0.003478854
3))

#### Time events ####

# prepare periods of fetal growth
double(period,i,deltaNRGdepot,deltaFMnrg,delta
FFMnrg,integNRGdepot,prevNRGdepot,prevFM
nrg,prevFFMnrg,prevFM,prevFFM,FM,FFM)

sequence{
while(i <288){ # number of days

sleep(0.00001)
integNRGdepot=NRGdepot
deltaNRGdepot=NRGdepot
deltaFMnrg=FMnrg
deltaFFMnrg=FFMnrg
deltaFMnrg=FMnrg
deltaFFMnrg=FFMnrg

sleep(0.99999)
deltaNRGdepot = NRGdepot-prevNRGdepot
integNRGdepot =
prevNRGdepot+deltaNRGdepot
deltaFMnrg=FMnrg-prevFMnrg
deltaFFMnrg=FFMnrg-prevFFMnrg
FM = prevFM+deltaFM
FFM = prevFFM+deltaFFM
i=i+1}}
```

Results

- The piecewise equation for FM fraction consisted of 3 linear regressions for 0 to ≤ 25, 25 to ≤ 40, and > 40 wk GA. (Eq. 1 and Fig. 1)
- Gompertz equations obtained the best fitting performance for both cumulative energy deposition and FMnrgF. (Eq. 2 and 3 and Fig. 2)
- The energy-mass model predicted well the reference fetal weight-GA curve.
- The population model included BSV (< 20%) on 2 parameters of the Gompertz model for cumulated energy deposition. (Table 1)
- The predicted individual fetal growth curve fitted well the trajectory of the observed fetal weight up to birth. (Fig. 3)

Eq.1 FM Fraction = 0.003299 + 0.000727 × GA (d) if GA ≤ 25 wk
-0.215923 + 0.00953 × GA (d) if 25 < GA ≤ 40 wk
0.142634 + 0.000555 × GA (d) if GA > 40 wk

Eq.2 Cumulative Energy deposition (kcal) = *MAXNRG* × exp(*a* × exp(*b* × GA(d))))
where *MAXNRG* = 145165.3 if GA ≤ 25 wk, 35755 otherwise
a = -10.8 if GA ≤ 25 wk, -16.3 otherwise
b = -5.05 if GA ≤ 25 wk, -9.51 x 10^{-3} otherwise

Eq.3 FMnrgF = 1.28 × exp(-9.31 × exp(-3.82 × FM Fraction$^{0.280}$)))

Table 1. Typical Values of Fitted Parameter in Population Model for Fetus Growth

Description	Parameter	Estimate
Effect of mother energy intake on *a* (Eq 2)	daEI	-0.110
Effect of mother energy intake on *b* (Eq 2)	dbEI	-0.169
Effect of mother energy intake on *MAXNRG* (Eq 2)	dMAXNRGEI	0.219
Effect of fetus sex on *a* (Eq 2)	dasex1	-0.0375
Effect of fetus sex on *b* (Eq 2)	dbsex1	-0.0268
Effect of fetus sex on *MAXNRG* (Eq 2)	dMAXNRGsex1	-0.0354
Multiplicative residual error	stdev0	0.105
BSV on *a* (Eq 2) (Variance)	na	0.00325
BSV on *b* (Eq 2) (Variance)	nb	0.00307

Conclusions

- Reverse engineering based on a closed model assumption of fetal caloric intake may predict fetal and birth weights.
- This effort constitutes a first step in quantifying the flow of nutrients from mother to fetus.

Acknowledgment

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References

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