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Anogenital Distance and Prenatal Androgen Exposure in Female Fetus and Newborns: A Systematic Review

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ABSTRACT

The aim of this systematic review is to examine the relationship between anogenital distance (AGD) and prenatal androgen exposure in female offspring, and to assess whether there is sufficient scientific evidence that AGD could be a biomarker of in utero exposure in girls. A systematic approach was adopted to the screening and selection of the studies through Pub Med database. 959 documents were found in Pub Med search, 919 of them were excluded for lack of relevance, and 40 studies were included in the review. A significant portion of the selected studies (25 papers) focuses on the effect of exposure to endocrine disrupting agents (EDAs) such as phthalates, bisphenol A, and perfluoroalkyl substances. The other exposure factors examined in the studies are polycystic ovary syndrome, smoking and alcohol use, and maternal stressful life events. In 19 studies, a significant association has been reported between prenatal exposure factors and AGD length in female fetus and newborns. In the remaining 21 studies, no significant association was found. In conclusion, although there is still no a clear and conclusive evidence, a growing body of research provides data supporting that AGD may be considered a reliable marker of in utero androgen exposure in female infants. Our review highlights significant knowledge gaps with regard to some androgen or anti-androgen exposure factors. Much more research needed to understand the relationship of anogenital distance with in utero hormonal milieu and offspring's reproductive system development.

KEYWORDS

Anogenital distance; prenatal androgen exposure; females; fetus; newborn.

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Introduction

Androgen or anti-androgen exposure in prenatal period can cause structural and physiological consequences on offspring's reproductive system development.[1,2] In animal studies, a critical time period in early fetal life, called masculinization programming window, particularly vulnerable to endocrine disruption and during which genital development is programmed, has been identified.[3] Similar to animal models, there is some evidence of the existence of such an androgen-sensitive period in humans, and it is likely between 8-14 weeks of gestation.[4,5] Endocrine disruptions occurring in this period can affect reproductive system development, and have consequences later in life.[6]

Even subtle changes in maternal androgen levels may have effects on offspring's reproductive system development.[7] In men, this is associated with cryptorchidism, hypospadias, poor semen quality and prostate cancer, and defined as the testicular dysgenesis syndrome.[8] The data on the effects of the fetal androgen or antiandrogen exposure in females is more limited. In animal studies, it was demonstrated that excessive prenatal exposure to androgens could cause the development of PCOS-like metabolic consequences and poor ovarian reserve and infertility in females.[9,10]

Anogenital distance (AGD) is the distance from the anus to the genitals. Increasing evidence suggests that AGD is a biomarker of androgen exposure in early fetal life.[11,12] Many experimental animal studies have showed that prenatal androgen exposure can increase AGD in female offspring, while anti-androgenic exposure is associated with decreased AGD in male offspring.[5,13] Consistent with animal data, numerous studies support the link between AGD and androgen or antiandrogen exposure in fetal life in humans.[11,12,14]

The relationship between prenatal events and changes in AGD, and between AGD and reproductive outcomes, has been investigated mostly in males by epidemiological studies. Prenatal exposure to antiandrogenic chemicals such as endocrine disrupting agents (phthalate esters, dioxin, bisphenol, etc.) and paracetamol, decreases AGD length in male infants.[13-15] There is growing evidence that decreased AGD is associated with cryptorchidism, hypospadias and penile length in infancy and poor semen quality and count in male adults.[16]

