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The effect of polycystic ovary syndrome history on neonatal anogenital distance: a prospective study in Turkish population

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ABSTRACT

Aim: Embryonic anogenital length depends on fetal sex and testosterone. Children of women with a history of polycystic ovary syndrome (PCOS) who became pregnant may have different anogenital lengths due to hyperandrogenemia. Therefore, the aim of this study was to compare the anogenital lengths of male and female newborns of women with and without a history of PCOS.

Material and Method: The study was designed prospectively. Pregnant women with PCOS and control group who gave birth at term (≥37-42 weeks) between March 2019 and March 2020 in University of Health Sciences, Tepecik Training and Research Hospital, Department of Obstetrics and Gynecology were included in this study.

Results: A total of 119 patients, including 21 mothers with PCOS and female newborns, 35 mothers with female newborns in the control group, 21 mothers with PCOS and male newborns and 42 mothers with male newborns in the control group, were included in this prospective study. Anogenital distance-anus fourchette (AGD-AF) measurement was significantly higher in the female newborns from mother with PCOS than in the female newborns from control group (18.1±2.5 vs. 14.1±1.6, p=0.046). Also, AGD-AF was 20.3±3.5 in the PCOS with hirsutism group and 15.2±1.5 in the PCOS without hirsutism group, and the difference between them was statistically significant (p=0.041).

Conclusion: The anogenital distance may change in female newborns in the presence of maternal PCOS. Considering that AGD reflects fetal testosterone exposure, the findings may reflect increased testosterone exposure in female fetuses of pregnant women with PCOS. The results pave the way for new studies.

Keywords: Anogenital distance, polycystic ovary syndrome, fetus, newborn, testosterone

INTRODUCTION

The first 6-week period in human embryos is the "undifferentiated stage" in which the bipotential organ plans are formed. During this period, primitive sex cells (germ cells) have not yet differentiated (1). Sexual development proceeds as a hormone-dependent and dynamic process after the sixth week of gestation. From this week onwards, the genital tubercle lengthens and forms the phallus in the male and the clitoris in the female (2). Anogenital distance (AGD) is defined as the distance between the fetal caudal extremity and the base of the genital tubercle, and this distance is fetal sex and testosterone dependent (3). Testosterone is required for sexual differentiation in males. AGD and phallic length increase with the effect of dihydrotestosterone (DHT) (4). Polycystic ovary syndrome (PCOS) is a metabolic disease that is common in women of reproductive age and affects approximately 4% to 20%, associated with oligo-ovulation or anovulation, androgen excess symptoms and multiple ovarian cysts (5). This disease is a syndrome also known as ovarian hyperandrogenemia, and excess testosterone is the hallmark of the disorder (6).

In previous studies, it has been shown that maternal exposure to androgenic or anti-androgenic environmental agents affects AGD in the fetus (7). Given this situation, newborn of women with a history of PCOS may have different androgen exposure, and hence different AGD, from women with a normal reproductive cycle (8,9).

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Studies on this subject are very limited due to the difficulty in finding the sample size and the difficulty of conceiving patients with PCOS (9,10). In this prospective study conducted in term pregnant women, it was planned to investigate the effects of pre-pregnancy PCOS history and environmental factors on the AGD of the newborn. In addition, AGD values were examined according to pre-pregnancy PCOS symptoms.

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Tepecik SUAM Non-interventional Clinical Researches Ethics Committee (Date: 13.02.2019, Decision No: 2019/2-2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All participants were informed and informed voluntary consent was obtained.

Study Design

The study was designed prospectively. Pregnant women with PCOS and control group who gave birth at term (≥37-42 weeks) between March 2019 and March 2020 in University of Health Sciences, Tepecik Training and Research Hospital, Department of Obstetrics and Gynecology were included in this study. Participants were selected from pregnant women who were admitted to the delivery room and gave birth. Information about hirsutism, oligomenorrhea and polycystic ovary appearance in ultrasonography of pregnant women with PCOS was questioned before delivery.

Data of newborns were collected in the delivery room after the first postnatal examination. The body length, head circumference and birth weight of the newborns were measured. In male newborns, anogenital distance-anus scrotum (AGD-AS): The distance between the center of the anus and back of the scrotum and anogenital distance-anus penis and (AGD-AP): The distance between the center of the anus and the posterior base of the penis were measured. (**Figure 1**).

