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Research Paper

First trimester maternal sex steroids and head circumference in newborns

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ABSTRACT

Objectives: There is indirect evidence (from digit ratio [2D:4D] research) that prenatal oestrogen is positively related to neonate head circumference (HC), with stronger effects in males. Here we test this theory directly by considering the relationship between maternal first trimester sex steroids (oestradiol [E] and testosterone [T]) and the HC of neonates.

Material and methods: Measures of E and T were obtained from mother's blood at 6–8 weeks (E1, T1), and 10–11 weeks (E2, T2). Neonate HC, length, and weight were recorded together with maternal anthropometrics.

Results: There were 47 neonates (24 boys) and their mothers. Mothers with girls had higher values of E1, T1 and E2 than mothers with boys. There were no mother-neonate sex differences for age, height, weight, BMI, and weight gain during pregnancy. Neonates showed no sex differences for HC, length or birthweight. HC was negatively related to age at pregnancy and positively related to E1. There were no other univariate correlations with HC. Multiple regression with HC as dependent variable showed a positive relationship with E1 and male sex and no effects for maternal age, T1, E2 or T2. Splitting by sex showed positive correlations between HC and male or female E1 with the former stronger than the latter.

Conclusion: HC was positively correlated with maternal E1, independent of T1, E2, T2 and maternal anthropometrics. Splitting by sex, the relationship between HC and E1 was stronger for male neonates compared to female neonates. Our direct findings support earlier reports of positive correlations between prenatal E (which were indirectly measured by 2D:4D) and HC, and that these effects are stronger for boys than girls.

1. Introduction

There is evidence that first trimester sex steroids may influence brain size. Thus, digit ratio (2D:4D), a positive correlate of prenatal oestrogen and a negative correlate of prenatal testosterone [1], has been reported to be positively related to neonate head circumference [2,3] and adult total cerebral cortex [4]. Moreover, this pattern of effects is sex dependent in that it has been noted to be stronger in males in comparison to females. Digit ratio is a prenatal biomarker and not a direct hormonal measure. The purpose of this study was to test this theory more directly by considering the relationship between maternal first trimester sex steroids (oestrogen [E] and testosterone [T]) and the HC of neonates.

HC is a correlate for overall brain size in children, with strong associations with CT and MRI measures [5]. Larger HC indicates a high intracranial volume, which is the total space occupied by brain tissue, cerebrospinal fluid, and vasculature [6]. HC measured in newborns has been reported to be a predictive factor for future health outcomes, including cognitive and motor development. This is the case in both full-term [7] and pre-term infants [8,9]. Its predictive role is especially reliable in premature babies, as the newborn's head circumference and early postnatal rate of head growth are strongly associated with later neurodevelopmental impairment [10]. However, HC of full-term neonates is also a reliable correlate of intelligence independent of birthweight and length of infant [11]. Brain volume differences between males and females (males>females) are present prenatally [6], This prenatal sexual dimorphism in HC suggests that its ontogeny is associated with early sex steroids as measured by 2D:4D.

Digit ratio is sexually dimorphic (males<females with effect size of about $d = 0.5$) and is a proxy for first trimester sex steroids [1,12,13]. Experimental studies with rodents (e.g. [14]) and correlational studies of maternal hormones during human pregnancy [13] have provided evidence that 2D:4D is negatively and positively related to foetal testosterone and oestrogen respectively and the dimorphism is established in the first trimester of foetal development [15]. Growth of the

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digits in children and juveniles has little influence on the magnitude of and the sex difference in 2D:4D [16], and large-sample studies have shown there is no evidence of an effect of allometry on the sexual dimorphism (e.g. [17,18]).

There are two reports of positive associations between 2D:4D and neonatal HC [2,3]. The former measured 2D:4D in adults and the latter in neonates. In addition there is one report of positive associations with 2D:4D and brain size in males but not in females [4]. The significant correlations included total cerebral cortex, total cerebellar white matter and total cerebellar cortex. Moreover, the relationship between 2D:4D and total intracranial volume showed a positive correlation which trended toward significance.

