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Context

Metformin is used in attempt to reduce pregnancy complications associated with polycystic ovary syndrome (PCOS). Little is known about the metformin impact on fetal development and growth.

Objectives

Exploring the metformin effect vs. placebo on fetal growth and birth anthropometrics in PCOS-offspring compared to a reference population in relation to maternal BMI.

Design

Post-hoc analysis of an RCT

Setting

Double-blind, placebo-controlled, multicenter study

Patients

258 offspring born to PCOS-mothers

Intervention

2000 mg metformin (N=131) or placebo (N=121) from 1st trimester to delivery.

Main outcome measure

Mean abdominal diameter and bi-parietal diameter (BPD) at gestational weeks 19 and 32. Head circumference (HC), birth-length and weight related to a reference population of healthy offspring, expressed as gestational age - and gender adjusted z-scores.

Results

Metformin vs placebo exposed offspring had larger heads at gestational week 32 (BPD 86.1mm vs 85.2mm, p=0.03) and at birth (HC 35.6cm vs 35.1cm, p<0.01). Analyses stratified by maternal pre-pregnancy BMI, larger heads were observed only among offspring of overweight/obese mothers. Among normal-weight mothers the effect of metformin compared to placebo was reduced length (z-score: -0.96 vs. -0.42, p=0.04) and weight (z-score: -0.44 vs. 0.02, p=0.03). Compared to the reference population, offspring born to PCOS-mothers (placebo group) had reduced length (z-score -0.40 (-0.60, -0.40)), but similar birth-weight and HC.

Conclusions

Metformin exposure resulted in larger head-size in offspring of overweight mothers, traceable already in utero. Maternal pre-pregnancy BMI modified the metformin impact on offspring anthropometrics. Anthropometrics of offspring, born to PCOS mothers differed from the reference population.

Metformin vs. placebo on fetal growth and birth anthropometrics in pregnancies of women with PCOS. Metformin increased offspring head size, maternal BMI interacted with offspring anthropometrics. .

1. Introduction

Polycystic ovary syndrome (PCOS) affects 5-13% of women in childbearing age (1). Prevalence varies according to applied criteria and population. Women with PCOS have poorer metabolic health and increased risk of developing complications in pregnancy, such as gestational diabetes mellitus, preeclampsia and preterm delivery (2-6). Birth characteristics are associated to metabolic health later in life (7), but the effect of maternal PCOS status on newborn anthropometric data, as well as metabolic health is scarce and diverging. A population-based study from Australia reported increased number of small for gestational age (SGA) among offspring born to mothers with PCOS (8). A retrospective study from Austria (9) showed no increased risk of growth deviation according to PCOS. A population based study from Sweden found more large-for-gestational age (LGA) offspring born to mothers with PCOS (3,10,11).

Metformin is an oral anti-diabetic drug used in the treatment of type 2 diabetes mellitus. It is cheap and assumed safe. The effect of metformin on insulin sensitivity, lipid metabolism and inflammation has induced a wider area of application. During the last decades, women with gestational diabetes mellitus (GDM), PCOS and obesity have been treated with metformin in an attempt to improve pregnancy outcome, but this practice is not based on solid scientific evidence. Metformin passes the placental barrier, but teratogenicity is not reported (12). There is little knowledge about possible effects of metformin on growth, metabolism, endocrine and nervous system development in the fetus and cognitive and psychologic effects later in life.

In five studies on GDM, in which mothers were randomized to metformin or insulin, no difference was seen in offspring birth weight (12-16). One study report increased length at birth in newborns (16) and another on shorter and lighter (12) newborns in the metformin group. In two large randomized control trials (RCT), metformin was compared to placebo in obese pregnant women and no effect on birth weight was observed (17,18).

In our initial analysis of women with PCOS in the PregMet RCT(19), there was no difference in pregnancy complications and newborn data between the metformin and placebo groups, except head size. Head size of the metformin-exposed newborns was larger (19).

In the present study we examined the *in utero* ultrasound measurements of the fetuses to explore the effect of metformin vs. placebo on fetal anthropometrics, and birth anthropometrics in PCOS-offspring compared to a reference population. The results were related to maternal BMI.

