Reproductive Toxicology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Fertility and anogenital distance in women

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ARTICLE INFO

Article history:
Received 29 March 2017
Received in revised form 14 July 2017
Accepted 18 July 2017
Available online xxx

Keywords:
Anogenital distance
Endocrine disrupting agents
Early life exposures

ABSTRACT

Background: Human and animal studies have found an association between prenatal androgen exposure and the anogenital distance (AGD). The aims of this study were to study the association between female AGD, reproductive health and background characteristics.
Methods: This was a cross sectional study, in which AGD were measured in 300 pregnant women who were recruited early during the first stage of labor. Demographic and health characteristics were collected and studied in association with AGD measurements.
Results: AGD presented with normal distribution (mean 40.3 mm ± 10.7) and was positively associated with maternal age (beta = 0.032, 95%CI 0.007–0.05, p = 0.01) and negatively associated with infertility treatments (beta = −1.06, 95%CI −1.99 to −0.12, p = 0.03). AGD was not associated with parity, ethnicity, height and other characteristics.
Conclusions: Adult females AGD is associated with age and fertility problems. Adult female AGD, used as a marker of early life exposure to EDCs, is possibly associated with reproductive characteristics.

1. Background

Both human and animal studies have found anogenital distance (AGD) to be a marker of a feminized or masculinized phenotype [1–4]. AGD is the distance measured between the center of the anus and the posterior or anterior border of the genitalia (AGD from anus to posterior fourchette is marked as AGD_{AF}; and to anterior clitoris AGD_{AC}). AGD is associated with in-utero androgens levels, so that it is sexually dimorphic, with males' AGD measuring longer than females [5–7]. While recent studies have suggested AGD shows plasticity throughout life, this difference between the sexes, which emerges in early gestation during the formation of the genitalia, is considered to remain steady [1,2,8].

Early life is a critical period of development, during which exposures may have a critical effect on the formation and function of the organism throughout its entire life [9]. *In-utero* exposure to synthetic chemicals disrupting the endocrine function (endocrine disrupting chemicals, EDCs), such as phthalates, perfluoroalkyl substances, dioxins and paracetamol, have been associated with AGD's length, mainly in male newborns and infants [10–19].

AGD, as a marker of early life hormonal environment, particularly as a marker of EDC in utero exposure has been identified as one of the endpoints in the US Environmental Protection Agency guidelines for human reproductive toxicity studies (USEPA). Gilboa et al. [20] have published charts of normal male and female fetal AGDs measured via maternal fetal ultrasonic imaging, and most studies focus on AGD in newborns.

AGD measured in newborns was found to be associated with male reproductive health including congenital malformations, semen quality and prostate cancer [21–24]. In females associations were suggested with endometriosis and ovarian function in females [25,26].

2. Objectives

With inconsistent findings regarding in-utero exposures and AGD in females, and the very limited studies on the possible clinical implications in adult females, we aimed to clarify the association between AGD in healthy parturients, and demographic and obstetric characteristics. Additionally, we aimed to study the distribution of AGD in adult females and introduce standards for normal AGD among healthy adult females. Setting these standards will

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http://dx.doi.org/10.1016/j.reprotox.2017.07.009
0890-6238/

Table 1
AGD and Background Characteristics of the Study Population.[a]

	Total N = 300	AGD_{AF}[b]			P
		Short n = 121(40.3)	Intermediate n = 107 (35.7)	Long n = 72 (24.0)	
Age (years), mean ± SD	*26.69 ± 5.26*	25.7 ± 5.01	27.2 ± 5.48	27.7 ± 5.11	0.025
Ethnicity, n (%)					0.35
Jewish	*151(50.3)*	55 (45.5)	56 (52.3)	40 (55.6)	
Bedouin	*149 (49.7)*	66 (54.5)	51 (47.7)	32 (44.4)	
Height (cm), mean ± SD	*160.9 ± 5.92*	161.4 ± 6.0	160.3 ± 5.2	161.0 ± 6.7	0.37
Gestational age (weeks), mean ± SD	*39.34 ± 1.42*	39.45 ± 1.5	39.19 ± 1.28	39.38 ± 1.48	0.37
Birthweight (grams) mean ± SD	*3225 ± 453*	3279 ± 440	3200 ± 430	3292 ± 502	0.33
Parity (n of births), median (range)	*2 (1–15)*	2 (1–15)	2 (1–11)	2.5 (1–14)	0.039
Number of vaginal deliveries, median (range)	*2 (1–13)*	1 (1–13)	2 (1–11)	2 (1–10)	0.06
Newborn Sex, male, n (%)	*149 (5.3)*	56 (47.9)	57 (58.2)	36 (54.5)	0.31
Effacement (cm), mean ± SD	*4.5 ± 1.6*	4.9 ± 1.7	4.6 ± 1.3	4.6 ± 1.7	0.26
Months between pregnancies, median (range)[c]	*24 (5–224)*	24 (5–108)	24 (11–224)	21 (12–120)	0.51
Pregnancy associated hypertension disorder, n (%)	*17 (5.7)*	6 (5.0)	8 (7.5)	3 (4.2)	0.58
Gestational diabetes melitus, n (%)	*14 (4.7)*	2 (1.7)	9 (8.4)	3 (4.2)	0.053
Infertility treatment, n (%)	*5 (1.7)*	4 (3.3)	0 (–)	1 (1.4)	0.15