These associations with 2D:4D and HC constitute a body of evidence that leads us to predict a positive relationship between prenatal oestrogen and brain size (HC) of newborns which is independent of prenatal testosterone and with an effect size which is greatest for male neonates. Digit ratio is a correlate of first trimester sex steroids [13,15]. Therefore, more specifically the relationship between prenatal oestrogen and HC should be found for first trimester hormone levels. The purpose of this study was to test these predictions.

2. Material and methods

Our sample of mother-neonate pairs was drawn from a cohort described by Kasielska-Trojan et al. [13]. The participants were recruited from the Obstetrics and Gynaecology out-patient clinic in a Polish Mother's Memorial Hospital – Research Institute. It included all women ($n = 72$) who were admitted to the out-patient clinic in early pregnancy (<7 weeks gestation) between June 2021 and September 2022. They declared willing to continue obstetrics care in the Clinic and agreed to participate in the Study. All participants were White.

Regarding the mothers, the following were recorded: age, weight before pregnancy, weight gain during pregnancy, height, BMI and first trimester hormone levels. The latter were obtained from the mother's blood (2.8 ml) and consisted of testosterone and oestrogen concentrations at 6–8 week and 10–11 week of gestation. All blood tests were done in one laboratory (in Polish Mother Research Institute) by one laboratory specialist. For total oestrogen (17β-estradiol) the measurements were conducted by the Elecsys Estradiol III test (Roche Diagnostics GmbH, results reported in pg/mL). For total testosterone Elecsys Testosterone II test (Roche Diagnostics GmbH, results reported in ng/mL). Both tests were based on electrochemiluminescence "ECLIA", in cobas e601 analyzer. Regarding the neonates, weight and recumbent length were recorded.

Our focus in the current study was on HC which was not reported earlier. For HC measurement, this was performed just after birth by the neonatologist with a measurement tape and recorded with the accuracy to 5 mm. The measurement was repeated and a mean value was recorded in the child's medical card. All mothers of the children included in the initial project were contacted and asked to send a photograph of the child's card, including HC, to AKT. The original cohort of 72 mothers was contacted via e-mail and/or telephone (according to the preferred mode of contact declared at enrolment) three times, with two follow-up reminders issued at one-week intervals. Complete data records were ultimately obtained for 47 children, yielding a response rate of 65.3%.

This protocol was agreed by the local ethics committee (RNN/331/19/KE).

2.1. Statistical analysis

Means (SD), skewness and kurtosis values were calculated for maternal and neonatal variables. Sex differences were tested with *t*-tests where skewness and kurtosis values were < 1 and Mann-Whitney *U* tests where one or both values of skewness and kurtosis were > 1. Univariate correlations were calculated (product-moment *r* or Spearman rank r_s) between HC and maternal variables (age at pregnancy, height, weight, BMI before pregnancy, weight gain and sex steroids) and the neonate variables of weight, and length. A multiple regression test was performed with dependent variable HC and independent variables maternal age, sex of neonate (dummy variable: male neonates = 1; female neonates = 2), and sex steroids E1, T1, E2 and T2.

Table 1
Differences between mothers who had male or female neonates and between male and female neonates. Where traits show values of skewness and kurtosis of <1 the differences were tested with *t*-tests. Where traits show a value of ≥1 for skewness and/or kurtosis the differences were tested with the Mann-Whitney *U* test.