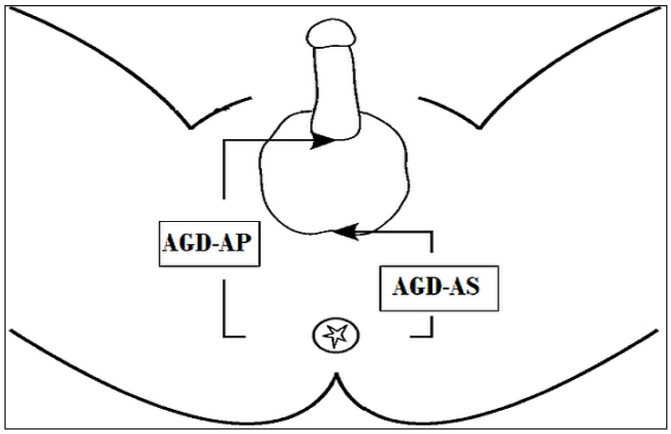

Figure 1. Neonatal anogenital distance (AGD) measurement in males

In female newborns, anogenital distance-anus fourchette (AGD-AF): The distance between the center of the anus and posterior fourchette and anogenital distance-anus clitoris (AGD-AC): The distance between the center of the anus and the clitoris floor were measured. (**Figure 2**). Each measurement was made by a single person (B.B.), repeated three times, and the average of these three values was used in the analysis.

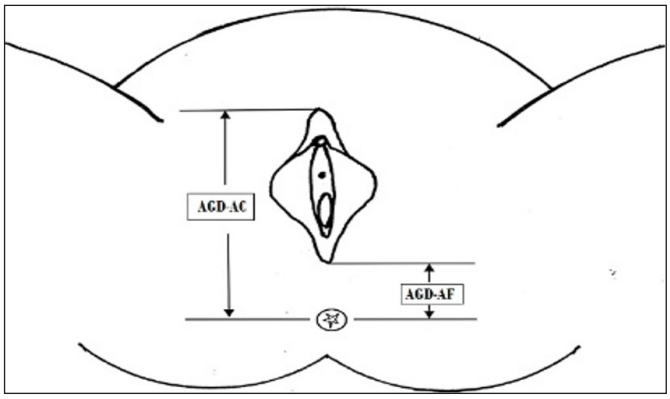

Figure 2. Neonatal anogenital distance (AGD) measurement in females

Study Participants

As inclusion criteria; singleton and term (≥37 weeks, <42 weeks) pregnant women with PCOS history and control group who gave birth in our hospital were included. Multiple pregnancies, in vitro fertilization (IVF) pregnancies, fetuses with major or minor fetal anomalies, pregnant women with any disease (such as: thyroid disease, diabetes, hypertension/preeclampsia etc.) pregnant women using medication, pregnant women with fetal growth restriction (FGR) were excluded from the study. For the number of samples, power analysis was performed with G-power 3.1.9.7 version using similar studies in the literature. Accordingly, the minimum number of patients for each group was calculated as 11.

Statistical Analysis

Statistical Package for the Social Sciences version 26.0 (IBM Corporation, Armonk, New York, USA) was used for data analysis. Significance level was taken as $p < .05$ in all analyzes. Shapiro-Wilk test was used to determine the distribution of the data. Student's t-test was used for normally distributed data in comparisons and data were presented as mean ± (SD). Mann-Whitney U test was used to compare the data that could not show normal distribution and the data were shown as median ± (min, max). Chi-square test was used to compare categorical variables and Odds ratio (95% Confidence interval) calculations were made.

RESULTS

A total of 119 patients, including 21 mothers with PCOS and female newborns, 35 mothers with female newborns in the control group, 21 mothers with PCOS and male newborns

and 42 mothers with male newborns in the control group, were included in this prospective study. Maternal, obstetric and neonatal characteristics of study participants who gave birth to female fetuses were analyzed in **Table 1**. Accordingly, maternal ages and body mass indexes (BMIs) of both groups were statistically similar. In the group of mothers with PCOS, 4 (19%) mothers were smokers, and 7 (20%) mothers from the control group were smokers (p=0.930). The mean gestational age at delivery of both groups was statistically similar (39±2.2 vs. 39.2±1.4, p=0.736). The birth weight (3443.3±665.9 vs 3231±3594), head circumference (33.6±1.3 vs 33.6±1.77) and body length (49.3±1.7 vs 49.8±1.2) of newborns was similar between the groups (p=0.189, p=0.881, and p=0.286, respectively). AGD-AF measurement was significantly higher in the female newborns from mother with PCOS than in the female newborns from control group (18.1±2.5 vs. 14.1±1.6, p=0.046). However, AGD-AC measurement was similar between the groups (36.7±2.7 vs. 36.3±2, p=0.512). (**Table 1**).