2. Subjects and Methods

The PregMet study was a prospective, randomized, placebo-controlled, multicenter trial of pregnant women with PCOS (19). The aim of the study was to investigate whether metformin exposure from first trimester to delivery could prevent pregnancy complications. Eleven health-care centers in Norway (three university hospitals, seven local hospitals, and one gynecological specialist practice) recruited women to the study during 2005-2009. Primary endpoints were prevalence of preeclampsia, preterm delivery, gestational diabetes mellitus, and a composite of the diagnoses. Inclusion criteria in the PregMet study were 1) PCOS diagnosed according to the Rotterdam criteria, 2) age 18-45 years, 3) gestational age between 5 and 12 weeks, and 4) singleton viable fetus shown on ultrasonography. Exclusion criteria were ALAT >90 IU/liter, serum creatinine >1.70 mg/dl, known alcohol abuse, previously diagnosed diabetes mellitus or

fasting serum glucose higher than 126 mg/dl at the time point of inclusion. All participants received written and individual verbal counseling on diet and lifestyle at inclusion. Thereafter treatment with metformin 500mg (metformin hydrochloride, Metforminâ, Weifa AS, Oslo, Norway), or identically coated placebo tablets was initiated. The participants were instructed to take two tablets twice daily, a total of 2000mg daily, for the rest of the study period. To counteract a possible metformin action on vitamin B levels, patients were advised to take 0,8mg of folate daily and one daily multivitamin tablet. Study medication was stopped at delivery. Randomization was performed at the Trondheim University Hospital Pharmacy in blocks of ten and stratified according to metformin use at conception. The method was random drawing of an envelope by two pharmacy employees, one executing the drawing and the other monitoring the drawing.

This study has been described in detail elsewhere (19).

A. Study population

In total, 274 pregnancies were included and randomized. One patient was misdiagnosed, three miscarried and 12 dropped out (Fig 1). These 16 pregnancies were excluded due to lacking ultrasound data. Present analyses comprise 258 pregnancies. 84% of all participants took more than 85% of the study medication, and were classified as having good/acceptable compliance.

B. Ultrasound measurements

All ultrasound examinations were performed by doctors and specialized midwives trained to perform routine ultrasound examinations. The equipment used was the preferred, up-to-date ultrasound devices used in every-day clinical practice during the study period. Estimated date of delivery and gestational age were calculated from crown-rump-length (CRL) and/or BPD in the first trimester. Trans-vaginal ultrasound examinations in the first trimester were performed at the time of inclusion. Estimated date of delivery and gestational age were calculated from crown-rump-length (CRL) or bi-parietal diameter (BPD) at the first trimester scan and based on the algorithm implemented in the first trimester screening program from Fetal Medicine Foundation (https://fetalmedicine.org) (20,21). Transabdominal ultrasounds measurements were performed at gestational week 19 (+/- 1 week) and week 32 (+/- 1 week) with measurements of BPD (outer to outer measurement of skull diameter) and mean abdominal diameter (MAD)

Measurements of BPD and MAD in the second and third trimester referred to references in “eSnurra” (22,23)

C. Offspring anthropometrics

Midwives and nurse assistants measured head circumference, length and weight of the offspring immediately after delivery. For head circumference, length and weight at birth, gestational age and gender adjusted z-scores were calculated based on Niklasson’s standard values from a large Swedish population [20]. The standard is based on singleton fetuses without chromosome abnormalities or major birth defects.

The z-scores express the deviation between observed values and the standard population mean adjusted for gender and gestational age at birth.

D. Statistical analyses

All data entry, data management and data analyses were analyzed according to the intention-to-treat principle. Baseline characteristics for the two maternal groups were compared using t-tests for continuous variables, and χ^2-tests for categorical variables. The effect of metformin, as well as the effect of metformin in relation to maternal BMI was analyzed using linear regression

analyses. Offspring characteristics for different maternal BMI groups were compared using t-test for both the metformin and placebo group. P-value <0.05 was considered statistically significant.

The statistical analyses were performed by IBM SPSS version 23 and R version 2.13.1 (Copyright © 2011 The R foundation for Statistical Computing).

E. Role of the funding source

The Liason Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU) funded the study. Weifa AS, who supplied the study drug free of charge, and had no role in the collection, analysis and interpretation of the data or writing the report, and decision to submit the paper.

