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Anogenital distance of women in relation to their mother's gynaecological characteristics before or during pregnancy

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Abstract Animal models suggest that anogenital distance (AGD) at birth reflects androgen concentrations during in-utero development and predicts adult AGD. Several human observational studies show an association between menstrual cycle irregularities and a hyperandrogenic environment and that may result in a potential alteration of the female reproductive tract during in-utero development. This study examined associations between AGD of young women and their mother's gynaecological characteristics before or during pregnancy. This is cross-sectional study of 100 college-age volunteers in southern Spain. Physical and gynaecological examinations were conducted on the young women and their mothers completed epidemiological questionnaires on lifestyles and gynaecological history. Linear regression analysis was used to examine the association between AGD measurements (anus-four-chette (AGD_{AF}) and anus-clitoris (AGD_{AC})) of women and their mother's gynaecological characteristics. Longer AGD_{AF} was associated with the presence of mother's menstrual cycle irregularities before pregnancy (P = 0.03). Longer female AGD has been related to excess androgen exposure *in utero* in toxicological studies. The current findings may be consistent with studies in which an association between menstrual cycle irregularities and an hyperandrogenic environment has been reported, which therefore may result in a potential modification of the female offspring's reproductive tract during in-utero development, including AGD.

KEYWORDS: androgens, anogenital distance, irregular cycles, prenatal exposure, reproductive tract, women

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Introduction

Anogenital distance (AGD) is a sexually dimorphic trait in placental mammals (Greenham and Greenham, 1977; Kurzrock et al., 2000; Salazar-Martinez et al., 2004; Sathyanarayana et al., 2010; Swan, 2008; Thankamony et al., 2009). AGD is androgen dependent and about twice as long in males as in females (Macleod et al., 2010; Salazar-Martinez et al., 2004; Scott et al., 2008; Swan, 2008; Thankamony et al., 2009). Rodent studies have shown that AGD is determined *in utero* and persists during adulthood (Hotchkiss et al., 2004).

On the other hand, several animal studies have shown that the female reproductive tract is susceptible to virilization by exogenous androgen exposure prior to, as well as during, the in-utero masculinization programming window (Dean et al., 2012; Wolf et al., 2002; Wu et al., 2010). As Wu et al. (2010) showed, prenatal exposure of females to exogenous androgens results in longer and more masculine AGD. Therefore, AGD can be used as a sensitive biomarker of exposure to androgens or antiandrogens (mainly phthalate esters) during in-utero development (Foster, 2006; McIntyre et al., 2001; Saillenfait et al., 2009; Wolf et al., 2004). In humans, there are a few observational studies that support these findings, both in baby boys (Swan, 2008; Swan et al., 2005) and girls (Huang et al., 2009).

Less is known about AGD in human females, but there are several published articles of virilization of the lower urogenital tract after either prenatal endogenous or exogenous exposure to androgenic hormones (Callegari et al., 1987; Goldman and Bongiovanni, 1967). For example, a number of studies have suggested that several characteristics of the mother during or prior to a pregnancy, such as polycystic ovary syndrome, may result in fetal exposure to high concentrations of circulating androgens (Sir-Petermann et al., 2002). Recently, Mendiola et al. (2012) reported a positive association between AGD measures and the presence of greater ovarian follicular number in young women, suggesting that the androgenic environment during early fetal life may influence the reproductive system development, including AGD. The aim of this study was to explore the relationship between AGD of young women and their mother's gynaecological characteristics before or during pregnancy, as indirect markers of hormonal environment during their in-utero development.

Materials and methods

Study population

Briefly, as described by Mendiola et al. (2012), the Murcia Young Women's Study (MYWS) is a cross-sectional study of healthy young university students (18–23 years old) in the Spanish region of Murcia. MYWS was carried out between 9 February 2011 and 25 November 2011. Out of 124 students who contacted the study, 109 met eligibility criteria and 100 attended the clinical appointment. At a scheduled clinic visit, subjects underwent a gynaecological examination in the early follicular phase, including a transvaginal ultrasound. Both the young participants and their mothers completed an epidemiological questionnaire on lifestyles and gynaecological history. Participants were compensated for their participation (ϵ 40 gift card). Written informed consent was obtained from all subjects. The Research Ethics Committee of the University of Murcia approved this study (no. 495/2010, approved 14 May 2010).

Physical examination and gynaecological history

Body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres. In addition, for each subject two variants of anogenital measurement were taken: anus-clitoris (AGD_{AC}) and anus-fourchette (AGD_{AF}) (Figure 1). To improve precision, two examiners made each of these measurements three times, taking in total six measures for each of AGD_{AF} and AGD_{AC} . The mean of the six measurements was used as the estimate. Moreover, a complete gynaecological history was obtained from each subject, including history of gynaecological diseases (salpingitis, endometriosis, other) (yes/no), self-reported menstrual cycle length (days) and previous irregular menstrual cycles (yes/no).

Maternal questionnaire

The questionnaire was sent to the university students' mothers' address, provided by the participants on the day of the clinic appointment. Of 100 questionnaires mailed to the young women's mothers, a response was obtained from 75 of them (75%). The questionnaire collected information on gynaecological diseases (salpingitis, endometriosis, polycystic ovaries, etc.) (yes/no) and diagnosis of irregular menstrual cycles (yes/no) before getting pregnant with their daughters. Information was also obtained on complications during pregnancy (hypertension, diabetes, pre-eclampsia, threatened abortion, etc.) (yes/no) and smoking during pregnancy (yes/no). Moreover, this work included a variable reflecting the number of stressful life events during preg-

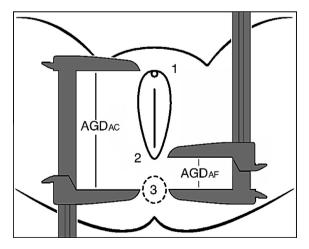


Figure 1 Landmarks for two measurements of anogenital distance: AGD_{AC} , from the anterior clitoral surface to the centre of the anus (point 1 to point 3); and AGD_{AF} , from the posterior fourchette to the centre of the anus (point 2 to point 3). Adapted with permission from Sathyanarayana et al. (2010).

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