	Males		Females		*t* or *U*	*p*
	Mean	SD	Mean	SD		
Mothers						
Age years	30.83	4.60	29.96	4.21	*t* = 0.68	.50
Height cm	168.00	5.07	166.22	7.04	*t* = 1.00	.32
Weight kg	68.00	13.37	65.30	13.52	*U* = 229	.32
BMI	23.98	3.72	23.64	4.60	*U* = 239	.44
Weight gain kg	14.17	2.48	14.44	2.94	*U* = 269	.88
E1 pg/mL	1142.54	646.27	2034.52	735.83	*t* = 4.42	<.0001
T1 ng/mL	0.459	0.210	0.648	0.241	*t* = 2.88	.006
E2 pg/mL	2054.63	870.66	2707.20	680.69	*t* = 2.854	.007
T2 ng/mL	0.468	0.197	0.599	0.310	*U* = 200	.11
Neonates						
HC cm	34.44	1.57	34.39	0.90	*t* = 0.14	.89
Weight gm	3337.08	610.44	3244.78	396.12	*t* = 0.61	.54
Length cm	54.50	3.48	53.13	2.56	*t* = 1.53	.13

3. Results

There were 47 mother-neonate pairs (24 mothers with boys) in the sample.

3.1. Descriptive statistics

Means (SD), Skewness (S) and kurtosis (K):

Mothers: age 30.40 (4.39) years, S = −0.294, K = −0.799; height 167.13 (6.11) cm, S = −0.045, K = −0.31; weight 66.68 (13.37) kg, S = 1.49, K = 2.16, BMI 23.81 (4.13), S = 1.26, K = 1.80; weight gain 14.30 (2.69), S = 0.39, K = 2.99: Hormones at 6–8 weeks, E1 1579.04 (819.10), S = 0.19, K = −0.94; T1 0.52 (0.24), S = 0.40, K = 0.04; at 10–11 weeks E1 2373.97 (842.23), S = −0.82, K = 0.89; T2 = 0.3 (0.2), S = 1.89, K = 6.06.
Neonates: head circumference 34.42 (1.09) cm, S = 0.17, K = −0.63, recumbent length 53.83 (3.11) cm, S = 0.55, K = −0.20; birthweight 3291.92 (513.36) gm, S = 0.052, K = 2.15.

3.2. Tests for mean sex differences (t- or Mann-Whitney U tests)

Mothers: there were no significant maternal-neonate sex differences for age, height, weight, BMI, and weight gain during pregnancy. For maternal hormones, compared to mothers with boys, mothers of girls had higher values which were significant for E1 ($p < .0001$), T1 ($p = .006$) and E2 ($p = .007$), for T2 the difference was not significant ($p =$

Table 2
Multiple regression output with HC as the dependent variable and independent variables sex of neonate (dummy variable: males = 1, females = 2), and maternal variables age, E1 at 6 to 8 weeks, T1 at 6 to 8 weeks, E2 at 10 to 11 weeks, and T2 a 10 to 11 weeks.

Trait	Coefficient	St. error	St. coeff.	*t*	*p*
Sex of neonate	−0.741	0.357	−0.345	2.072	.045
Age of mother	−0.032	0.035	−0.131	−0.925	.36
E1 6 to 8 weeks	0.001	0.0003	0.573	2.868	.007
T1 6 to 8 weeks	1.320	1.019	0.296	1.296	.20
E2 10 to 11 weeks	0.0002	0.0002	−0.114	−0.628	.53
T2 10 to 11 weeks	−1.264	0.077	−0.308	−1.442	.16

.09).

Neonates: there were no significant sex differences for HC, recumbent length, or birthweight (Table 1).

3.3. Correlations between HC and maternal and neonate traits

Univariate correlations (product-moment [r] or Spearman Rank [r_s] tests) showed HC was negatively related to maternal age at pregnancy ($n = 47$, $r_s = -0.30$, $p = .04$) and positively related to E1 ($n = 47$, $r = 0.38$, $p = .008$). There were no significant relationships between HC and maternal height ($r = 0.06$), weight ($r_s = 0.09$), BMI before pregnancy ($r_s = 0.03$), weight gain during pregnancy ($r_s = 0.02$) and the sex steroids T1 ($r = 0.11$, $p = .48$), E2 ($r = 0.16$, $p = .28$) and T2 ($r_s = 0.05$, $p = .76$).