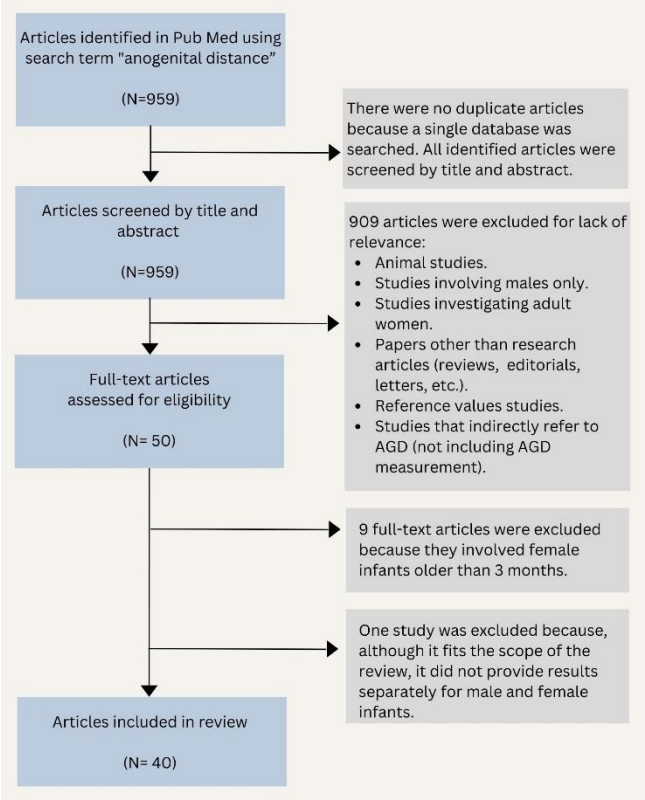
Compared to studies on men, data on the factors affecting AGD in females, and whether it is associated with any reproductive outcomes is limited. The aim of this review is to examine the relationship between offspring's AGD and prenatal exposure to androgenic or anti-androgenic factors in girls, and to assess whether there is sufficient scientific evidence that AGD could be a biomarker of in utero exposure.

Method

In this review, we use Pub Med database for literature search. A systematic approach was adopted to the screening and selection of the studies. Pub Med was searched by the keyword "anogenital distance" till February 15, 2023. To do an extensive search, we didn't use any other keyword along with "anogenital distance" to delimit the search. As a result of the search, 959 documents were found (see Figure 1). Because only one database was used, there were no duplicate results. Only papers in English were included in the review.

All of the 959 documents found in Pub Med search were analyzed through their abstract and title. Only original research articles were included in the literature review, and all other types of papers such as reviews, guidelines, editorials, and letters were excluded.

Figure 1: Flow chart of the selection of reviewed studies.



This review is limited to articles dealing with the factors affecting anogenital distance in females in the prenatal period. Therefore, the articles that are out of this scope were excluded from the study. The vast majority of these excluded articles are animal studies, studies involving males only, and studies involving adult females only. In addition, studies aiming to measure only AGD reference values were also excluded. These studies, which generally focus on newborns, aim to measure the AGD ranges and ratios, and do not address to factors affecting AGD. In some studies, AGD is indirectly mentioned. These studies do not involve AGD measurement, and therefore they were also excluded from the review. As a result, 909 out of 959 papers were excluded from the review due to lack of relevance, and the full-texts of the remaining 50 articles were accessed and examined.

This review has been limited to studies on female fetuses and newborns, since it aims to examine the factors affecting AGD in the prenatal period. Although the term "newborn" (or "neonate") is generally used for 1 month after birth, we included in this review the studies involving infants younger than 3 months. Hence, we excluded 9 studies investigating girls older than 3 months. One study was also excluded because it did not provide separate results for boys and girls, and 40 studies were ultimately included in the review.

Results and Discussion

The summary of 40 studies included in the review is presented in Table 1. In 37 of the 40 studies, AGD was measured in newborns infants. In two of the remaining three studies, the AGD measurement was performed in terminated fetuses. In one study, AGD was measured by fetal ultrasonography. 35 studies included both girls and boys. In five studies, AGD was measured only in girls.

Endocrine Disrupting Agents and Anogenital Distance

The relationship between endocrine disrupting agents (EDAs) such as phthalates, bisphenol A, pesticides and perfluoroalkyl substances, and AGD is the most frequently investigated issue in the reviewed studies (25 of 40 studies).

Even at appropriate environmental doses, EDCs can interfere with the action of hormones, disrupt homeostasis and alter an individual's physiology throughout their entire lifespan, from fetal development to adulthood. The extent of long-term outcomes depends on many variables, including the interaction of genes and environment, the developmental exposure window, the individual's metabolism and genetic history.[5]

