ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Importance of anogenital distance parameters on duloxetine success in women with stress urinary incontinence

Authors: Mazhar Ortac, M. Firat Ozervarli, Ufuk Caglar, Resat Aydin, Senol Tonyali, Omer Sarilar, Faruk Ozgor

DOI: 10.5603/gpl.101635

Article type: Research paper

Submitted: 2024-07-18

Accepted: 2024-10-24

Published online: 2025-03-20

ORIGINAL PAPER / GYNECOLOGY

Importance of anogenital distance parameters on duloxetine success in women with stress urinary incontinence

Mazhar Ortac[1], M. Firat Ozervarli[1], Ufuk Caglar[2], Resat Aydin[1], Senol Tonyali[1], Omer Sarilar[2], Faruk Ozgor[2]

[1]*Department of Urology, Istanbul Medical School, Istanbul, Türkiye*
[2]*Department of Urology, Haseki Training and Research Hospital, Istanbul, Türkiye*

Corresponding author:
Mazhar Ortac
Department of Urology, Istanbul Medical School, Istanbul, Türkiye
e-mail: mazhar.ortac@istanbul.edu.tr

ABSTRACT

Objectives: To clarify the impact of anogenital distance (AGD) on duloxetine success in the management of women with stress urinary incontinence (SUI).

Material and methods: Patients who have been diagnosed with SUI, were evaluated for inclusion in the study. Distance between anus and clitoris (AGD_{AC}), distance between anus and fourchette (AGD_{AF}), and length of genital hiatus (GH) were measured. All patients started duloxetine 20 mg twice daily for 2 weeks, and then patients received 40 mg duloxetine twice daily. Patients were categorized into two groups (patients who benefited from duloxetine and patients who did not benefit from duloxetine). Patient characteristics and AGD parameters were compared between these two groups.

Results: In total, 178 women were included in study and mean duration of SUI was 2.9 years. The mean body mass index (BMI) was significantly higher in patients with unsuccessful therapy ($p = 0.001$). In contrast, nulliparous rate was significantly higher in patients who benefited from duloxetine ($p = 0.043$). The distance of AGD_{AC} (71.4 mm vs 77.9 mm, $p = 0.001$) and distance of GH were significantly shorter (21.7 mm and 26.7 mm, $p = 0.001$) in

patients who were successfully treated with duloxetine. Multivariate regression analysis found that BMI < 30 kg/m^2, shorter AGD_{AC}, and GH lengths were significantly related with duloxetine success (p = 0.037, p = 0.036, and p = 0.039, respectively).

Conclusions: This study showed that duloxetine improved SUI in more than half of women and obesity was a predictive factor for duloxetine failure. In addition, shorter AGD_{AC} length and shorter GH distance were significantly associated with duloxetine success in the management of SIU.

Keywords: AGD_{AC}; AGD_{AF}; anogenital distance; Duloxetine; genital hiatus; stress urinary incontinence

INTRODUCTION

Stress urinary incontinence (SUI) is described as unintentional urine leakage due to abdominal pressure increments linked to coughing, physical exercise or weight lifting [1]. Previous studies demonstrated the relationship between SUI and loss of self-confidence, deterioration of social life, and increased health costs [2]. Jha et al. [3] claimed that almost 25% of women suffer from SUI and SUI-related problems. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was approved for the first time for SUI by the European Medicines Agency in Europe and Food and Drug Administration in United States of America, as an alternative to surgery for the management of SUI [4]. Previous studies stated that duloxetine decreased the incontinence episode frequency in women up to 60%, but factors related to duloxetine success are still under investigation including number of births, obesity, gynecological operations and perineal anatomic features [5].

The effect of perineal anatomy on SUI is one of the most discussed topics in gynecology practice. Athanasopoulos et al. [6] calculated anal-coccyx length, fourchette-coccyx distance and perineal body length in women with SUI, and the authors did not find significant correlations between perineal parameters and SUI. In contrast, Shin et al. [7] found that women with shorter urethral length had more risk of being faced with SUI. Anogenital distance (AGD), simply defined as the distance from anus to external genitalia, is affected by androgenic factors during the prenatal period. Sanchez-Ferrer et al. [8] evaluated pelvic organ prolapse (POP) and AGD, and found significant correlations between increased genital hiatus length and pelvic organ prolapses. In another study, the authors claimed that longer anus to clitoris length was a predictive factor for SUI [9].