A multiple regression test was performed with dependent variable HC and independent variables maternal age, sex of neonate (dummy variable: male neonates = 1; female neonates = 2), E1, T1, E2 and T2. There was a positive relationship between sex of neonate and HC (standardised coefficient = −0.345, $p = .045$), indicating that male neonates had higher HC than female neonates. The positive relationship between E1 and HC remained and was strengthened (standardised coefficient = 0.57, $p = .007$), indicating that high E1 in early 1st trimester (6 to 8 weeks) was related to a large neonate HC. Maternal age, T1, E2 and T2 were not related to HC (Table 2).

In order to further explore the relationship between HC and variables sex and E1, the sample was split into male ($n = 24$) and female ($n = 23$) neonates and product-moment correlations calculated. For male neonates there was a positive correlation with HC ($r = 0.52$, $p = .009$) and for female neonates a positive but smaller correlation with HC ($r = 0.43$, $p = .04$) (Fig. 1 for male and female regression lines for HC on E1).

4. Discussion

In our sample of 47 mother-neonate pairs there were 24 male and 23 female infants. Maternal values of E1, T1 and E2 were significantly higher for the latter compared to the former. There were no other maternal-neonate sex differences. Neonates showed no sex differences for HC, recumbent length or weight. Regarding correlations with HC, there was a significant positive association with E1 but no relationships with E2 or with testosterone (T1 or T2). In addition, HC was negatively related to maternal age at pregnancy. Multiple regression analysis showed male neonates had higher HC than female neonates and HC was positively related to E1. These associations were independent of maternal age, T1, E2 or T2. Splitting the total sample by sex of neonate we found the correlation between HC and E1 was $r = 0.52$, $p = .009$ for 24 mother-male neonate pairs and $r = 0.43$, $p = .04$ for 23 mother-female neonate pairs. Therefore, our findings support the predictions from earlier 2D:4D studies that HC is positively related to maternal prenatal oestrogen, and that the effect size of the correlation is greater for mother-male neonate pairs compared to mother-female neonate pairs.

We note that the HC relationship to oestrogen relates to maternal hormone levels at 6 to 8 weeks (E1) and not to later levels at 10 to 11 weeks (E2). It is also independent of maternal testosterone at 6 to 8 weeks (T1) and 10 to 11 weeks (T2). The overall impression is that oestrogen/HC effects occur in a narrow time window, i.e. very early in gestation. HC is strongly related to total brain volume in neonates [19]. However, HC is a proxy for global brain size. It does not relate to specific areas of the brain which may be influenced by prenatal testosterone rather than oestrogen. For example, the volume of the hippocampus [20] is related to low (masculinized) 2D:4D.

