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Anogenital distance and Gynaecological diseases: a narrative review

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ABSTRACT

Anogenital distance (AGD) (i.e. the distance measured from the anus to the genital tubercle) is an androgen-dependent, dimorphic feature, which is dependent on the *in-utero* hormonal environment. Human studies have shown alterations in the AGD associated with reproductive health in adult individuals, both males and females. In particular, recent studies have investigated whether differences in AGD length could be associated with gynaecological diseases, such as endometriosis and polycystic ovary syndrome (PCOS), as in these conditions prenatal hormonal exposure could represent a risk factor for developing the disease later in life. In this narrative review, we aimed to review the most updated scientific evidence on the relation between AGD and the presence of endometriosis and PCOS. Studies suggest that a shorter AGD seems to be related to the presence of endometriosis, whereas a longer AGD seems to be associated with an increased risk of PCOS. In light of these findings, we discuss how AGD measurement in adult women could represent a novel, simple, and easily reproducible biomarker of endometriosis and PCOS. However, scientific evidence is limited, and further well-designed studies are needed to corroborate current findings.

SOMMARIO

La distanza anogenitale (AGD) (ovvero la distanza misurata dall'ano al tubercolo genitale) è una caratteristica corporea androgeno-dipendente, che risente dell'esposizione ormonale intrauterina. Studi sull'uomo hanno evidenziato che alterazioni della AGD possono essere associate a malattie dell'apparato riproduttivo, sia negli uomini che nelle donne. In particolare, studi recenti suggeriscono una correlazione tra differenze nella lunghezza della AGD e presenza di patologie ginecologiche, come l'endometriosi e la sindrome dell'ovaio policistico (PCOS). In queste condizioni, infatti, l'esposizione ormonale prenatale (in particolare a ormoni steroidei) può rappresentare un fattore di rischio per lo sviluppo della malattia in età adulta. In questa review narrativa della letteratura vengono riportate le più attuali evidenze sulla relazione tra AGD e la presenza di endometriosi e PCOS. I risultati degli studi a disposizione suggeriscono che una AGD più corta possa essere correlata alla presenza di endometriosi, mentre una AGD più lunga ad un aumentato rischio di PCOS. Alla luce di questi risultati viene discusso il ruolo della misurazione dell'AGD in donne adulte, quale potenziale biomarker (semplice e facilmente riproducibile) di endometriosi e PCOS. Tuttavia, le evidenze scientifiche a disposizione appaiono insufficienti, e sono necessari studi per confermare i limitati risultati attuali.

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INTRODUCTION

Anogenital distance (AGD) is a sexually, androgen-dependent, dimorphic feature that represents the distance measured from the anus to the genital tubercle (1). There is considerable evidence in animal and human models that AGD represents a biomarker of the prenatal hormonal environment (2,3). During the prenatal and early human life, the endocrine system is involved in the formation and ensuring proper function of various systems, including the reproductive system, which is highly sensitive to steroids hormones. In males, the development of the reproductive system depends on *in-utero* androgen exposure, whereas in females on lack of androgen (4).

AGD has been shown to depend on androgen exposure, and it is approximately 50–100% longer in human males compared to females (5). In addition, observational studies suggest that AGD is one of the most sensitive biomarkers of in utero exposure to endocrine-disrupting chemicals, defined as an exogenous substance that alters functions of the endocrine system (6,7).

In rodents, AGD has been demonstrated to reflect the extent of androgen to which the female foetus is exposed during early in utero development. Thus, prenatal exposure of females to exogenous androgens ends in longer and more masculine AGD (8-10). Human studies have shown alterations in AGD associated with reproductive health. For instance, significantly shorter AGD has been reported in male with cryptorchidism and hypospadias (11-13), and in men with poorer semen quality (14) and reduced testicular volume (15) compared with controls.

Recent studies have investigated whether differences in AGD length could be associated with gynaecological diseases, such as endometriosis and polycystic ovary syndrome (PCOS). In fact, in both conditions, prenatal hormonal exposure could represent a risk factor for developing the disease later in life. In this narrative review, we aimed to review the most updated evidence, which suggests a link between AGD and the development of benign gynaecological diseases, such as endometriosis and PCOS.