Table 1. Summary of the selected studies

Study	Country	Fetus or newborn	Study population	Exposure measure	Exposure factor	Main Results
Torres-Sanchez et al. (2008)	Mexico	Newborn	34 females 37 males	Maternal blood	Dichlorodiphenyldichloroethylene	No association in females. Associated with decreased AGD in males*.
Huang et al. (2009)	Taiwan	Newborn	32 females 33 males	Amniotic fluid Maternal urine	Phthalates	Associated with decreased AGD in females. No association in males.
Barrett et al. (2013)	USA	Newborn	136 females 137 males	Questionnaire	Maternal stressful life events	Associated with increased AGD in females. Weakly, but not significantly, associated with shorter AGD in males.
Papadopoulou et al. (2013)	Spain	Newborn	112 females 119 males	Questionnaire	High-fat diet	Associated with longer AGD in girls. Associated with shorter AGD in boys.
Wafeiadi et al. (2013)	Spain Greece	Newborn	118 females 119 males	Maternal blood	Dioxins and di-oxin-like compounds	No association in females. Associated with decreased AGD in in males.
Barrett et al. (2014)	USA	Newborn	149 females 140 males	-	Maternal characteristics (age, parity)	No association in females. Maternal age is associated with increased AGD in males. Parity is associated with decreased AGD in males.
Adibi et al. (2015)	USA	Newborn	275 females 266 males	Maternal urine	Phthalates	Associated with increased AGD in females. Associated with decreased AGD in males.
Singal et al. (2015)	India	Newborn	524 females 553 males	-	Maternal characteristics (age, gravidity, parity)	No association in females and males
Swan et al. (2015)	USA	Newborn	373 females 366 males	Maternal urine	Phthalates	No association in females. Associated with decreased AGD in in males.
Barrett et al. (2016)	USA	Newborn	372 females 366 males	Questionnaires for SLEs, Maternal urine	Maternal stressful life events (SLEs), Phthalates	No association in females both for SLEs and phthalates. Associated with shorter AGD in males only in lower stress group. No association between phthalate concentrations and AGD in males in higher stress mothers.
Bornman et al. (2016)	South Africa	Newborn	364 females 388 males	Maternal blood	Dichlorodiphenyltrichloroethane	No association in both females and males.

Fowler et al. (2016)	UK	Fetus (11-21 weeks)	56 females 70 males	-	Maternal smoking	No association in females. Associated with increased AGD in males.
Lassen et al. (2016)	Denmark	Newborn	241 females 273 males	Maternal urine	Triclosan	No association in both females and males.
Lind et al. (2016)	Danmark	Newborn	231 females 316 males	Maternal blood	Perfluoroalkyl substances	Associated with decreased AGD in girls. No association in males.
Barrett et al. (2017)	USA	Newborn	385 females	Maternal urine	Bisphenol A	Associated with decreased AGD in females.
Dalsager et al. (2017)	Denmark	Newborn	420 males 326 females	Maternal urine	Pesticides	No significant association in both females and males. But there is a tendency towards a longer AGD in females, and a tendency towards a shorter AGD in males.
Wenzel et al. (2017)	USA	Newborn	158 females 222 males	Maternal urine	Phthalates	Associated with decreased AGD in girls.
Arbuckle et al. (2018)	Canada	Newborn	198 females 198 males	Maternal urine	Phthalates Phenols	No association between prenatal phenols and AGD in females. Association between AGD and phthalates varies according to phthalate metabolites in females. MEP was associated with increased AGD, and MBzP was associated with decreased AGD. In males, MnBP and the sum of low molecular weight phthalates was positively associated with anopenile distance.
Barrett et al. (2018)	USA	Newborn	300 females	Maternal medical history	Polycystic ovary syndrome (PCOS)	Maternal PCOS are associated with increased AGD in females.
Loreto-Gómez et al. (2018)	Mexico	Newborn	82 females 74 males	Maternal blood	Persistent organic pollutants (POP)	No association in females. Associated with decreased AGD in males.
Mammadov et al. (2018)	Cyprus	Newborn	58 females 72 males	Neonatal blood	Bisphenol A	No association in females. Associated with decreased AGD in males.
Sun et al. (2018)	China	Newborn	437 females 545 males	Maternal urine	Bisphenol A	No association in females and males.
Xia et al. (2018)	China	Newborn	436 females 544 males	Paternal medical history	Pre-pregnancy paternal alcohol use..	Associated with decreased AGD in both females and males.