3. Results

Maternal baseline characteristics did not differ between the placebo and metformin groups, in terms of BMI, blood glucose, ethnicity, smoking and PCOS phenotypes (Table 1). Adherence to study medication was similar in the two groups. (Table1)

The effects of metformin vs. placebo on fetal growth are shown in Table 2. There was no difference between the groups in BPD at gestational week 19, but metformin exposed offspring had larger BPD than offspring in the placebo group at gestational week 32 (Δ BPD 0.9 mm, p=0.027). At birth head circumference (HC) was larger in the metformin group compared to placebo (Δ HC 0.5 cm, p=0.007). HC in the metformin group was also larger than the reference population expressed as head circumference z-score (95% CI): 0.3 (0.005, 0.52). MAD at gestational weeks 19 and 32 weight and length did not differ between the metformin and placebo groups.

The effect of metformin on birth anthropometrics differed according to maternal pre-pregnancy weight (BMI <25kg/cm^2 or BMI ≥25kg/cm^2). The results from the interaction analyses are shown in Table 3. HC at birth was increased in the metformin group, only among offspring born to overweight women (ΔHC z-score 0.50, p=0.002). Among normal-weight women, HC did not differ between the metformin and placebo groups (ΔHC z-score -0.20, p=0.367). Thus, the metformin effect on HC differed between maternal weight categories by z-score 0.71, and this interaction effect reached statistical significance (p=0.011).

Length was significantly reduced by metformin among normal-weight mothers (Δ length z-score -0.54, p=0.025), but not among overweight mothers. The difference in metformin effect on length between maternal BMI categories was 0.62 (p=0.038). Also birthweight was reduced by metformin only in normal-weight mothers (Δ birthweight z-score -0.45, p=0.041). The difference in metformin-effect on birth weight z-score between maternal weight groups was 0.53 (p=0.055). All these interactions are of borderline statistical significance.

Sub-group analyses according to hyper-androgen and normo-androgen maternal phenotype, showed a larger HC; 35.8 cm vs. 35.2 cm, p= 0.020, and HC z-score 0.67 vs. 0.27, p=0.008 in metformin vs. placebo exposed offspring, only among the hyper-androgen phenotypes. Among normo-androgen phenotypes, there was no difference in HC; 35.0 cm vs. 34.5 cm, p=0.237, and HC z-score 0.17 vs. 0.17, p=0.992 between the metformin and placebo groups.

In analyses stratified on offspring gender, metformin exposed girls, but not boys, seemed to have a larger BPD at week 32 and larger HC at birth. Once adjusted for maternal BMI, there was no difference in metformin effect according to gender (data not shown). We also analyzed data according to compliance. The difference in HC and HC z-score remained significant among those with good compliance (84%), and not present among those with poor compliance (16%).

The effect of PCOS on offspring anthropometrics was analyzed in the placebo group and expressed by z-score deviation from the reference population. The PCOS offspring were shorter than the reference population, birth length z-score -0.40 (-0.60, -0.20) (Table 2). Birth weight z-score 0.06 (-0.11, 0.24) and HC z-score 0.03 (-0.14, 0.22) did not differ from the reference population. In contrast to the metformin group, maternal BMI (<25 kg/cm^2 or BMI ≥25kg/cm^2) had no effect on offspring birth weight, length or head circumference (Table 4.)

4. Discussion

The main and novel finding of the present follow-up study is that metformin exposed offspring had larger head circumference compared to offspring in the placebo group. This was evident already at gestational week 32. Birth weight and length did not differ between the metformin and placebo groups.

This is the first study on PCOS exploring the effect of metformin on fetal and newborn anthropometrics in an RCT setting where the metformin group and placebo group are randomized with no baseline differences in known potential influencing factors. Little is known about the metformin effect on fetal and newborn head size. In one study on gestational diabetes, metformin was compared to insulin. Head size of offspring in the metformin and insulin groups did not differ (16). Among women with obesity randomized to metformin or placebo during pregnancy, offspring had similar head circumferences (18). Our results deviate from these previous studies and the difference is most likely explained by the variation in underlying diagnoses. Also, differences in study design, population number, aim, medical treatment, maternal weight and ethnicity may have contributed to the differing results. Head circumference correlates accurately to brain volume (24,25), and large head size is associated with good cognitive function and cardiovascular health (25,26). Thus, large head at birth is a surrogate marker for brain development and potentially a beneficial effect.