AGD AND ENDOMETRIOSIS

Endometriosis is an estrogen-dependent chronic inflammatory gynaecological disorder associated with pelvic pain symptoms and infertility (16), defined by histological lesions caused by the growth of endometrial-like tissue outside of the uterine cavity. Endometriosis affects about 5% of women of reproductive age (17). Endometriosis lesions could be schematically subdivided in peritoneal implants, ovarian endometrioma, deep infiltrating nodules or plaques, and extra-pelvic localizations (17). In the majority of the patients, pain can be managed via pharmacological inhibition of ovulation and menstruation (16,17), however, in some cases, a surgical approach should be considered, in particular in women with deep infiltrating forms (18,19).

The exact etiopathogenetic origin of the disease is still to be defined. The most widely accepted hypothesis is represented by the retrograde menstruation theory, characterised by the backward flux of menstrual debris that contains viable endometrial cells through the fallopian tubes into the pelvic cavity (20). However, some authors suggest an intrauterine origin of the disease (21,22), and the potential role of early-life influences, such as intrauterine hormonal environmental exposure to oestrogens or anti-androgens, are receiving growing consideration as a risk factor for endometriosis in adult life (23-29). In addition, accumulating evidence suggests that immune cells, adhesion molecules, extracellular matrix metalloproteinase and pro-inflammatory cytokines activate/alter peritoneal microenvironment, creating the conditions for differentiation, adhesion, proliferation, and survival of ectopic endometrial cells (30,31). Finally, a recent review (32) evaluated the potentially pivotal role of ion channel, in particular CFTR, AQPs, and ClC-3, in the etiopathogenesis of endometriosis.

As regards to the association between AGD and endometriosis, the hypothesis is that a prenatal estrogenic environment will result in a relatively shorter AGD, which may represent an indirect marker of higher risk of having endometriosis or developing endometriosis later in life.

In 2016, a Spanish control-study (1) assessed the relations between AGD measurements and the presence of endometriomas (OMA) and deep infiltrating endometriosis (DIE) in adult women. The investigators measured both AGD_{AC} (i.e., the distance from the anterior clitoral surface to the upper verge of the anus) and AGD_{AF} (i.e., the distance from the posterior fourchette to the upper verge of the anus) (**figure 1**). A total of 114 women with endometriosis (n = 82 with OMA; n = 32 with DIE) and 105 controls have been enrolled. AGD_{AF}, rather than AGD_{AC}, was associated with

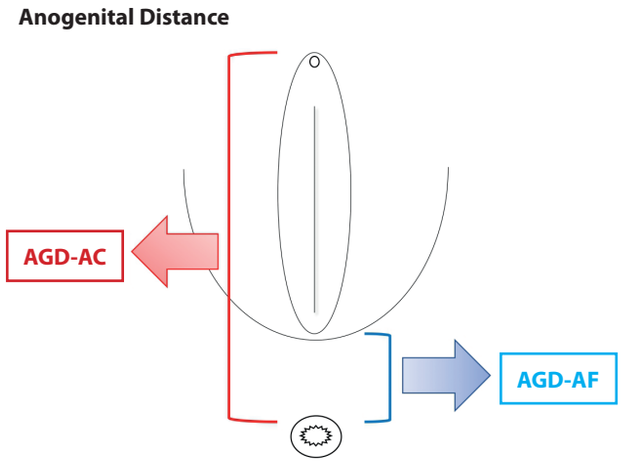

Figure 1. *Landmarks for two measurements of anogenital distance (AGD): AGD_{AC} from the posterior fourchette to the upper verge of the anus (right).*

the presence of endometriomas and/or DIE. Considering the whole endometriosis group (n = 114), women in the lowest tertile of the AGD_{AF} distribution, compared with the upper tertile, were 7.6-times (95% CI 2.8–21.0; P-trend <0.001) more likely to have endometriosis. Among women with DIE, those with AGD_{AF} below the median, compared with those with AGD_{AF} above the median, were 41.6-times (95% CI 3.9–438; P-value = 0.002) more likely to have endometriosis. These results are in line with those of another Spanish unmatched control-study (33). Women with endometriosis had a significantly shorter AGD_{AF} compared to controls (23.5 mm [5.8] versus 27.3 [5.7]; P <0.001).