Arbuckle et al. (2019)	Canada	Newborn	153 females 147 males	Maternal history (stress)	Maternal stressful life events	Associated with increased AGD in both females and males.
Glintborg et al. (2019)	Danmark	Newborn	695 females 866 males	Maternal medical history	PCOS	No associations in females. Associated with decreased AGD in males.
Arbuckle et al. 2020	Canada	Newborn	196 females 205 males	Maternal blood	Perfluoroalkyl substances	No associations in females. Associated with decreased AGD in males.
Ercin et al. (2020)	Türkiye	Newborn	200 females 247 males	-	IVF pregnancy	No associations in both females and males.
Karaeem et al. (2020)	Nigeria	Newborn	116 females 124 males	Neonatal blood	Testosterone	Associated with increased AGD in both female and male newborns. The correlation is stronger in males.
Perlman et al. (2020)	Israel	Fetus (26-37 weeks)	12 females 15 males	Maternal medical history	PCOS	Associated with increased AGD in both female and male fetus.
Sheinberg et al. (2020)	Israel	Newborn	82 females 93 males	Maternal serum	Polychlorinated Biphenyls	No association in females. Associated with decreased AGD in males.
Sun et al. (2020)	China	Newborn	383 females 493 males	Measured by satellite-based modeling approach	Fine particulate matter (PM2.5)	Associated with shortened AGD in both male and females.
Vieiralves et al. (2020)	Brazil	Fetus (12-22 weeks)	34 females	-	Anencephaly	No association.
Christensen et al. (2021)	Faroe Islands	Newborn	231 females 232 males	Maternal blood	Perfluoroalkyl substances	No associations in females. Associated with increased AGD in males.
Jensen et al. (2021)	Danmark	Newborn	189 females 283 males	Maternal urine Neonatal blood	Paraben	Associated with increased AGD in females. Associated with decreased AGD in males.
Kızılay et al. (2021)	Türkiye	Newborn	112 females 128 males	-	Maternal smoking	Associated with increased AGD in female newborns. No association in males.

Lesseur et al. (2021)	USA	Newborn	45 females 49 males	Maternal urine	Glyphosate	No associations in both females and males.
Luan et al. (2021)	China	Newborn	142 females	Cord plasma	Polybrominated diphenyl ethers	Associated with increased AGD in females.
Li et al. (2022)	China	Newborn	362 females	Maternal blood	Perfluoroalkyl substances	Associated with increased AGD in females.
Wang et al. (2022)	China	Newborn	280 females 317 males	-	Pre-pregnancy body mass index, Gestational weight gain.	No associations in females. Maternal excessive gestational weight gain was associated with lower AGD in males. No association with pre-pregnancy BMI.
Shen et al. (2023)	China	Newborn	1146 females 1186 males	Daily ambient PM2.5 levels were predicted using machine learning algorithms	Fine particulate matter (PM2.5)	Associated with decreased AGD in both females and males.

Note: This review only focuses on female fetuses and newborns. However, in this table we briefly summarize also the results for males to give a more holistic view of the studies reviewed.

In vitro studies showed that phthalates have an activating effect on the estrogen and androgen receptor.[17] In our review, six studies focused on the correlation between the phthalates exposure and anogenital distance length in female infants. Two studies reported that phthalates exposure decreased AGD[18,19], while one study showed an increasing effect[20]. No relationship was found in two other studies.[13,21] Moreover, one study reported that association between AGD and phthalates varies according to phthalate metabolites. While the exposure to mono-benzyl phthalate was associated with decreased AGD, the mono-ethyl phthalate exposure was associated with increased AGD.[22]

In a review paper focusing on prenatal exposure to phthalates in mother and offspring, Qian et al. concluded that phthalates exposure could affect gonadal hormones in pregnant women, and that could result serious maternal and neonatal complications, especially sex-specific adverse outcomes.[17] A meta-analysis including ten studies reported a significant association between phthalates metabolite and AGD in boys, but no association in girls.[23]

Perfluoroalkyl substances (PFAS) are the second most investigated EDAs in our review corpus (four studies), and these studies also reveal quite divergent results. While PFAS exposure was associated with increased AGD in one study[24], another study reported that it decreased AGD length in female infants.[25] No relationship was found in two other studies.[26, 27]

There are three studies examining the effect of bisphenol A: One showed a significant relationship with decreased AGD[28], two other studies did not report any association.[29, 30]

The relationship between prenatal exposure to fine particulate matter (PM2.5) and female offspring's AGD was examined by two studies, and they found significant association with shortened AGD in newborn girls.[31, 32]

Two studies revealed that there was a significant positive relationship between polybrominated diphenyl ethers[33] and paraben[34] exposure and AGD length in female infants.