Previous researches evaluated the impact of AGD on pelvic organ prolapses, polycystic ovary syndrome and SUI. However, to our knowledge, no study has analyzed the

effect of AGD on duloxetine success in the management of SUI. In the present study, our purpose was to clarify the impact of AGD on duloxetine success in the management of women with SUI.

MATERIAL AND METHODS

Patients who were admitted to the gynecology outpatient clinic and patients who have been diagnosed with SUI, were evaluated for inclusion in the study, and study data were prospectively recorded between January 2019 and June 2022. Ethical committee approval was obtained from the local ethics committee, and all participants signed informed consent forms. Patient age, body mass index (BMI), presence of diabetes mellitus, parity status, and duration of SUI were recorded. Also, incontinence episode frequency (IEF) was noted for each patient. Physical examination in lithotomy position was done for all participants, and distance between anus and clitoris (AGD_{AC}), distance between anus and fourchette (AGD_{AF}), and length of genital hiatus (GH) were measured. Additionally, the Pelvic Organ Prolapse Quantifications System (POP-Q) was used to determine POP. To evaluate presence of SUI, all patients performed the valsalva maneuver with an empty bladder and bladder with 300 cc fluid. Presence of mixed and/or urge type incontinence, presence of neurogenic bladder, history of pelvic surgery and radiotherapy, history of gynecologic or bladder cancer, and history of SUI surgery were exclusion criteria. Also, patients who ≤ 18 years old, patients with active urinary infection, patients who faced undesirable side effects to duloxetine and patients who could not continue treatment for 12 weeks were excluded from study.

Anogenital distance parameters

In the lithotomy position, all patients were positioned with 45° angle of thighs, and a stainless steel digital caliper (VWR® International, LLC, West Chester, PA, USA) was used during measurements. The AGD_{AC} was accepted the length from the upper edge of the anus and clitoris, and AGD_{AF} was accepted as the length between upper edge of the anus to posterior fourchette. Length of GH was measured from posterior midline of the hymen or edge of the perineum nucleus to the center of urethral meatus. To avoid inaccurate measurements, two health care providers measured AGD parameters twice.

All patients started duloxetine 20 mg twice daily for 2 weeks, and then patients received 40 mg duloxetine twice daily. The full dose of 80 mg duloxetine was continued for 12 weeks. Duloxetine was considered successful in patients whose incontinence episode frequency was reduced by 50%. To evaluate the impact of ADG on duloxetine success in the

management of women with SUI, patients were categorized into two groups (patients who benefited from duloxetine and patients who did not benefit from duloxetine). Patient characteristics and AGD parameters were compared between these two groups.

Statistical analysis

The Statistical Package for the Social Sciences version 25 (SPSS IBM Corp., Armonk, NY, USA) program was used. Shapiro–Wilk test and Q-Q plots were performed to evaluate normality of variable distribution. Normally-distributed data were analyzed with the Student t test, and non-normally distributed data were analyzed with the Mann–Whitney U test. Quantitative data are described as mean ± standard deviation. The χ^2 test or Fisher's exact test were performed for comparison of categorical parameters. Multivariate analysis was performed to clarify parameters affecting duloxetine success in the treatment of SUI. The data were evaluated at 95% confidence level and $p \leq 0.05$ was accepted as statistically significant.

RESULTS

In total, 178 women were included in study and mean duration of SUI was 2.9 years. The mean age and mean BMI of the study group were 56.8 years and 27.9 kg/m^2, respectively. Forty patients (22.5%) patients had diabetes mellitus and nulliparous rate was 21.4% (38 patients). The mean length of AGD_{AC}, AGD_{AF}, and GH were 74.4 mm, 24.0 mm and 24.0 mm, respectively. In total, 41 (23.0%) patients and 18 (10.2%) patients were classified as POP-Q stage 1 and POP-Q stage 2, respectively. Characteristics of the study population are presented in Table 1.