In 2018, the same Spanish group (34) assessed the predictive ability of a combination of AGD and anti-Müllerian hormone (AMH) to diagnose the presence of endometriosis without surgery. A total of 57 women with endometriosis (n = 45 with OMA; n = 12 with DIE) and 93 controls were recruited. Women with endometriosis had significantly shorter AGD_{AF} (22.8 ± 4.6 vs 27.2 ± 5.7 mm; P<0.001) and lower AMH levels (2.2 ± 2.5 vs 3.3 ± 1.9 ng/mL; P=0.003). Women with serum AMH below the clinical cut-off (1 ng/mL) were 17.40-times more likely to have the disease (95% CI 5.64–53.82). The area under the ROC curve of combined AMH and AGD_{AF} was 0.77 (95% CI 0.70–0.85). The authors concluded that AGD_{AF} and serum AMH levels could be combined in a non–invasive model to predict endometriosis.

These results indicate a possible association between AGD_{AF} and presence of endometriomas and DIE, suggesting that the intrauterine hormonal milieu during prenatal life may play a central role in the development of the disease.

AGD AND POLYCYSTIC OVARY SYNDROME

PCOS is one of the most common endocrine and reproductive disorders in reproductive age, with an estimated prevalence of 5-10% of women. However, the exact pathophysiology of this disease is still unclear. It has been proposed that environmental factors, such as excessive in utero androgen exposure, may play a fundamental role in the development of the disease (35). In fact, androgen excess is present in around 70% of women with a diagnosed PCOS (36). Moreover, clinical observations also support a potential foetal origin of PCOS. Women with foetal androgen excess disorders, including congenital adrenal hyperplasia or congenital adrenal virilising tumours, have an augmented incidence of PCOS during adulthood, despite the normalisation of androgen levels with treatment or removal of the neoplasia after birth (37-39).

Characteristics of the studies that analysed the association between AGD and PCOS are summarized in **table I**. The potential association between AGD and PCOS was firstly evaluated by Wu *et al*. (40) in a case-control study of 156 women with PCOS and 180 reproductively healthy women. In all patients, both AGD_{AF} and AGD_{AC} were measured. The authors demonstrated an association between longer AGD, in particular AGD_{AF}, and the presence of PCOS. In particular, women with AGD_{AF} in the highest tertile were 18.8 times (95% CI 9.6–36.6; P < 0.001) more likely to have PCOS compared with those in the lowest tertile. Women with AGD_{AC} in the highest tertile were 6.7 times (95% CI 3.7–12.1; P < 0.001) more likely to have PCOS than those in the lowest tertile. In addition, the authors collected blood samples in order to analyse total testosterone, FSH and LH levels in all participants. In the PCOS group, multiple linear regression analyses revealed that both AGD measures were positively associated with total testosterone levels (β = 0.246 for AGD_{AC}, β = 0.368 for AGD_{AF}; P = 0.003 and P < 0.001, respectively).

Another case-control study (41) confirmed the presence of longer AGD in Mediterranean women with PCOS. In this study, 285 women (n = 126 women with PCOS; n = 159 controls) were recruited. In bivariate analyses, women with PCOS showed significantly longer AGD_{AF} (27.8 versus

Table 1. *Studies evaluating anogenital distance (AGD) in women with polycystic ovary syndrome (PCOS).*