The other studies in our review corpus investigating the effect of in utero exposure to dioxins and dioxin-like compounds[35], dichlorodiphenyltrichloroethane[36,37], triclosan[38], pesticides[39], phenols[22], persistent organic pollutants[40], polychlorinated biphenyls[41], and glyphosate[42] on AGD length in newborn girls have not found any association.

Nelson et al. investigated in a systematic review the association between in utero exposure to EDAs and AGD in both boys and girls. They concluded that despite a growing literature associating prenatal exposure to environmental endocrine disrupting agents with offspring's AGD, evidence for a clear association remains limited.[12]

Polycystic Ovary Syndrome (PCOS) and Testosterone

Excess testosterone is one of the key features of PCOS, and this could affect the reproductive system in women with PCOS. In a systematic review, Pan et al. examined association between PCOS and anogenital distance in adult women, and reported that AGD was significantly longer in patients with PCOS compared to the controls.[43] In our review, three studies investigated the effect of maternal PCOS on the offspring's reproductive system development. Two studies found that there is a significant positive association between maternal PCOS and offspring's AGD in girls, and this revealed that daughters of mothers with PCOS could be exposed in utero to elevated testosterone exposure.[44, 45] In one study, however, no association was found.[46]

Another study focuses on the relationship between AGD and total serum testosterone level in newborns. It reported that total serum

testosterone levels had a positive correlation with the AGD length in female newborns.[47n]

Smoking and Alcohol Use

Tobacco products contain toxic compounds and may have disrupting effects on reproductive system development.[48] Smoking was found associated with lower estrogen levels and increased androgen levels in pregnant women.[49] In our review, two studies investigated the effect of the maternal smoking on female offspring's anogenital distance. One study reported a significant increase AGD in female infants exposed to maternal smoking.[48] The other study did not find any association.[6] Another study focused on the relationship between paternal alcohol consumption before conception and female offspring's AGD, and showed a significant negative association.[50]

Maternal Stressful Life Events

There is some evidence in animal studies that exposure to maternal stress in prenatal period can have a masculine effect on the offspring's reproductive system in females.[7] Three studies in the review corpus examined the effect of prenatal maternal stress on AGD in female infants. A significant association with increased AGD was found in two studies[7, 51], and no association in one study.[21]

Maternal characteristics and other factors

The relationship between maternal characteristics (maternal age, gravidity and parity) and AGD length in female offspring was investigated in two studies, and no association was found.[52,53] Similarly, no relationship was reported between maternal pre-pregnancy body mass index and AGD in female infants.[54] However, maternal high-fat-diet score was found associated with longer AGD in newborn girls.[55] One study looked at whether there was a difference in AGD between newborn infants conceived through assisted reproduction technologies and those conceived naturally, and found no significant difference.[56] Finally, one study examined AGD difference between female fetuses with anencephaly and normocephalic fetuses, and did not reveal any significant difference.[57]

Conclusion

In this review, we investigated through the literature the association between in utero androgen or anti-androgen exposure and offspring's AGD in girls. In nearly half of the reviewed studies (19 studies), a significant association has been reported between prenatal exposure factors and anogenital distance length in female fetus and newborns. In the remaining 21 studies, no significant association was found. These studies cover a wide range of exposure factors, and the findings vary according to the factor type. In addition, although the number of studies has increased considerably in recent years, there are very few studies on some exposure factors. With all this in mind, it can be said cautiously that a growing number of studies in recent years shows a significant association between the exposure to factors affecting the hormonal environment in utero, and offspring's AGD in girls. However, the results are far from giving a clear picture, and in a considerable portion of the studies no association was found.

In recent years, AGD has increasingly been used as a tool to study in utero androgen or anti-androgen exposure in fetus and newborns. In this review, we sought to assess whether there is substantial evidence that offspring's AGD could be a biomarker of prenatal androgen exposure in females. Our conclusion is that although the evidence is still limited, a growing body of research provides data supporting that AGD may be considered a reliable marker of in utero androgen exposure in female infants. However, our review

highlights also significant knowledge gaps with regard to some androgen or anti-androgen exposure factors that have been very little studied. Much more research needed to understand the relationship of anogenital distance with in utero hormonal milieu and offspring's reproductive system development.

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