Table 1. Maternal, obstetric, and neonatal characteristics of study participants who gave birth to female fetuses

	Female newborns from mother with PCOS n=21	Female newborns from control group n=35	P
Maternal age (year) median (min,max)	28 (18-35)	29 (18-38)	0.529
Parity (n,%)			0.264
Nulliparous	7 (33.3%)	7 (20%)	
Multiparous	14 (66.7%)	28 (80%)	
BMI (kg/m2)	31.1±3.7	30.1±2.8	0.225
Smoking (n,%)	4 (19%)	7 (20%)	0.930
Gestational age at delivery (week) (mean±SD)	39±2.2	39.2±1.4	0.736
Delivery type (n,%)			0.833
Vaginal delivery	12 (57.2%)	21 (60%)	
Cesarean section	9 (42.8%)	14 (40%)	
Birth weight (g) (mean±SD)	3443.3±665.9	3231±3594	0.189
Head circumference of newborns (cm) (mean±SD)	33.6±1.3	33.6±1.77	0.881
Body length of newborns (cm) (mean±SD)	49.3±1.7	49.8±1.2	0.286
AGD-AF (mm) (mean±SD)	18.1±2.5	14.1±1.6	0.046
AGD-AC (mm) (mean±SD)	36.7±2.7	36.3±2	0.512

Abbreviations: BMI: Body mass index, AGD-AF: The distance between the center of the anus and posterior fourchette, AGD-AC: The distance between the center of the anus and the clitoris floor

Maternal, obstetric and neonatal characteristics of study participants who gave birth to male fetuses were analyzed in **Table 2**. Accordingly, maternal ages and BMIs of both groups were statistically similar. In the group of mothers with PCOS, 2 (9.5%) mothers were smokers, and 5 (11.9%) mothers from the control group were smokers (p=0.776). The mean gestational age at delivery of both groups was statistically similar (39.5±0.3 vs. 39.2±1, p=0.756). The birth weight (3554.8±174.6 vs 3514.2±332.4), head circumference (34.9±0.5 vs 34.8±1.2) and body length (50.7±1.1 vs 51.2±1.3) of newborns was similar between the groups (p=0.802, p=0.718, and p=0.656, respectively). AGD-AS measurement (24.8±1.2 vs. 23.5±3.5, p=0.195) and AGD-AP (55.4±1.5 vs. 55±4.1, p=0.406) measurement was similar between the groups. (**Table 2**).

Table 2. Maternal, obstetric, and neonatal characteristics of study participants who gave birth to male fetuses

	Male newborns from mother with PCOS n=21	Male newborns from mother with PCOS n=42	P
Maternal age (year) median (min,max)	29 (18-39)	28 (18-37)	0.718
Parity (n,%)			0.236
Nulliparous	4 (19%)	14 (33.3%)	
Multiparous	17 (81%)	28 (66.7%)	
BMI (kg/m2)	31.1±0.9	31.8±3.2	0.336
Smoking (n,%)	2 (9.5%)	5 (11.9%)	0.776
Gestational age at delivery (week) (mean±SD)	39.5±0.3	39.2±1	0.756
Delivery type (n,%)			0.444
Vaginal delivery	13 (61.9%)	30 (71.4%)	
Cesarean section	8 (38.1%)	12 (18.6%)	
Birth weight (g) (mean±SD)	3554.8±174.6	3514.2±332.4	0.802
Head circumference of newborns (cm) (mean±SD)	34.9±0.5	34.8±1.2	0.718
Body length of newborns (cm) (mean±SD)	50.7±1.1	51.2±1.3	0.656
AGD-AS (mm) (mean±SD)	24.8±1.2	23.5±3.5	0.195
AGD-AP (mm) (mean±SD)	55.4±1.5	55±4.1	0.406

Abbreviations: BMI: Body mass index, AGD-AS: The distance between the center of the anus and back of the scrotum, AGD-AP: The distance between the center of the anus and the posterior base of the penis

Anogenital distance measurements were compared by dividing the PCOS group into two groups according to the presence or absence of hirsutism. AGD-AF was 20.3±3.5 in the PCOS with hirsutism group and 15.2±1.5 in the PCOS without hirsutism group, and the difference between them was statistically significant (p=0.041). AGD-AC measurement was similar in PCOS with and without hirsutism groups (37.7±2.9 vs. 35.3±2.1, p=0.306). In addition, AGD-AS (26.2±1.7 vs. 23±1.1, p=0.156) and AGD-AP (58.4±2.6 vs. 54.4±0.5, p=0.332) measurements were similar in both groups. (**Table 3**).