The metformin-effect of larger HC and HC z-score was only seen among offspring of mothers with hyper-androgenic phenotype whereas in the normo-androgenic phenotype there was no difference between the groups. However, due to small sample size, metformin effect according to maternal androgen status must be interpreted with great caution and should be addressed in future studies.

The effect of prenatal metformin exposure seems to translate differently depending on maternal BMI and/or metabolic status. Offspring exposed to metformin, born to normal weight mothers had significantly smaller head circumference, were shorter and lighter compared to metformin exposed offspring of overweight/obese mothers. While in the placebo group, we found no difference in head size, birth length and birth weight between offspring of normal weight and overweight/obese mothers. This indicates a growth restrictive impact of metformin among normal-weight mothers with PCOS. Interestingly, Salomäki et al. reported similar findings in a mouse model (27,28). Mice on regular diet and metformin during pregnancy, had litters with lower birth weight and higher weight gain on a high fat postnatal diet (27). In contrast, in mice on high-fat diet, metformin did not influence offspring birthweight, and had a protective effect on the metabolic phenotype of the offspring (28). Salomäki et al. postulated that metformin exposure in utero programs the metabolic phenotype (27), by mimicking a “dietary restriction”-like state.

This corresponds to the actions of metformin at a cellular level, where it acts as a mild inhibitor of the MRC1 leading to decreased cellular respiration (29). This activates the AMPK

kinase which shuts down energy consuming processes and switches the cell from anabolic to catabolic state, resulting in decreased lipid, glucose and protein synthesis and cell growth (29).

As in the study of Salomäki, we observe a growth restriction induced by metformin in offspring of normal-weight mothers. This may theoretically result in increased overweight later in life, in line with the "developmental origin of health and disease" (DOHaD) hypothesis (30).

Another important finding of the study, was that offspring born to mothers with PCOS (placebo exposed) had similar birth weight and head circumference, but were shorter at birth compared to the gestational age and gender adjusted standard population. This indicates that the PCOS *per se* has a "growth restrictive" effect on offspring body length at birth. This is interesting as mean BMI of mothers with PCOS (29.5 kg/m^2) was significantly higher than mean BMI of the standard population (23.8 kg/m^2), and one would expect that both birth weight, and the prevalence of high birth weight would to be increased among women with PCOS. The disproportional anthropometric measures found in the study (offspring were shorter, but not lighter) indicate that offspring were born relatively fatter than the reference population. Increased leptin concentration in the umbilical cord blood has been reported in offspring of mothers with PCOS (31). This may reflect fetal adiposity, which is in line with the results from the current study.

Another observation in the placebo group was that birth anthropometrics did not differ between offspring of normal-weight and overweight/obese mothers. Thus, our results indicate a growth restrictive effect of PCOS on offspring anthropometrics that is relatively more pronounced in offspring of overweight/obese mothers.

Two counteracting physiological mechanisms related to fetal growth may explain a putative stronger growth restrictive effect of PCOS with increasing maternal BMI. First, maternal overweight/obesity promotes fetal growth through high glucose transfer to the fetus and induces increased fetal insulin production resulting in "fatter" fetuses. Second, elevated maternal androgens induce placental differentiations, lower placental weight and results in growth restriction, as reported in other mouse models (32,33). If these two counteracting mechanisms are significantly in play, our data indicate that the balance between them differ between organs (skeletal vs fat mass/and growth of other organs).

More convincing data is needed on the potential of metformin to decrease pregnancy complications before metformin can be recommended in non-diabetic pregnancies. So far precaution is advised when prescribing metformin to normal weight mothers with PCOS without well-documented indication.

5. Conclusion

In conclusion, metformin altered offspring anthropometrics. Maternal BMI modified the effect of metformin resulting in increased head size in offspring of overweight/obese mothers, and shorter and thinner offspring in normal weight mothers. Head size alteration was traceable already in utero. Placebo exposed offspring born to mothers with PCOS were shorter but not lighter than the reference population. Metformin administration to normal-weight mothers with PCOS might restrict fetal growth.

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Figure 1.

