Placental Analytics, LLC

Project: Reconstructing placental shape and surface vasculature for analyses of pregnancy stress
Our goal is the development and operationalization of improved methods of placental measurement that will allow better understanding of how newborn, childhood and potentially adult diseases have their genesis in gestational stress.
Where we work
Collaborators

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► Michael Yampolsky, PhD and Alex Shlakter, PhD (U of Toronto, Toronto CA)
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The Placenta in History
Neat and clean
How fragile is human pregnancy?

► (At least half of all conceptions do not survive to the next menstrual period).
  ▪ Overwhelming majority “wrong chromosome number ‘accidents’.”

► Of those that have a heart beat at 6 weeks gestation, 30-40% die by 14 weeks.

► By 14 weeks, the risk of death is 5-10%.

► After 28 weeks, the risk of death is 1-3%.

► By being born, you won the lottery!
Once born, do we each “play the same hand”?

- There are many factors that influence our post-birth “life course”.
  - Money, class, parent education, climate, nutrition etc
- But at birth, are we dealt the “same cards” biologically?
Intrauterine life and

► Placental function
  - Lung (all $O_2$)
  - GI tract (all nutrients)
  - Major site of cardiovascular resistance (50% of each fetal heart beat)
  - Endocrine
  - Excretory

► Risk in
  - Fetal/perinatal morbidity/mortality
  - Neonatal morbidity/mortality
  - Childhood morbidity/mortality
  - Lifelong health risks
“Fetal origins” of diseases and developmental injury

Figure 1. Long-term consequences of early loss of critical neurons after developmental damage. DA, dopaminergic. The impact of early developmental damage is not immediately evident but produces disease years or decades later as the number of neurons decreases with advancing age.
Systematic Review of Studies in Children, Adolescents & Adults: The Relationship between BW and BP

Hazard Ratios for CVD Death in 15,726 Women born in Hertfordshire, England

Osmond C, Barker DJP. BMJ 1993; 307:1519-1524
Lifelong health and BW

► After adjustment for genetics and all facets of extrauterine life, adult health risks vary with BW.

► Genetics aside, 80% of BW is mediated via placental function.
Viscera are generally not random shapes
Not **random**
Not random
Not random
Normal placenta
The placenta may assume (under certain conditions) a mathematically (but not biologically) “random” shape.

The mathematics of that shape = the maternal environment.
Why can placental shape be irregular?

► Placental trophism
  - Placenta grows where it can, dies where it can’t
  - “Determined” by the uterine environment (broadly defined).
  - Variability = placental stress and (potentially fetal) pathology.
When are abnormal shapes generated?

- Nonuniform expansion

Asymmetric disk growth ➔
UC “displacement”

Villous atrophy ➔
△ disk shape

Embryo folding, ➔
fetal and placental
belly buttons

- Villous arborization ➔ disk thickness
Why measure?

► **When** in pregnancy
  - The earlier the stress, the greater the risk of fetal effect.

► **How** **severe**
  - The more severe the stress, the greater the risk of fetal effect.

► **How** **many**
  - “Multiple hits” increase fetal risk.
How do we measure placentas?

Current standard tools

- Shape
- Cord eccentricity
- Larger and smaller diameters
- Disk thickness
- NOTE: No one has ever quantitated chorionic vasculature
“Standard” placental shape and its measures
Cord eccentricity
Thickness can (also) vary
Fetal origins of disease and BW: What is “normal?"

- BWT = - 4147 + (9.693 × AC) + (11.92 × HC) + (21.21 × DeltaUS) + (3.429 × GA × Rate3rd × [Parity + 1])

- US Patent 6695780 – “Methods, systems, and computer program products for estimating fetal weight at birth and risk ofmacrosomia”
- (1 of 61 equations provided in the patent)
Two placentas, same weight, different proportions....

Do they yield the “same” baby?
What is the math of the BW-PW relationship?

► Does only placental weight matter in “making a baby”?
  - No, other placental proportions have reliable effects on birth weight after adjusting for placental weight (Salafia et al, PPE, 2008).

► Multivariate regression ⇒ equation for BW “predicted” by any set of placental measures.
  - Observed BW/Predicted BW == O/E R.
Observed/expected ratio (O/E R)

- O/E R = 1 when BW matches placental measures exactly.
- <1 ⇒ fetal growth is less than predicted by placental measures.
- >1 ⇒ fetal growth is greater than predicted by placental measures.
- A BW of 3500 g can have an O/E R ≤, =, or >1.
- If ▲OER is a BW-independent predictor of later outcomes, this would be an important public health tool.
Hypothesis

- Altered placental proportions that influence birth weight affect childhood body proportions independent of birth weight.
- As your BW increases, your childhood BMI increases.
- But the bigger you are for your placental proportions, the leaner you are.
Hypothesis

- Altered placental proportions (and different chorionic and fetal stem vascular architecture) alter placental resistance.

