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Investigation of anogenital distance as a diagnostic tool in endometriosis

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KEY MESSAGE

An association between endometriosis, an oestrogen-dependent disease and anogenital distance, a biomarker of the prenatal hormonal milieu has been reported, supporting a potential intrauterine cause for this condition. This is the first study reporting that anogenital distance could be used as a diagnostic tool in endometriosis, especially deep infiltrating endometriosis.

A B S T R A C T

An association between anogenital distance (AGD) and endometriosis has been reported, suggesting that AGD may be a useful clinical tool in endometriosis. The predictive ability of AGD of women in discriminating presence and type of endometriosis was examined. A case-control study was conducted at the University Hospital 'Virgen de la Arrixaca', Murcia, Spain, between 2014 and 2015. A total of 114 participants diagnosed with endometriosis using ultrasound findings and 105 controls were recruited. Two AGD measurements were obtained: one from the anterior clitoral surface to the upper verge of the anus (AGD_{AC}), and another one from the posterior fourchette to the upper verge of the anus (AGD_{AF}). Parametric and non-parametric tests and

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receiver operator characterstic analyses were used to determine relationships between AGD and presence of endometriosis and subgroups (ovarian endometriomas or deep infiltrating endometriosis [DIE]). The AGD_{AF}, but not AGD_{AC}, was associated with presence of endometriomas, DIE (*P*-values, <0.001–0.02), or both. The highest area under curve (0.91; 95% CI 0.84 to 0.97) was obtained for the DIE subgroup with the AGD_{AF} measurement, with a sensitivity and specificity of 84.4% and 91.4%, respectively. AGD_{AF} can therefore efficiently discriminate the presence of DIE and may be a useful clinical tool.

Introduction

Anogenital distance (AGD) is a sexually dimorphic feature in placental mammals, almost twice longer in males than in females (Greenham and Greenham, 1977; Kurzrock et al., 2000). Human observational studies have shown that girls have shorter AGD than boys (Salazar-Martinez et al., 2004; Thankamony et al., 2009; Torres-Sanchez et al., 2008). In experimental models, AGD at birth reflects hormonal exposure during prenatal life and predicts AGD in adulthood (Dean et al., 2012; Hotchkiss et al., 2004; Macleod et al., 2010; Wolf et al., 2002; Wu et al., 2010). In animals, it is well established that more androgens results in longer AGD. Similarly, studies in human males have shown that association. Exposure to antiandrogens results in shorter (more feminine) AGD in infant males (Swan et al., 2005, 2015). The link between higher oestrogens exposure *intra utero* and shorter AGD (which would be our model here) has been reported by our group recently (Mendiola et al., 2016), and as far as we know has not yet been explored in other adult human studies. Evidence from animal models (Boberg et al., 2013; Christiansen et al., 2014) and human studies, however, have shown that maternal exposure to xenoestrogen substances, i.e. bisphenol A, phytoestrogens and monobutyl phthalate, reduces AGD in newborn females (Huang et al., 2009). Therefore, we hypothesized that AGD length is modulated by the intrauterine hormonal androgen–oestrogen environmental milieu, and, consequently, it may be used as a surrogate and reliable biomarker of that prenatal hormonal environment.

Endometriosis is a prevalent chronic oestrogen-dependent disease characterized by the presence of endometrial glands and stroma outside the uterus cavity (Vercellini et al., 2014). Different types of endometriosis include endometriotic cyst (endometriomas) and deep infiltrating endometriosis (DIE) (Vercellini et al., 2014). Clinical manifestations include pain (chronic pelvic pain, dysmenorrhoea, dyspareunia) and infertility (Denny and Mann, 2007; Mahmood et al., 1991). Pain may be incapacitating (Jones et al., 2004), especially in DIE cases. Although the cause of endometriosis remains unknown, an intrauterine origin (Signorile et al., 2010, 2012) and the role of early-life influences (such as hormonal environmental exposure to oestrogens in uterus) are receiving increasing consideration as a risk factor for endometriosis in adulthood (Buck Louis et al., 2007, 2013; Ferrero et al., 2014; Hediger et al., 2005; Mendiola et al., 2016; Rizner, 2009; Somigliana et al., 2011; Vannuccini et al., 2016; Wolff et al., 2013). Increased rate of endometriosis was described in women prenatally exposed to diethylstilbestrol (Missmer et al., 2004). Exposure to these oestrogenic and antiandrogen compounds later in life, in adulthood, may also lead to the establishment of endometriosis by enhancing invasive and proliferative activities of endometrial cells (Kim et al., 2015). Upson et al. (2013a, 2013b, 2014) reported several significant associations between environmental endocrine disruptors compounds (phthalates, organochlorine pesticides or bisphenol A) and endometriosis risk. The development of the uterine endometrial gland begins *in utero* and is completed in puberty (Gray et al., 2001). Early hormonal signalling disruptions may result in altered morphology and function from very early on.

The AGD is known to be a reliable biomarker of the prenatal hormonal environment, and a strong association has been recently reported shorter between AGD and the presence of endometriomas, DIE, or both, in women (Mendiola et al., 2016). The aim of this work is to communicate the predictive ability of AGD measurements to discriminate presence of endometriosis (endometriomas, DIE, or both).

Materials and methods

Study population

A case-control study was conducted between September 2014 and May 2015 in the Department of Obstetrics and Gynecology of the University Hospital 'Virgen de la Arrixaca' in Murcia (Spain). The study population were premenopausal women aged between 18 and 50 years, who were not pregnant, after oncological treatment or had genitourinary prolapse. Cases (*n* = 114) included prevalent and newly diagnosed endometriosis illnesses in women attending the Endometriosis Unit of the Hospital. The diagnoses were established by medical history and confirmed by transvaginal ultrasounds (TVUS) of endometriotic cyst (endometriomas) or deep infiltrating endometriosis (DIE) (Abrao et al., 2007; Hsu et al., 2010; Johnson et al., 2013; Somigliana et al., 2010; Vercellini et al., 2014). The definition of DIE was endometriosis infiltrating the peritoneum by more than 5 mm. Therefore, women with endometriosis were further classified as endometriomas (*n* = 82) and DIE (*n* = 32) using symptoms, signs and ultrasound findings. Thirty-six per cent of the cases with suspected malignant adnexal masses or incapacitating physical symptoms, despite treatment with contraceptives or GnRH analogues, had endometriosis surgery in our study.

Endometriosis can only be definitively diagnosed by surgery; however, as it is not ethical to screen a population with surgery, studies of prevalence and of risk factors have been based only on clinically diagnosed cases (Eskenazi et al., 2001). Controls (*n* = 105) were women without endometriosis attending the gynaecological outpatient clinic for routine exams. Nine controls reported clinical symptoms compatible with endometriosis but the diagnoses were not confirmed by TVUS and were included in the study. Written informed consent was obtained from all participants. This study was approved by the Ethics Research Committee of the University of Murcia on 25 May 2016.

Gynaecological history and physical examination

Cases and controls were interviewed in person by gynaecologists. Two gynaecologists using the same methodology carried out all the clinical evaluations. All participants completed health questionnaires,

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