Table 3. Anogenital distance of pregnant women with PCOS with and without hirsutism

Female	PCOS with hirsutism n=14	PCOS without hirsutism n=7	P
AGD-AF (mm) mean±SD)	20.3±3.5	15.2±1.5	0.041
AGD-AC (mm) (mean±SD)	37.7±2.9	35.3±2.1	0.306
Male	**PCOS with hirsutism n=12**	**PCOS without hirsutism n=9**	
AGD-AS (mm) (mean±SD)	26.2±1.7	23±1.1	0.156
AGD-AP (mm) (mean±SD)	58.4±2.6	54.4±0.5	0.332

Abbreviations: AGD-AF: The distance between the center of the anus and posterior fourchette, AGD-AC: The distance between the center of the anus and the clitoris floor, AGD-AP: The distance between the center of the anus and the posterior base of the penis, AGD-AS: The distance between the center of the anus and back of the scrotum

DISCUSSION

In this study, it was shown that female newborns born to women with PCOS history had higher AGD-AF measurements indicating testosterone exposure. In addition, when the PCOS group is examined within itself, AGD-AF measurement increases significantly in the presence of hirsutism. The findings may indicate the effect of testosterone in female fetuses.

Anogenital distance is accepted as a sensitive indicator of masculization of the external genitalia (11). Maternal androgens pass to the fetus via the placenta, and fetal androgens pass into the maternal circulation in the same way. In previous animal and human studies, it has been shown that maternal administration of androgenic and anti-androgenic agents affects AGD in the fetus (7). In various studies, it has been shown that AGD is shortened in the use of Bisphenol A, Triclosan, and Phthalate (7,12). In one study, females born to high-stress couples had a significantly longer AGD than females born to low-stress couples. In the same study, no significant difference was observed between males (13). All AGDs increase in female or male infants of women exposed to testosterone during pregnancy (14). This has also been supported in animal experiments (15). Based on this situation, Barret et al. (9) in 2018, AGDs of newborns of pregnant women with PCOS were examined. In this study, longer AGD-AF measurements were observed in the daughters of mothers with PCOS compared to the control group. However, AGD-AC measurements of both groups were similar. This result is similar to our study. Male fetuses were not evaluated in this study. Unlike this study, male fetuses were examined in our study and it was found that having a mother with PCOS did not affect AGD. Glintborg et al. (10) analyzed the AGDs of both male and female infants at 3 months born to mothers with PCOS in 2019. There was no effect of being a mother with PCOS on AGD in both female and male infants. In their study, maternal testosterone levels were also examined and maternal testosterone levels (total and free testosterone) were positively associated with AGD-AS and AGD-AP in boys, while AGD measurements in girls were not found to be associated with maternal testosterone levels. We think that the different result in this study (similarity of AGD-AF measurements between groups in female fetuses) may be due to the measurement performed at different times (at the 3rd month), racial differences, and patient selection criteria.

We compared the anogenital distance measurements in the PCOS group by dividing them into two groups according to the presence or absence of hirsutism. To the best of our knowledge, such a comparison has been made for the first time in the literature. The closest to our comparison is Barret et al. (9) in 2018, they compared the AGDs of the isolated hirsutism group (without PCOS), PCOS with hirsutism group and control group. They did not observe a significant AGD difference in the unadjusted analyzes between all three groups. In our study, we observed a significantly higher AGD-AF value in the PCOS with hirsutism group compared to the PCOS without hirsutism group. This difference may be due to testosterone exposure, which is the cause of hirsutism, but this needs to be supported by testosterone measurements.

The AGD is longer in males than females and is routinely used to determine sex (11,16). These lengths are also an indirect indicator of fetal androgen activity. In the study of Fowler et al. (17), AGD was found to be 1.4 times longer in males than females at 11-13 weeks, 1.8 times longer at 14-16 weeks, and twice times longer at 17-20 weeks. However, in the first trimester, when external genital organ differentiation has just begun, the role of these lengths in sex determination is also limited. Salazar-Martinez et al. (3) reported the male/female distance ratio at birth as 1.9, while Sathyanarayana et al. (2015) (18) reported as 1.5. In our study, AGDs of male fetuses were higher in both the PCOS group and the control group, which is consistent with the literature. Also, AGD is associated with varying degrees of birth weight, depending on the population studied (3,19,20). In fact, this correlates with fetal sex as well, because male fetuses are generally heavier than female fetuses.

This study had some limitations. First, we could not measure blood testosterone levels of pregnant women. Other limitation was that the diagnosis of PCOS was based on the patient's questioning in most cases. Our strengths are our prospective projection of single center data on a subject. To the best of our knowledge, this is the first study on this subject in the Turkish population. We also tried to examine a transparent population by excluding IVF pregnancies and pregnancies with drug use. We think that the results of the study will contribute to the literature.

CONCLUSION

The anogenital distance may change in female newborns in the presence of maternal PCOS. Considering that AGD reflects fetal testosterone exposure, the findings may reflect increased testosterone exposure in female fetuses of pregnant women with PCOS. The results pave the way for new studies; as a result of long-term AGD follow-up of newborns born to women with PCOS and lifestyle changes and treatments of PCOS patients, AGD values can be investigated further.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Tepecik SUAM Non-interventional Clinical Researches Ethics Committee (Date: 13.02.2019, Decision No: 2019/2-2).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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