

Premenstrual Dysphoric Disorder is Associated with the Longer Length from Clitoris to Urethra

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Abstract

Background: Premenstrual dysphoric disorder (PMDD) is a common, recently recognized, psychiatric condition among reproductive women, reflecting abnormal responsivity to ovarian steroids. Moreover, the organizational effects of prenatal sex hormones during the embryonic environment that may determine individual sensitivity to fluctuation of sex hormones, have got attentions, but there have been considerably less of researches on this topic. The aim of this research was to investigate the possible role of prenatal androgen in the PMDD.

Methods: Anogenital distance (AGD), the distance between a woman's clitoris and her urethral meatus (CUMD), left and right 2D:4D ratios were measured in 77 subjects (25 patients with PMDD), as these anthropometric indicators are considered to indirectly reflect prenatal androgen exposures in utero.

Results: Patients with PMDD had a longer CUMD than controls (25.03 ± 4.73 vs 22.07 ± 4.30 , $P=0.008$), while there were no significant difference between PMDD group and control group in the AGD and right and left 2D:4D ratios.

Conclusion: Atypical high prenatal androgen exposure might predispose individuals to be susceptible to PMDD.

Plain English Summary

Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome, characterized by mood symptoms (and also involved sex dissatisfaction) among reproductive women, reflecting abnormal responsivity to ovarian steroids. Moreover, the organizational effects of prenatal sex hormones during the embryonic environment that may determine individual sensitivity to fluctuation of sex hormones, have got attentions, but there have been considerably less of researches on this topic. The aim of this research was to investigate the possible role of prenatal androgen in the PMDD.

Anogenital distance (AGD), the distance between a woman's clitoris and her urethral meatus (CUMD), left and right 2D:4D ratios were measured in 77 subjects (25 patients with PMDD), as these anthropometric indicators are considered to indirectly reflect prenatal androgen exposures in utero.

Patients with PMDD had a longer CUMD than controls (25.03 ± 4.73 vs 22.07 ± 4.30 , $P=0.008$), while there were no significant difference between PMDD group and control group in the AGD and right and left 2D:4D ratios.

In conclusion: the PMDD was associated with the longer CUMD, it might be an underling factor of sexual difficulties of women with PMDD. As the CUMD is supposed to be a sensitive indicator with prenatal androgen levels, therefore, atypical high prenatal androgen exposure might predispose individuals to be susceptible to PMDD.

Background

Premenstrual dysphoric disorder (PMDD) is a severe form of premenstrual syndrome, characterized by mood symptoms appearing in a cyclic manner during the premenstrual period [1]. The irritability and anger are regarded as the cardinal symptoms, and depressed mood, tension and affect lability are also common complaints [1, 2]. 3–5% of women of menstrual age may suffer from the disorder. These symptoms of PMDD significantly impair daily functioning, including sexual dissatisfaction [1, 2]. PMDD has been recently designated as a separate entity under Depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (<http://www.dsm5.org/Pages/Default.aspx>)[3]. The etiology of PMDD is unclear. Potential biological contributors include central nervous system sensitivity to reproductive hormones, genetic factors, and psychosocial factors such as stress [4].

It is well-known that the actions of the prenatal hormones were organizational and enduring [5]. The organizational effects of prenatal sex hormones during the embryonic environment may determine individual sensitivity to fluctuation of sex hormones in reproductive-age women [6–8]. Kaneoke et al measured the second to fourth digit ratios (2D:4D) to investigate the role of prenatal sex hormone in the pathogenesis of PMDD [9], as a number of studies have supported that 2D:4D is a biomarker for the balance between fetal testosterone and estrogen. They found right- and left-hand 2D:4D were differentially related to the severity of premenstrual symptoms, and the prenatal sex hormones (e.g., testosterone and estrogen) exposure might contribute to individual differences in the severity of premenstrual symptoms.

Anogenital distance (AGD) is a sexually dimorphic with males' AGD measuring longer than females, and considered as a sensitive marker of in utero exposure to androgens, based on animal models and the human literature[10, 11]. The distance between a woman's clitoris and her urethral meatus (CUMD) is a segment of AGD, and has been also considered to likely reflect the extent of prenatal androgen exposure [12]. Based on many recent researches, the AGD rather than the 2:4 digit ratio is more likely to provide an accurate biomarker of fetal androgen exposure in humans [10, 13, 14]. To our knowledge, to date, no published work has examined the association between the CUMD/AGD and PMDD.