Source	Country	Study design	Number of patients enrolled	AGDAF and AGDAC (mm)	Outcomes
Wu *et al*., 2017 (40)	China	Case-control	336 (PCOS *n* = 156; controls *n* = 180)	AGD_{AF}: PCOS: 26.6 ± 4.0 Controls: 22.0 ± 3.7 AGD_{AC}: PCOS: 104.9 ± 9.1 Controls: 97.1 ± 9.4	Longer AGD was related to the presence of PCOS. In particular, women with AGD_{AF} in the highest tertile were 18.8 times (95% CI 9.6–36.6; P < 0.001) more likely to have PCOS compared with those in the lowest tertile. Women with AGD_{AC} in the highest tertile were 6.7 times (95% CI 3.7–12.1; P < 0.001) more likely to have PCOS than those in the lowest tertile.
Sanchez-Ferrer *et al*., 2017 (41)	Spain	Case-control	285 (PCOS *n* = 126; controls *n* = 159)	AGD_{AF}: PCOS: 27.8 ± 5.6 Controls: 26.5 ± 5.1 AGD_{AC}: PCOS: 80.5 ± 11.3 Controls: 76.0 ± 10.4	Women with PCOS showed significantly longer AGD_{AF} and AGD_{AC} compared to controls in bivariate analyses (P < 0.05).
Hernández-Peñalver *et al*., 2018 (42)	Spain	Case-control	285 (PCOS *n* = 126; controls *n* = 159)	AGD_{AF}: PCOS: 27.8 ± 5.6 Controls: 26.5 ± 5.1 AGD_{AC}: PCOS: 80.5 ± 11.3 Controls: 76.0 ± 10.4	Women with PCOS showed significantly longer AGD than controls.
Simsir *et al.*, 2019 (35)	Turkey	Prospective cohort study	130 (PCOS *n* = 65; controls *n* = 65)	AGD_{AF}: PCOS: 23.0 ± 6.0 Controls: 21.0 ± 5.0 AGD_{AC}: PCOS: 101.0 ± 12.0 Controls: 98.0 ± 17.0 Ratio $AGD_{AC/AF}$ PCOS 4.4 ± 1.0 Controls 4.9 ± 1.0	No statistically significant differences in AGD_{AF} and AGD_{AC} measurements, although both measurements were longer in the PCOS group. The strongest predictor of PCOS is the ratio of AGD_{AC} and AGD_{AF}.

26.5 mm; $P = 0.048$) and AGD_{AC} (80.5 versus 76.0 mm; $P = 0.001$) compared to controls. The authors further analysed data in tertiles and ORs, and in the final adjusted models, only AGD_{AC} was associated with the presence of PCOS (P 0.002–0.008). Women with AGD_{AC} in the upper versus the lowest tertile were 2.9-times more likely to have PCOS (95% CI 1.4–5.9; P, trend = 0.008). The correlation between AGD_{AC} and PCOS was also demonstrated in another Spanish case-control study (42).

A recent prospective cohort study (35) of 130 Turkish women (n = 65 women with PCOS; n = 65 healthy controls) investigated the possible association between AGD and the presence of the disease. Unlike previous studies, Simsir *et al.* (35) also calculated the AGD Ratio (AGD_{AC}/AGD_{AF}). No statistically significant differences were found in AGD_{AF} and AGD_{AC} measurements, although both measures were longer in the PCOS group. However, the mean ratio of AGD_{AC} to AGD_{AF} for the PCOS and control group were 4.4 ± 1.0 and 4.9 ± 1.0, respectively ($P = 0.003$). Regression analysis demonstrated that this ratio positively correlates with the waist to hip ratio and negatively correlate with the free androgen index. The authors suggested the use of AGD $Ratio_{AC/AF}$ instead of single measurements as a novel biomarker for PCOS.

A recent interesting Danish study (43) evaluated whether the presence of higher testosterone levels during pregnancy in women with PCOS is associated with longer offspring AGD. The study population included 139 mothers with PCOS and 1422 controls. Surprisingly, AGD measures were comparable in offspring of women with PCOS compared with controls, despite significantly higher maternal levels of total testosterone and free testosterone in women with the disease versus controls (both P <0.001). The authors suggested that longer AGD in adult women with PCOS could be the result of increased testosterone levels in puberty, perhaps in combination with weight gain. However, these results are not in line with previous finding. In 2018, Barrett *et al*. (44) reported that new-born girls of mothers with PCOS have a longer AGD than daughters born to women without PCOS, and the authors suggest that a longer AGD may be related to the presence of elevated exposure to intrauterine testosterone.

DISCUSSION AND CONCLUSION

In recent years, AGD measurement in adult women has been receiving a growing amount of interests, due to its potential role as a novel, simple, and easily reproducible biomarker of different gynaecological diseases, such as endometriosis and PCOS.