We suggest that maternally-derived oestrogen is an important factor

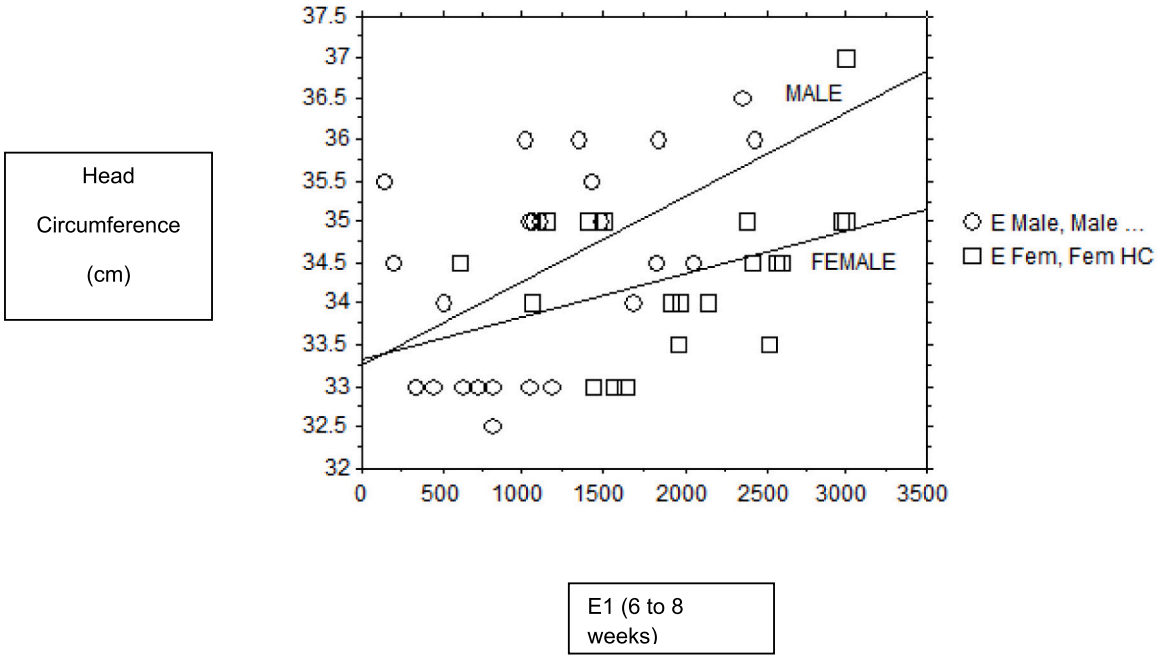

Fig. 1. The relationship between E1 (17β-estradiol) measured in early first trimester (6 to 8 weeks) and head circumference (cm) of 47 neonates split by sex (males $n = 24$; females $n = 23$). The formula for the male regression line: $y = .001x + 33.277$. $r^2 = 0.274$, and for the female regression line: $y = .001x + 33.312$. $r^2 = 0.186$.

in the evolution of human brain size (for discussion see [3]). Human evolution is characterised by a progressive increase in oestrogenisation of the foetus. Thus, the "oestrogenised ape hypothesis" posits that increases in maternally-derived foetal oestrogen and/or reductions in sensitivity to androgen have driven increases in human brain size [3,21,22]. Other theoretical models of increases in human brain size have also emphasised the importance of maternal sex steroids e.g. the "Placental Steroid model" of human brain evolution [23]. However, it has been pointed out that a drive toward greater human oestrogenisation will also lead to deleterious consequences among males, which will include increases in rates of schizophrenia, heart disease and reductions in fertility [3].

We acknowledge our study has limitations with regard to sample size. However, our study has strengths in that we had two samples of hormones from mother's blood which were spread over the first trimester. This enabled us to determine the developmental window for the link between first trimester oestrogen and HC.

In conclusion, we have found that maternal oestrogen levels in the 6 to 8 weeks of gestation are positively related to HC of the neonate and that the correlation was strongest for male neonates. The association was independent of weight and length of the neonate, levels of maternal testosterone at 6 to 8 weeks and maternal oestrogen and testosterone at 10 to 11 weeks. Our finding is consistent with reports of a positive correlation between maternal 2D:4D and HC in neonates, with stronger effects for males compared to females. High 2D:4D is thought to be a biomarker for high first trimester oestrogen and low testosterone. Thus, our finding constitutes evidence in support of 2D:4D as a proxy for first trimester sex steroid levels.

Ethical

The protocol for the study was approved by the local ethics committee (by the Bioethical Committee of the Medical University of Lodz - RNN/331/19/KE).

CRediT authorship contribution statement

John T. Manning: Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Conceptualization. **Marek Kałuża:** Resources, Methodology, Investigation. **Bogusław Antoszewski:** Writing – review & editing, Supervision, Conceptualization. **Anna Kasielska-Trojan:** Writing – review & editing, Project administration, Investigation, Data curation, Conceptualization.

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