Methods

Participants and grouping

The 77 participants are women who visited the gynecological or psychosomatic clinic of hospitals between June 2018 and June 2020 and agreed on participation after listening to explanations about the study. Eligibility criteria included age 18–45, regularly menstruating, nulliparous with no pregnancy lasting more than 12 months, not currently receiving any treatments to control the secretion of hormones (including taking birth control pills, administering gonadotropin releasing hormone, and hormone replacement therapy), no evidence of any hormonal disorder (including polycystic ovary syndrome), no

history of injury to or surgery on the genital region, no history of congenital anatomical abnormalities in genital organs including Mullerine Agenesis, and no history of an injury to the 2nd or 4th digit of both hands.

25 participants had symptoms in the past year and next two menstrual cycles, that corresponded to diagnosis criteria of PMDD, while other 52 participants were regarded as control group, as they did not present any premenstrual symptoms, or their manifestations were insufficient to diagnostic standards of PMDD. The diagnosis of PMDD is based on the fulfillment of seven (A to G) criteria, as described in the DSM-5 (<http://www.dsm5.org/Pages/Default.aspx>) [3]. Criterion A refers to the existence of five items in most menstrual cycles and to stage-specificity of the cycle in the past year. Criterion B and Criterion C, dealing with the specific symptoms of the disorder, require another five items in most menstrual cycles in the past year. Criterion D underscores the clinical significance or interference of symptoms with daily-life activities. Criterion E refers to the specificity of PMDD as compared with mood and anxiety disorders, etc. Criterion F requests the existence of two month's daily prospective ratings. Finally, Criterion G refers to the absence of a medical or drug-induced cause of the disorder

Anthropometry

Anthropometric data were got on the same day. Height was measured by rounding off to the nearest tenth in centimeter (cm). Weight was measured by rounding off to the nearest tenth in kilogram (kg). Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. The AGD and CUMD measurements were taken using a digital caliper (Carbon Fiber Composites Digital Caliper, Wuxi Kaibaoding Tool Limited Company, Jiangsu, China) in millimeter(mm), following procedures described elsewhere [12, 15]. The subjects were first placed in the supine position and changed to the lithotomy position in which the legs are spread apart to be put on rests. The AGD-AC was measured as the distance from the center of the anus to the anterior clitoral surface (Fig. 1); The AGD-AF was measured as the distance from the center of the anus to the posterior fourchette. The CUMD was measured as the distance from the underside of clitoral glans to the center of the urinary meatus. In order to improve accuracy, two examiners performed each of these measurements three times, the mean value of the six measurements of each distance was used.

Measurement of Digit Ratio: A photograph of both hands was taken using a digital camera. The hands were held in supination and fingers completely extended. The lengths of index and ring fingers of both hands were measured from the bottom crease of each digit to the finger tip, using tools in Adobe Photoshop [16]. For each hand, the digit ratio (2D:4D) was subsequently calculated, namely dividing index finger (2D) length by ring finger (4D) length. Mean of right and left hand ratio was taken as mean 2D:4D ratio for each individual.

Statistical analyses

All analyses were conducted in SPSS Version 23. The variables were summarized by arithmetic mean \pm standard deviation (SD). Unpaired Student's *t*-tests were used for comparison of variables between cases and controls. A *P* value of < 0.05 was deemed significant.

Results

The general characteristics of controls and cases with PMDD were shown in Table 1. The demographic data, including ages, menarche age, height, weight and BMI were not different between PMDD group and control group. Patients with PMDD had a longer CUMD than controls (25.03 ± 4.73 versus 22.07 ± 4.30 , *P* = 0.008), while there were no significant difference between PMDD group and control group, as to AGD-AC, AGD-AF, right and left 2D:4D ratio.

Table 1
Comparison of the general characteristics of controls and cases with premenstrual dysphoric disorder (PMDD).