Regarding endometriosis, shorter AGD_{AF} seems to be related with the presence of endometriosis. However, we have to underline that all the available evidence derives from the same Spanish study group (1,33,34). Moreover, in all these case-control studies, women were not matched for age, BMI, and parity. Ideally, only nulliparous women should be included in order to avoid any bias related to changes in external genital anatomy after vaginal delivery and episiotomy. The authors suggested an association between shorter AGD_{AF} and higher endometriosis risk, especially in case of deep infiltrating forms (1,33,34). As previously explained, prenatal exposure to androgens results in a longer AGD, whereas a prenatal estrogenic environment in a shorter one. Hypothetically, a shorter AGD, reflecting the intrauterine hormonal milieu, could represent an indicator of the presence of endometriosis and could suggest that endometriosis, especially deep infiltrating forms, might have a prenatal origin. However, studies investigating AGD in affected women are scanty, and further research from different study groups is needed to confirm the potential role of AGD as a biomarker of endometriosis.

Regarding PCOS, the strength of association between a longer AGD and the presence of the disease seems more reliable. Data derived from different study groups and the potential role of androgen in the pathophysiology of the disease has strong foundations. However, a recent Danish study (43) did not find an association between higher maternal testosterone levels and longer AGD in the offspring, questioning the impact of prenatal hormonal exposure on AGD length.

In conclusion, AGD could represent a cheap and easily reproducible biomarker of different gynaecological diseases, however further well-designed studies are needed to corroborate current findings.

CONFLICT OF INTERESTS

All the authors declare that they have no conflicts of interest.

REFERENCES

1. Mendiola J, Sánchez-Ferrer ML, Jiménez-Velázquez R, Cánovas-López L, Hernández-Peñalver AI, Corbalán-Biyang S, et al. Endometriomas and deep infiltrating endometriosis in adulthood are strongly associated with anogenital distance, a biomarker for prenatal hormonal environment. Hum Reprod. 2016;31(10):2377-83. doi: 10.1093/humrep/dew163.
2. Greenham LW, Greenham V. Sexing mouse pups. Lab Anim 1977;11:181–4.
3. Kurzrock EA, Jegatheesan P, Cunha GR, Baskin LS. Urethral development in the fetal rabbit and induction of hypospadias: a model for human development. J Urol 2000;164:1786–92.
4. Yamada G, Satoh Y, Baskin LS, Cunha GR. Cellular and molecular mechanisms of development of the external genitalia. Differentiation 2003;71(8):445-60.
5. Dean A, Sharpe RM. Clinical review: Anogenital distance or digit length ratio as measures of fetal androgen exposure: relationship to male reproductive development and its disorders. J Clin Endocrinol Metab. 2013;98(6):2230-8.
