DOES SIZE AT BIRTH EXPLAIN ADULT URINARY PROGESTERONE CONCENTRATIONS IN GERMAN WOMEN?

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INTRODUCTION

Developmental hypotheses propose that variation in adult reproductive functioning is partly an outcome of varying energy availability during gestation and childhood.[1-4]

- **Low energy availability *in utero* is an indicator of a poor quality environment, and has been hypothesized to result in more sensitive adult ovarian functioning.**[5-7]
- **Size at birth is used as a proxy for *in utero* conditions.**[8]
- **Developmental hypotheses predict that women with a greater size at birth will have higher ovarian hormone concentrations.**[1, 2]

But in fact, contradictory results have been found for the relationship between size at birth and adult ovarian hormone concentrations.

- **As predicted, Polish women with a higher ponderal index (PI**=weight[kg]/length[m^3]) **at birth had *higher* salivary estradiol concentrations in adulthood.**[9]
- **In contrast, Norwegian women with higher weight at birth had *lower* adult salivary estradiol concentrations.**[10]

Progesterone is a common measure of ovarian functioning, but no study has examined its relationship with size at birth.

METHODS

- **Sample: 55** healthy German women, aged 24-40 yrs, BMI=18-27 kg/m^2, not using hormonal contraception or any hormonal therapy, for at least 3 months prior to sample collection, and not trying to become pregnant.
- Daily urine samples were assayed for **pregnanediol glucuronide (PdG)**. All hormone concentrations are expressed as ng PdG/mg creatinine to control for differences in urine concentration. Inter-assay coefficients of variation were 11.7% and 11.4% for high- and low-value quality controls, respectively.
- Progesterone indices were defined as ($\int$ of PdG from x to y)/(y-x), where x to y is any span of days and PdG at any time is defined by linear interpolation of the observed urinary PdG data. For **mean peak luteal PdG**, x=day of peak PdG -2.5, and y=day of peak luteal PdG +2.5.[11]
- **Statistics:** All statistics were run in SPSS Version 21.0 (IBM Corp., released 2012. Armonk, NY). Variables were checked for normality. Adult BMI, adult age, and ponderal index were transformed (BMI=x^3, age=$1/x^2$, PI=$1/x^2$) to meet the normality assumption of linear regressions. Q-Q plots of model residuals and residuals plotted against fitted values did not indicate any violations of assumptions of normality and homogeneity of residuals.[12] Inspection of dffits and dfbetas did not reveal any obvious influential cases.[12] Variance Inflation Factors (VIF) did not reveal any collinearity issues.[12]

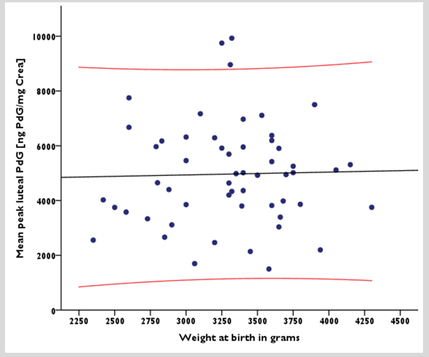
RESULTS

Neither weight nor ponderal index at birth are correlated with adult urinary progesterone concentrations in this sample of German women.

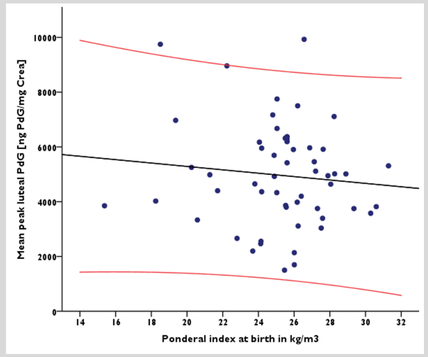
Predictor variables	Mean	Std Dev	Minimum	Maximum
Adult age [years]	29.8	4.9	22.3	40.6
Adult BMI [kg/m^2]	22.5	2.4	19	28.3
Adult weight [kg]	63	8.2	48.4	87
Adult height [cm]	167	5.1	155.3	176.1
Birth weight [grams]	3300.4	447.1	2350	4300
Birth length [cm]	50.8	2.8	44	58
Birth ponderal index [kg/m^3]	25.2	3.1	15.4	31.3
Age at menarche [years]	13.4	1.5	9.9	17.5

Linear regression of mean peak luteal PdG as the dependent variable and birth weight [or PI at birth], current age, age at menarche, and adult BMI as the predictor variables was not significant (see Figures below)

R^2=0.089, $R^2_{adj.}$=0.016, $F_{(4,50)}$=1.216, p=0.316



R^2=0.096, $R^2_{adj.}$=0.023, $F_{(4,50)}$=1.323, p=0.274



Scatter plots of mean peak luteal urinary progesterone against untransformed values of birth weight and ponderal index. Black lines are the regression lines, red lines indicate the 95% confidence interval .

	Response variable: Mean peak luteal PdG [ng/mg Crea]	Standardized Coefficients				Collinearity Statistics
	Predictor variables	**Beta**	**Std. Error**	**t**	**p value**	**VIF***
Model 1- Birth weight	Weight at birth in grams	0.060	0.57	0.436	0.665	1.0
	Transformed BMI (1/BMI^2)	0.308	676891.23	2.081	***0.043***	1.2
	Age at menarche in years	-0.073	184.46	-0.502	0.618	1.2
	Transformed age (1/Age^2)	-0.039	714032.29	-0.284	0.778	1.0
Model 2- Ponderal Index at birth	Transformed PI at birth (PI^3)	-0.103	0.05	-0.762	0.449	1.0
	Transformed BMI (1/BMI^2)	0.304	670891.29	2.072	***0.043***	1.2
	Age at menarche in years	-0.084	183.14	-0.58	0.564	1.2
	Transformed age (1/Age^2)	-0.03	714723.39	-0.214	0.831	1.1

*VIF= Variance Inflation Factor; VIFs< 10 indicate no collinearity problems

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DISCUSSION

In the very few studies available, adult ovarian hormone concentrations are not consistently correlated with size at birth.

Our study adds to the ongoing discussion about the influence of conditions during development on adult ovarian functioning.

Our results suggest important considerations for inter-population differences and variation in methodology.

- ***German women have a high ponderal index at birth***
  - The mean PI at birth of the German sample (25.2 kg/m^3) is similar to the means for the *highest* PI tercile in two studies of Polish women (24.8 and 25.9 kg/m^3) in which interactions between estradiol concentrations and PI were observed only in the lowest tercile (18.8 and 17.7 kg/m^3).[9, 13]
  - Mean birth weight in our study (3300 g) is similar to the moderate birth weight category of the Norwegian study (3220-3530 g), suggesting that these two populations are comparable.[10]
  - Differences in birth weight and PI distribution may explain some of the differences in the results of these studies
- ***Inclusion of anovulatory cycles in previous studies may have biased estimates of mean estradiol concentrations downward.***[14]
  - Anovulatory cycles were excluded from our analysis.

WHY DOES IT MATTER?

Breast cancer risk has been correlated with size at birth.[15,16]

...But the proximate mechanisms connecting these two variables are still unclear.[17]

- **Cross-sectional studies provide limited insight into the relationship between in utero conditions and adult functioning and disease**
- **Longitudinal studies are required to understand the developmental origins of health and disease.**

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