AGD_{AF}: anogenital distance. Anus fourchette.
[a] Data presented as n (percent), unless stated otherwise.
[b] Short AGD: <39 mm; intermediate: 39–45 mm; long ≥45 mm.
[c] n = 152, non primiparous women.

allow studying effects of different in utero exposures and possibly improve early detection of future morbidity associated with early life exposures.

3. Material and methods

Three hundred pregnant women were recruited to participate in a study evaluating the association between perineal stretching and postpartum perineal integrity in a cross sectional study [27]. All pregnancies were singleton, at term and with cephalic presentation.

The protocol for AGD measurements in the original study is detailed elsewhere [27], and the anatomical landmarks used in the protocol are comparable to those developed by Salazar- Martinez et al. for human AGDAF measurements [6]. All measurements were performed by either one of two physicians, at three time points during delivery. The agreement between the physicians was not evaluated.

Background characteristics and health data were available from the interview performed in the initial study. Infertility treatments were defined as ovulation induction or IVF treatments. Delivery and newborn characteristics were available from the patients' hospital files. We based our analysis on the first measurement which was done upon admission to the labor and delivery ward, during the early active phase of labor.

The statistical analysis was done using SPSS software version 23.0 (IBM, Chicago, Illinois). Frequencies and distribution of AGDs were evaluated. AGD was studies both as a continuous and categorical variables, divided into three categories: short AGD (<39 mm), intermediate (39–45 mm) and long (≥45 mm), based on tertiles. Demographic and obstetric characteristics were compared between AGD categories, using one-way ANOVA, correlations, or chi-square tests. All analyses were two-sided, $p < 0.05$ considered statistically significant.

Variables associated with AGD in the univariable analysis ($p < 0.1$) were suspected as confounders and evaluated in multivariable analysis to test the associations between different maternal characteristics and AGD. This analysis was performed with and without outliers.

The study has been carried out in accordance with the code of ethics of the World Medical Association, and the study protocol was approved by the Soroka University Medical Center (SUMC) IRB committee. All study participants gave informed consent.

Table 2
Mean AGD_{AF} (mm) by main pregnancy and background characteristics.

	Mean AGD length, mm (SD)	P
Gestational Diabetes mellitus, n(%)		
Yes	42.1 (4.6)	0.19
No	40.2 (10.8)	
Fertility treatments, n (%)		
Yes	31.0 (9.3)	0.05
No	40.4 (10.6)	
Ethnicity, n (%)		
Jewish	41.0 (11)	0.22
Bedouin	39.5 (10.2)	

4. Theory

AGD measurements in adult females, as a marker of in-utero hormonal environment, may be associated with general and reproductive health characteristics, and possibly used as a tool for early detection of adverse reproductive health characteristics.

5. Results

Three hundred AGD_{AF} measurements were available. AGD was normally distributed with mean 40.3 mm (±10.7 mm), median 40.0 mm (IQR 32.0–45.0 mm). Characteristics of the total study population and by AGD categories are presented in Table 1.

As can be seen, parturients with shortest vs. longer AGDs were younger, and there was an association between AGD category and parity, gestational diabetes and history of vaginal deliveries. Mean AGD for women with 0, 1, 2, ≥3 previous deliveries were: 3.93 ± 1.1; 3.75 ± 1.0; 4.2 ± 1.1; 4.2 ± 0.8, respectively (p, ANOVA = 0.052).

No correlations were found between AGD and most characteristics, besides a positive correlation with maternal age ($r_{pearson} = 0.149$, $p = 0.01$). AGD by maternal age is presented in Fig. 1.

A linear regression yield a statistically significant beta of 0.03 (95%CI 0.007–0.053) between age and AGD.

Table 2 presents mean AGD by selected pregnancy, obstetric and demographic characteristics. No differences were found in mean AGD between women with and without GDM or by different ethnicity. Women who received fertility treatments had shorter AGD as compared with women who conceived spontaneously.

Several multivariable linear regression models were used to independently evaluate the association between AGD and maternal characteristics, including: maternal age, height, fertility treat-

Please cite this article in press as: T. Wainstock, et al., Fertility and anogenital distance in women, Reprod Toxicol (2017), http://dx.doi.org/10.1016/j.reprotox.2017.07.009