In comparison, patients who benefited and did not benefit from duloxetine had similar age, presence of diabetes mellitus, duration of SUI, length of AGD_{AF}, and POP-Q stages between the groups ($p = 0.312$, $p = 0.354$, $p = 0.665$, $p = 0.194$, and $p = 0.946$, respectively). The mean BMI was significantly higher in patients with unsuccessful therapy (29.4 kg/m^2 vs 26.7 kg/m^2, $p = 0.001$). In contrast, nulliparous rate was significantly higher in patients who benefited from duloxetine ($p = 0.043$). Additionally, the distance of AGD_{AC} (71.4 mm vs 77.9 mm, $p = 0.001$) and distance of GH were significantly shorter (21.7 mm and 26.7 mm, $p = 0.001$) in patients who were successfully treated with duloxetine (Tab. 2).

Multivariate regression analysis found that BMI < 30 kg/m^2 increased the success rate of duloxetine 2.092 times ($p = 0.037$). In contrast, parity was not found to be a factor influencing duloxetine outcomes ($p = 0.241$). Additionally, a decrease of 1 mm in AGD_{AC} was significantly associated with duloxetine success in the management of SUI in women (1.038

fold-time, p = 0.036). Moreover, decreased GH length was significantly related with duloxetine success (p = 0.039) (Tab. 3). The receiver operating characteristic (ROC) analysis demonstrated that AUC values for AGD_{AC} and GH were 0.672 and 0.707, respectively for prediction of duloxetine success (p = 0.001 and p = 0.001). The ROC analyses for AGD_{AC} and GH are presented in Figure 1A–B.

DISCUSSION

Anogenital distance is the anthropometric point which is affected by androgen during the prenatal phase. The AGD distance in women is half the length of AGD in men, but higher androgen levels in the prenatal period results in longer AGD in women and shorter AGD in men [10]. Previous reports demonstrated that shorter AGD in males was associated with lower testis volume, infertility and hypospadias, and longer AGD in females was related with congenital adrenal hyperplasia, endometriosis and polycystic ovarian syndrome [11, 12]. Also, some researchers investigated the impact of AGD on pelvic organ prolapse and incontinence in women; however, none of these studies focused on the effect of AGD on treatment outcomes. For the first time, we analyzed the impact of AGD parameters on duloxetine success in the management of women with SUI, and we found a significant correlation between duloxetine failure and obesity, increased AGD_{AC} length and GH distance.

The reflection of AGD_{AF} and AGD_{AC} in urogynecology practice is still under investigation. Sánchez-Ferrer et al. [8] found significant relationships between pelvic organ prolapses with increased AGD_{AC} distance and decreased AGD_{AF} length. Similarly, a study investigating AGD parameters and SUI incidence stated that patients with SUI had significantly longer AGD_{AC} and shorter AGD_{AF} distance in comparison to patients without SUI [9]. In the present study, we found significantly longer AGD_{AC} in patients who did not benefit from duloxetine. Additionally, our results revealed that AGD_{AF} length had no impact on duloxetine outcomes in the management of women with SUI. We hypothesize that with prolongation of AGD_{AC}, muscle mass per unit area will decrease in women with similar muscle mass, and this will reduce the resistance of the pelvic floor to increases in intra-abdominal pressure. In addition, prolonged AGD_{AC} measurement may be associated with further caudal displacement of the urethra, which may lead to duloxetine failure in women with SUI.

Patients with SUI had more frequent pelvic floor deficiency and previous studies attempted to clarify the correlation between pelvic floor deficiency and GH distance. Jones et al. [13] stated that longer GH distance resulted in the loss of vaginal support and higher rate

of pelvic organ prolapses. Also, Vakili et al. [14] found increased GH length was predictive factor for unsuccessful pelvic organ prolapse surgery. In another study, the authors claimed that longer GH was significantly related with higher SUI incidence in women [9]. In the present study, our results revealed that longer length of GH was a predictive factor for duloxetine failure. According to these results, we suggest that women with longer GH length should undergo surgery without wasting time on duloxetine treatment.