Variable	PMDD group, <i>n</i> = 25	Control group, <i>n</i> = 52	<i>P</i> value
Age(years)	27.88 \pm 6.90	29.52 \pm 6.56	0.316
Menarche Age(years)	13.21 \pm 1.06	13.17 \pm 1.17	0.900
Height(cm)	162.80 \pm 5.34	162.73 \pm 5.66	0.959
Weight(kg)	58.10 \pm 8.45	57.87 \pm 10.83	0.924
BMI(kg/m ²)	21.92 \pm 2.93	21.86 \pm 4.03	0.951
CUMD(mm)	25.03 \pm 4.73	22.07 \pm 4.30	0.008
AGD-AC(mm)	94.55 \pm 11.25	94.86 \pm 10.54	0.906
AGD-AF(mm)	28.62 \pm 6.57	30.07 \pm 5.76	0.327
Left2D:4D Ratio	0.976 \pm 0.037	0.980 \pm 0.044	0.667
Right2D:4D Ratio	0.972 \pm 0.032	0.967 \pm 0.037	0.516

Discussion

The PMDD is occurring at times of hormonal fluctuations, and the most effective treatment for PMDD is by suppression of ovulation and suppression of the cyclical hormonal changes by hormone therapy [1, 17]. These evidences supported that the direct activating effect of hormones plays an essential role in the pathogenesis of PMDD, and at least reproductive hormones may precipitate the presentation of PMDD. Moreover, recently, the possible role of organizational effects of prenatal sex hormones during PMDD has got attentions. The researches made by Kaneoke et al. who used the 2D:4D ratios as a marker of prenatal sex hormones exposure, indicated that the prenatal sex hormones exposure may influence individual differences in the severity of premenstrual symptoms [9], and could be a factor in the development of

PMDD. A recent preclinical animal study clearly showed that prenatal androgenization induced anxiety-like behavior in adult female rats, implying that prenatal exposure to high concentrations of testosterone may influence the development of neural networks and impose the risk of anxiety-like behavior later in life [18]. We used the 2D:4D ratios, AGD-AC, AGD-AF, and CUMD, as the indicators of prenatal androgen hormone exposure in order to study the association of PMDD with these measures. The left/right 2D:4D ratios, AGD-AC and AGD-AF between PMDD and controls did not show any difference, but a significant longer CUMD was seen in the patients with PMDD. As the CUMD is supposed to be positive association with prenatal androgen levels, therefore, atypical high prenatal androgen exposure might predispose individuals to be susceptible to PMDD.

Recently, several studies demonstrated that AGD in adult patients with the polycystic ovarian syndrome (PCOS) was longer than control, implying that extreme prenatal androgen exposure contributes to PCOS [15, 19, 20]. The PCOS is a hyperandrogenic, oligomenorrhea/amenorrhea, fertility problems and metabolic disorder found in 6–7% of reproductive-aged women [21]. Therefore, the clinical features and pathophysiological processes of PMDD are totally different from ones of PCOS. So it is not unusual that PMDD patients did not show abnormal AGD. But both of PMDD and PCOS were probably related to the higher prenatal androgen exposures, why did PMDD patients have a longer CUMD and PCOS patients have a longer AGD? It is awaited future studies. At present, it can be inferred that there are other factors led to discrepant perineum appearances.

Several reports demonstrated the presence of premenstrual symptoms correlated negatively with sexual satisfaction [22–24]. Sexual pleasure and orgasm during copulation in women depends on many factors, such as past experience, stimulation of one or all of these triggering zones, autonomic arousal, and partner- and contextual-related cues, etc.[25] The clitoral complex in relation to the urethra, vulva, and vagina is the essential sensory triggering zone[25]. A longer CUMD in a woman decreased her likelihood of experiencing orgasm in sexual intercourse, as the longer CUMD may decrease penile-clitoral contact during sexual intercourse or decrease penile stimulation of internal aspects of the clitoris [12]. Therefore, the longer CUMD might contribute the sexual difficulties of women with premenstrual symptoms, according to our results.

This is a preliminary study with limited samples. There are some major defects, for instance, we did not study the association of individual differences in the severity of premenstrual symptoms with the left/right 2D:4D ratios, AGD-AC, AGD-AF and CUMD. Moreover, we did not collect data about the sexual function/satisfaction of subjects, at same time.

Conclusion

The PMDD was associated with the longer CUMD, it might be one of underlying factors of sexual difficulties of women with PMDD. As the CUMD is supposed to be a sensitive indicator with prenatal androgen levels, therefore, atypical high prenatal androgen exposure might predispose individuals to be susceptible to PMDD.