6. Bornehag CG, Carlstedt F, Jo¨nsson BA, Lindh CH, Jensen TK, Bodin A, et al. Prenatal phthalate exposures and anogenital distance in Swedish boys. Environ Health Perspect 2015;123:101–7.
7. Swan SH, Sathyanarayana S, Barrett ES, Janssen S, Liu F, Nguyen RH, Redmon JB, TIDES Study Team. First trimester phthalate exposure and anogenital distance in newborns. Hum Reprod 2015;30:963–72.
8. Wolf CJ, Hotchkiss A, Ostby JS, LeBlanc GA, Gray LE Jr. Effects of prenatal testosterone propionate on the sexual development of male and female rats: a dose–response study. Toxicol Sci 2002, 65:71–86.
9. Dean A, Smith LB, Macpherson S, Sharpe RM. The effect of dihydrotestosterone exposure during or prior to the masculinization programming window on reproductive development in male and female rats. Int J Androl 2012, 35:330–9.
10. Wu XY, Li ZL, Wu CY, Liu YM, Lin H, Wang SH, et al. Endocrine traits of polycystic ovary syndrome in prenatally androgenized female Sprague-Dawley rats. Endocr J 2010, 57:201–9.
11. Hsieh MH, Breyer BN, Eisenberg ML, Baskin LS. Associations among hypospadias, cryptorchidism, anogenital distance, and endocrine disruption. Curr Urol Rep. 2008; 9:137–42.
12. Hsieh MH, Eisenberg ML, Hittelman AB, Wilson JM, Tasian GE, Baskin LS. Caucasian male infants and boys with hypospadias exhibit reduced anogenital distance. Hum Reprod. 2012; 27:1577–80.
13. Thankamony A, Lek N, Carroll D, Williams M, Dunger DB, Acerini CL, et al. Anogenital distance and penile length in infants with hypospadias or cryptorchidism: comparison with normative data. Environ Health Perspect. 2014;122:207–11.
14. Eisenberg ML, Hsieh MH, Walters RC, Krasnow R, Lipshultz LI. The relationship between anogenital distance, fatherhood, and fertility in adult men. PLoS One. 2011;6(5):e18973.
15. Eisenberg ML, Shy M, Walters RC, Lipshultz LI. The relationship between anogenital distance and azoospermia in adult men. Int J Androl. 2012;35(5):726-30.
16. Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril. 2016 Dec;106(7):1552-71.e2.
17. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014 May;10(5):261-75.
18. Laganà AS, Vitale SG, Trovato MA, Palmara VI, Rapisarda AM, Granese R, et al. Full-Thickness Excision versus Shaving by Laparoscopy for Intestinal Deep Infiltrating Endometriosis: Rationale and Potential Treatment Options. Biomed Res Int 2016;3617179.
19. Raffaelli R, Garzon S, Baggio S, Genna M, Pomini P, Laganà AS, et al. Mesenteric vascular and nerve sparing surgery in laparoscopic segmental intestinal resection for deep infiltrating endometriosis. Eur J Obstet Gynecol Reprod Biol. 2018;231:214-19.
20. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. Nat Rev Dis Primers. 2018 Jul 19;4(1):9. doi: 10.1038/s41572-018-0008-5.
21. Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Boccellino M, et al. New evidence of the presence of endometriosis in the human fetus. Reprod Biomed Online 2010;21:142–7.
22. Signorile PG, Baldi F, Bussani R, Viceconte R, Bulzomi P, D'Armiento M, et al. Embryologic