Table 1. Baseline data on women with polycystic ovary syndrome (PCOS) at inclusion, in first trimester of pregnancy to the PregMet study

	Metformin	**Placebo**	***p*-value**[a]
	N = 131	**N = 127**	
	Mean (SD)	**Mean (SD)**	
Age (years)	29.6 (4.3)	29.3 (4.4)	0.558
Height (cm)	167.3 (5.8)	167.7 (5.4)	0.549
Weight (kg)	82.9 (20.3)	79.3 (18.0)	0.131
BMI (kg/m²)	29.6 (7.1)	28.2 (6.4)	0.099
Systolic blood pressure (mmHg)	119 (12)	117 (11)	0.302
Diastolic blood pressure (mmHg)	74 (13)	72 (9)	0.268
Parity			0.825
Para 0	74	70	
Para ≥1	57	57	
Ethnicity	**N(%)**	**N(%)**	0.047
Caucasian	127 (97)	127 (100)	
Non-Caucasian	4 (3)	0 (0)	
GDM at inclusion	10 (4)	11 (4)	0.822
Smokers	14 (4.5)	7 (2.7)	0.172
Diagnostic criteria PCOS			
NIH diagnostic criteria [b]	91 (70)	87 (69)	
Rotterdam diagnostic criteria	40 (30)	40 (31)	
Androgen status			0.577
Hyperandrogenism	98 (75)	91 (72)	
Normoandrogenism	33 (25)	36 (28)	
Mode of conception			0.200
Spontaneous conception	76 (58)	75 (59)	
Ovulation induction	38 (29)	28 (22)	
IVF/ICSI	17 (13)	21 (7)	
Other	0 (0)	3 (2)	
Compliance of medication			0.552
Taken >85% of all study medication	108 (82)	108 (85)	
Taken <85% of all study medication	23 (18)	19 (15)	

[a] T-test was performed with equal variances assumed. Pearson Chi-square and Fishers exact test was performed. [b] National Institute of Health diagnostic criteria

Abbreviations: GDM, gestational diabetes mellitus. IVF, in vitro fertilization. ICSI, Intracytoplasmic Sperm Injection

Table 2. Anthropometric characteristics of offspring born to women with PCOS exposed to metformin or placebo

		Metformin		**Placebo**	**Δ M-P** (95% CI)[a]	***p*-value**[b]
	N	**Mean**	**N**	**Mean**		
BPD week 19 (mm, mean SD)	127	46.4 (3.1)	121	46.3 (3.4)	0.1 (-0.72, 0.92)	0.810
BPD week 32 (mm, mean SD)	126	86.1 (3.2)	122	85.2 (3.3)	0.9 (0.11, 1.73)	***0.027***
MAD week 19 (mm, mean SD)	125	43.6 (3.9)	121	43.7 (4.9)	-0.2 (-1.26, 0.96)	0.788
MAD week 32 (mm, mean SD)	126	90.4 (5.2)	120	89.9 (4.8)	0.5 (-0.80, 1.71)	0.476
Head circumference at birth						
cm, mean (SD)	130	35.6 (1.6)	126	35.0 (1.6)	0.5 (0.15, 0.92)	***0.007***
z-score, (95% CI)	130	0.3 (0.10, 0.49)	126	0.03 (-0.14, 0.22)	0.3 (0.005, 0.52)	***0.045***
Birth weight						
g, mean (SD)	131	3567 (540)	127	3545 (617)	22 (-120, 163)	0.763
z-score, (95% CI)	131	-0.05 (-0.23, 0.15)	127	0.06 (-0.11, 0.24)	-0.1 (-0.36, 0.16)	0.431
Birth length (cm, mean SD)						

cm, mean (SD)	130	50.1 (2.1)	124	50.0 (2.5)	0.1 (-0.51, 0.63)	0.826
z-score, (95% CI)	130	-0.52 (-0.72, -0.33)	124	-0.40 (-0.60, -0.20)	-0.13 (-0.40, 0.15)	0.375
Birth weight ≥ 90percentile[c] (N, %)	131	15 (12)	127	15 (12)		0.928
Birth weight ≤ 10percentile[c] (N, %)	131	12 (9)	127	13 (10)		0.832

[a] Δ M-P expresses the metformin effect on head circumference, length- and weight z-scores in offspring born to PCOS mothers
[b] T-test was performed with equal variances assumed
[C] Birth weight adjusted for gestational age
Abbreviations: BPD, bi-parietal diameter; MAD, mean abdominal diameter

Table 3. Effect of metformin on anthropometric measures at birth according to maternal BMI