Abbreviations

AGD: Anogenital distance; AGD-AC: distance from the center of the anus to the anterior clitoral surface; AGD-AF: distance from the center of the anus to the posterior fourchette; BMI: Body mass index; CUMD: distance between a woman's clitoris and her urethral meatus; DSM-5: Depressive disorders in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; PCOS: polycystic ovarian syndrome ; PMDD: premenstrual dysphoric disorder; 2D:4D ratios: second to fourth digit ratios.

Declarations

Authors' contributions

BZ and ZL conceived and designed the study. ZL, MX, YJ collected cases and made/helped the measurements. ZL analyzed data. BZ and ZL wrote the manuscript.

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Availability of data and material

The data and materials described in the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and was approved by the Ethics Committee at the Pudong new area mental health center affiliated to Tongji university school of medicine. The written informed consent was obtained from all subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

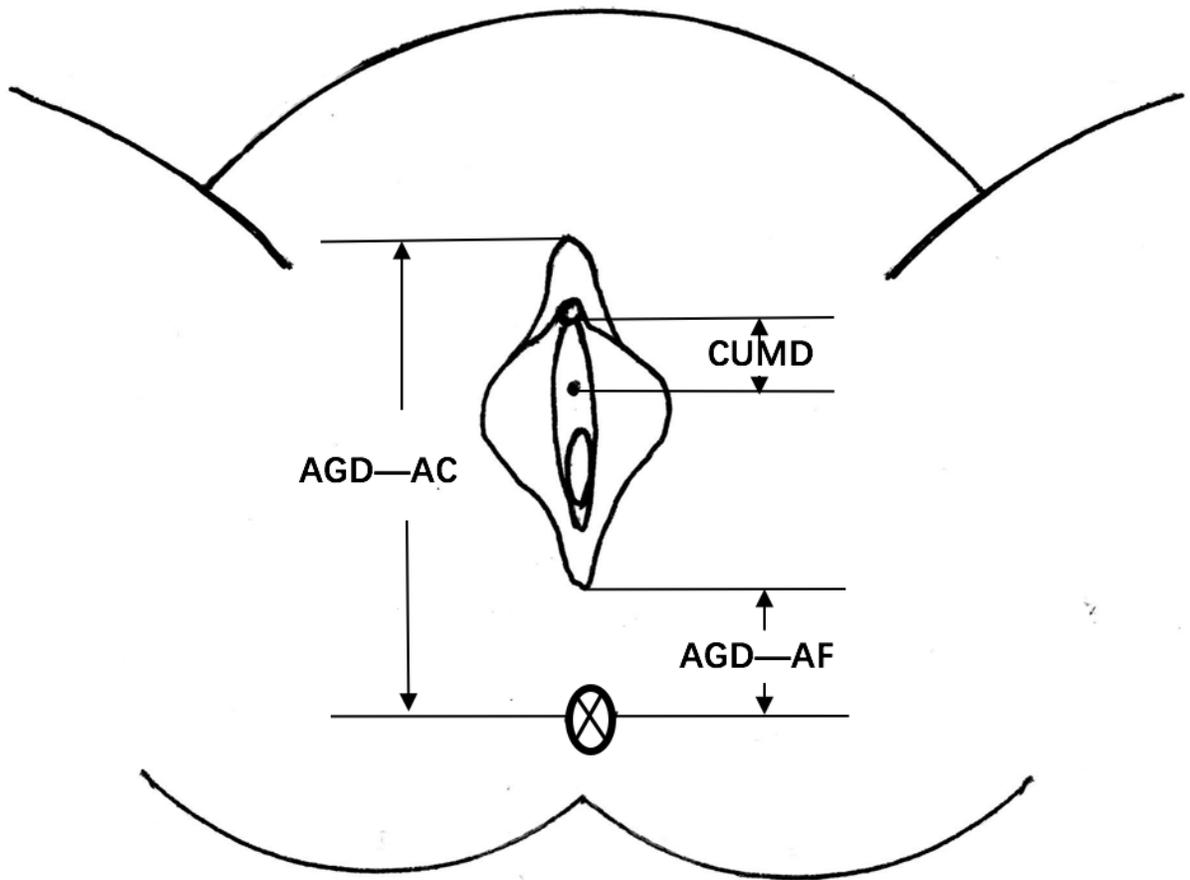


Figure 1

The AGD-AC was measured as the distance from the center of the anus to the anterior clitoral surface .