origin of endometriosis: analysis of 101 human female fetuses. J Cell Physiol 2012;227:1653–56.
23. Buck Louis GM, Hediger ML, Pena JB. Intrauterine exposures and risk of endometriosis. Hum Reprod 2007;22:3232–6.
24. Rizner TL. Estrogen metabolism and action in endometriosis. Mol Cel Endocrinol. 2009;307(1-2):8-18. doi: 10.1016/j.mce.2009.03.022.
25. Somigliana E, Vigano P, Abbiati A, Paffoni A, Benaglia L, Vercellini P, et al. Perinatal environment and endometriosis. Gynecol Obstet Invest 2011;72:135–40.
26. Buck Louis GM, Peterson CM, Chen Z, Croughan M, Sundaram R, Stanford J, et al. Bisphenol A and phthalates and endometriosis: the Endometriosis: Natural History, Diagnosis and Outcomes Study. Fertil Steril. 2013;100(1):162-9.e1-2.
27. Wolff EF, Sun L, Hediger ML, Sundaram R, Peterson CM, Chen Z, et al. In utero exposures and endometriosis: the Endometriosis, Natural History, Disease, Outcome (ENDO) Study. Fertil Steril. 2013 Mar 1;99(3):790-5.
28. Vannuccini S, Lazzeri L, Orlandini C, Tosti C, Clifton VL, Petraglia F. Potential influence of in utero and early neonatal exposures on the later development of endometriosis. Fertil Steril. 2016;105(4):997-1002..
29. García-Peñarrubia P, Ruiz-Alcaraz AJ, Martínez-Esparza M, Marín P, Machado-Linde F. Hypothetical roadmap towards endometriosis: prenatal endocrine-disrupting chemical pollutant exposure, anogenital distance, gut-genital microbiota and subclinical infections. Hum Reprod Update. 2020 Feb 28. pii: dmz044. doi: 10.1093/humupd/dmz044.
30. Laganà AS, Garzon S, Gotte M, Vigano P, Franchi M, Ghezzi F, et al. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. Int J Mol Sci 2019;20(22).
31. Laganà AS, Salmeri FM, Ben Frangez H, Ghezzi F, Vrtacnik-Bokal E, Granese R. Evaluation of M1 and M2 macrophages in ovarian endometriomas from women affected by endometriosis at different stages of the disease. Gynecol Endocrinol 2019; Oct 30:1-4. doi: 10.1080/09513590.2019.1683821. [Epub ahead of print].
32. Riemma G, Laganà AS, Schiattarella A, Garzon S, Cobellis L, Autiero R, et al. Ion Channels in The Pathogenesis of Endometriosis: A Cutting-Edge Point of View. Int J Mol Sci 2020; Feb 7; 21(3).
33. Sánchez-Ferrer ML, Mendiola J, Jiménez-Velázquez R, Cánovas-López L, Corbalán-Biyang S, Hernández-Peñalver AI, et al. Investigation of anogenital distance as a diagnostic tool in endometriosis. Reprod Biomed Online. 2017;34(4):375-82.
34. Sánchez-Ferrer ML, Jiménez-Velázquez R, Mendiola J, Prieto-Sánchez MT, Cánovas-López L, Carmona-Barnosi A, et al. Accuracy of anogenital distance and anti-Müllerian hormone in the diagnosis of endometriosis without surgery. Int J Gynaecol Obstet. 2019;144(1):90-6.
35. Simsir C, Pekcan MK, Aksoy RT, Ecemis T, Coskun B, Kilic SH, et al. The ratio of anterior anogenital distance to posterior anogenital distance: A novel-biomarker for polycystic ovary syndrome. J Chin Med Assoc. 2019 Oct;82(10):782-6.
36. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S, Gambineri A, et al. The polycystic ovary syndrome: a position statement from the European Society of Endocrinology. Eur J Endocrinol 2014;171:1–29
37. Merke DP, Cutler GB. New ideas for medical treatment of congenital adrenal hyperplasia. Endocrinol Metab Clin North Am 2001;30:121–35.
38. Stikkelbroeck NM, Beerendonk CC, Willemsen WN, Schreuders-Bais CA, FeitzWF, Rieu PN, et al. The long term outcome of feminizing genital surgery for congenital adrenal hyperplasia: anatomical, functional and cosmetic outcomes, psychosexual development, and satisfaction in adult female patients. J Pediatr Adolesc Gynecol 2003;16:289–96.
39. Stikkelbroeck NM, Hermus AR, Braat DD, Otten BJ. Fertility in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Obstet Gynecol Surv 2003;58:275–84.
40. Wu Y, Zhong G, Chen S, Zheng C, Liao D, Xie M. Polycystic ovary syndrome is associated with anogenital distance, a marker of prenatal androgen exposure. Hum Reprod 2017;32:937–43.
41. Sánchez-Ferrer ML, Mendiola J, Hernández-Peñalver AI, Corbalán-Biyang S, Carmona-Barnosi A, Prieto-Sánchez MT, et al. Presence of polycystic ovary syndrome is associated with longer anogenital distance in adult mediterranean women. Hum Reprod 2017;32:2315–23.
42. Hernández-Peñalver AI, Sánchez-Ferrer ML, Mendiola J, Adoamnei E, Prieto-Sánchez MT, Corbalán-Biyang S, et al. Assessment of anogenital distance as a diagnostic tool in polycystic ovary syndrome. Reprod Biomed Online. 2018;37(6):741-49.

43. Glintborg D, Jensen RC, Schmedes AV, Brandslund I, Kyhl HB, Nielsen TK, et al. Anogenital distance in children born of mothers with polycystic ovary syndrome: the Odense Child Cohort. Hum Reprod. 2019;34(10):2061-70.

44. Barrett ES, Hoeger KM, Sathyanarayana S, Abbott DH, Redmon JB, Nguyen RHN, Swan SH. Anogenital distance in newborn daughters of women with polycystic ovary syndrome indicates fetal testosterone exposure. J Dev Orig Health Dis 2018;9:307-14.