- These are associated with increased “baseline” (diastolic) childhood blood pressure independent of BMI and many other childhood and parental factors.
This is what we get with “poor” measures....!
Would better measures explain more?

- A one-parameter DLA model
- Set it for any value and let it run, and you will get a round shape.

Perturbed initial seed
Branching altered at 5%
Branching altered at 50%
Disk shape & cord insertion are not independent.

The placental vasculature grows out from its initial vascular core (the cord insertion) as a fractal.
“Regularly irregular”
Log $PW = \alpha + \beta \ (log\ BW)$

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha \ (exponentiated)$</td>
<td>1.03 (1.18)</td>
<td>0.38, 2.42</td>
</tr>
<tr>
<td>$\beta$</td>
<td>0.78 (0.02)</td>
<td>0.66, 0.89</td>
</tr>
</tbody>
</table>

CPP, $N=24,601$, Salafia et al, Placenta 2009
Kleiber’s law and $\frac{3}{4}$ scaling: other inferences

- Basal metabolic rate scales to body size $3/4$.
- Placental weight scales to $BW^{3/4}$.
- Basal metabolic rate $\sim$ Placental weight.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation</th>
<th>Sig. (2-tailed)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's Age At Start Of Pregnancy</td>
<td>Pearson</td>
<td>-0.059</td>
<td>0.036</td>
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<tr>
<td>Body Mass Index (C)</td>
<td>Pearson</td>
<td>0.143</td>
<td>0.000</td>
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<tr>
<td>Weight Gain In Kilograms</td>
<td>Pearson</td>
<td>0.029</td>
<td>0.312</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Pearson</td>
<td>0.022</td>
<td>0.443</td>
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<tr>
<td>Pre-Eclampsia</td>
<td>Pearson</td>
<td>0.108</td>
<td>0.000</td>
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<tr>
<td>Pre-Existing Diabetes</td>
<td>Pearson</td>
<td>0.058</td>
<td>0.039</td>
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<tr>
<td>Chronic Hypertension</td>
<td>Pearson</td>
<td>0.112</td>
<td>0.000</td>
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Placenta and birth weight

Total nutrients transferred
minus
Nutrients needed for placental health
minus
Energy of the cardiac circuit
= Birth weight

*Affected by altered placental shape
Placental shape: why bother?

- Placental shape is a flexible bag that assumes whatever shape will accommodate the placental vascular fractal tree.

- Changes in 2-D placental perimeter and cord insertion affect fetal growth, apparently through effects on the vascular fractal.
Your task

Hypotheses:

- The surface branching of the placental tree independently predicts birth weight (by affecting placental efficiency).
Chorionic vessels develop early in gestation.

- Chorionic vascular structure at term* correlated with placental vascularization at 11-14 weeks. (Schwartz, Salafia et al, SMFM, 2009)
$\Delta \beta \Leftrightarrow \Delta$ placental fractal
Chorionic vasculature is highly variable.
Methods

► Chorionic vasculature was manually traced using a Toshiba tablet computer.

► Intrarater / Interrater variability for MCVD 4% and 7.2% respectively.
Chorionic vascular variables

► Mean Chorionic Vascular Distance (MCVD)
  - $D_{\text{surface pixel to the nearest chorionic vessel}}$

► Normalized MCVD = $\frac{\text{MCVD}}{\text{Chorionic diameter}}$
CV “coverage” and BW

CV coverage highly correlated with BW

- $r = -0.49$
- $r^2 = 0.25$
- $p = 0.021$. 

![Graph showing correlation between CV coverage and BW]
Why is measuring branching important?
Contemporaneous branching

Figure 1. Timeline of lung development. Morphological stages and major events in the developing human and mouse lung.
Branching genes are shared.
Notch

Arterial and venous differentiation

“…Mutants exhibit a phenotype characterized by the absence of angiogenic vascular remodeling in the extraembryonic yolk sac, placenta and embryo…”

Notch signaling in vascular development and physiology
Prior work

Of two previously reported gene targeting experiments, the more extensive Fgfr2 deletion was lethal shortly after implantation, because of trophoblast defects, whereas the less extensive one survived until midgestation with placental insufficiency and defective limb outgrowth [Development (1998) 125, 753].

“Rescuing the trophectoderm defect in our Fgfr2 mutation led to phenotypes in limb and lung.”

Fgfr2 is required for limb outgrowth and lung-branching morphogenesis. PNAS 1999
Can placental structure “proxy” visceral structure?