	Maternal BMI <25				**Maternal BMI ≥25**					
	Metformin (M)	**Placebo (P)**	**Δ M-P** (95% CI)[a]	***p*-value[d]**	**Metformin (M)**	**Placebo (P)**	**Δ M-P** (95% CI)[b]	***p*-value[d]**	**(Δ M-P (BMI ≥25)) - (Δ M-P (<25))** (95% CI)[c]	***p*-value[d]**
Head circumference (z-score, 95% CI)	-0.02 (-0.34, 0.29)	0.18 (-0.13, 0.49)	-0.20 (-0.65, 0.24)	0.367	0.45 (0.23, 0.67)	-0.05 (-0.28, 0.18)	0.50 (0.19, 0.82)	***0.002***	0.71 (0.16, 1.25)	***0.011***
Length (z-score, 95% CI)	-0.96 (-1.30, -0.63)	-0.42 (-0.76, -0.09)	-0.54 (-1.01, -0.07)	***0.025***	-0.31 (-0.54, -0.07)	-0.38 (-0.63, -0.14)	0.08 (-0.26, 0.24)	0.655	0.62 (0.033, 1.20)	***0.038***
Weight (z-score, 95% CI)	-0.44 (-0.75, -0.13)	0.02 (-0.29, 0.33)	-0.45 (-0.89, -0.02)	***0.041***	0.15 (-0.07, 0.37)	0.08 (-0.14, 0.31)	0.07 (-0.24, 0.39)	0.650	0.53 (-0.01, 1.06)	***0.055***

[a]**Δ M-P (BMI <25)** expresses the metformin effect on head circumference, length- and weight z-scores in offspring of normal weight mothers
[b]**Δ M-P (BMI ≥25)** expresses the metformin effect on head circumference, length and weight s-scores in offspring of overweight/obese mothers
[c]**(Δ M-P (BMI <25)) - (Δ M-P (≥25))** expresses the *difference* in metformin effect on offspring head circumference, length- and weight z-scores between overweight and normal weight mothers
[d] Statistical testing performed by multiple linear regression analyses
Abbreviations: BMI, body mass index

Table 4. Characteristics in offspring born to women with PCOS exposed to metformin or placebo in utero according to randomization

		Placebo					**Metformin**			
		BMI <25		**BMI =/>25**	***p*-value[a]**		**BMI <25**		**BMI =/>25**	***p*-value[a]**
	N	**Mean**	**N**	**Mean**		**N**	**Mean**	**N**	**Mean**	
BPD week 19 (mm, mean SD)	42	46.5 (3.9)	79	46.2 (3.1)	0.640	44	46.5 (3.7)	83	46.4 (2.8)	0.798
BPD week 32 (mm, mean SD)	42	86.1 (3.3)	80	84.7 (3.2)	***0.020***	41	85.9 (3.1)	85	86.2 (3.3)	0.663
MAD week 19 (mm, mean SD)	42	43.1 (5.2)	72	44.0 (4.7)	0.326	44	43.5 (3.5)	81	43.6 (4.1)	0.886
MAD week 32 (mm, mean SD)	42	90.5 (4.7)	78	89.7 (4.8)	0.071	41	88.5 (4.6)	85	91.4 (5.3)	***0.003***
Head circumference										
cm, mean (SD)	44	35.2 (1.8)	82	35.0 (1.5)	0.450	43	35.0 (1.5)	87	35.9 (1.5)	***0.003***
z-score, (95% CI)	44	0.18	82	-0.50	0.211	43	-0.02	87	0.45	***0.022***
Birth weight	44	3537 (655)	83	3550 (600)	0.908	44	3327 (510)	87	3689 (516)	***0.000***
g, mean (SD)										
z-score, (95% CI)	44	0.02	83	0.08	0.739	44	-0.44	87	0.15	***0.003***
Birth length										
cm, mean (SD)	43	50.0 (2.6)	81	50.1 (2.4)	0.779	43	49.2 (1.9)	87	50.6 (2.1)	***0.000***
z-score, (95% CI)	43	-0.42	81	-0.38	0.861	43	-0.96	87	-0.31	***0.002***

[a] T-test was performed with equal variances assumed
Abbreviations: BPD, bi-parietal diameter; MAD, mean abdominal diameterc