Obesity is associated with intra-abdominal pressure increases. Han et al. [15] investigated the effect of BMI on SUI development, and found 25.6% SUI rate in women with BMI < 23.0 kg/m^2, and 50.5% SUI rate in women with BMI ≥ 27.0 kg/m^2. Schwertner-Tiepelmann et al. [16] investigated duloxetine use in women with SUI, and the authors found a significantly higher rate of duloxetine discontinuation in obese women. They claimed that the lower efficiency of duloxetine in obese cases resulted in this outcome. In contrast, Viktrup and Yalcin [17] used duloxetine for women with SUI, and the authors achieved greater increases in quality of life in patients with BMI > 28 kg/m^2. In the present study, BMI < 30 kg/m^2 was predictive for successful duloxetine treatment in women with SUI.

Furthermore, it is well-recognized that vaginal delivery significantly impacts pelvic floor function and anatomical structures, including AGD measurements. Vaginal birth is associated with stretching and potential injury to the pelvic floor muscles, which can contribute to increased anogenital distances such as AGD_{AC} and changes in genital hiatus dimensions, factors that we have identified as influencing duloxetine success. Previous studies have shown that women who have given birth vaginally often exhibit longer AGD_{AC} and greater genital hiatus length, correlating with increased risk of pelvic floor disorders, such as pelvic organ prolapse and stress urinary incontinence [8, 9, 13, 14]. In our study, nulliparous women were more likely to benefit from duloxetine, likely due to less pelvic floor damage from childbirth. This highlights the potential for using AGD parameters not only to predict SUI severity but also to guide clinical decisions regarding pharmacologic treatments. Based on these findings, it may be prudent to consider duloxetine more strongly for nulliparous women or those with minimal pelvic floor damage post-delivery, as multiparous women with altered pelvic floor anatomy might require alternative treatments, such as surgical interventions.

Even though this is first study to analyze the impact of AGD on duloxetine success in the treatment of women with SUI, the limited patient volume and lack of long-term outcome are accepted as limitations. Additionally, anthropometric features could be affected by race and genetic variations, and in our opinion, further studies which investigate the impact of

AGD on duloxetine success may clarify this subject. Lastly, we did not focus on menopausal status and hormone levels of women, that may affect AGD, which may be the subject of further studies.

CONCLUSIONS

In conclusion, the present study showed that duloxetine improved SUI symptoms in more than half of women with SUI and obesity was a predictive factor for duloxetine failure. In addition, shorter AGD_{AC} length and shorter GH distance were significantly associated with duloxetine success in the management of SIU. Our results should be confirmed by prospective randomized studies with higher patient numbers.

Article information and declarations

Data availability statement

The data that support the findings of this study are openly available.

Ethical statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Istanbul Haseki Training and Research Hospital (03.01.2019/2019–12). Informed consent was obtained from all individual participants included in the study.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mazhar Ortac. M. Firat Ozervarli and Ufuk Caglar contributed to data collection and material preparation. The first draft of the manuscript was written by Mazhar Ortac and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. M. Ortac — project development, data collection, data analysis, manuscript writing/editing. M.F. Ozervarli — data collection, project development. U. Caglar — data collection, project development. R. Aydin — data collection. S. Tonyali — data analysis, project development. O. Sarilar — project development. F. Ozgor — project development.

Acknowledgments

Not appicable.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Supplementary material

Not applicable.

REFERENCES

1. Nygaard IE, Heit M. Stress urinary incontinence. Obstet Gynecol. 2004; 104(3): 607–620, doi: 10.1097/01.AOG.0000137874.84862.94, indexed in Pubmed: 15339776.
2. Sahin MO, Sen V, Irer B, et al. The effects of menopause on the quality of life and long-term outcomes of transobturator tape treatment in women with stres urinary incontinence. Int Braz J Urol. 2020; 46(5): 716–724, doi: 10.1590/S1677-5538.IBJU.2019.0331, indexed in Pubmed: 32539254.
3. Jha S, Ammenbal M, Metwally M. Impact of incontinence surgery on sexual function: a systematic review and meta-analysis. J Sex Med. 2012; 9(1): 34–43, doi: 10.1111/j.1743-6109.2011.02366.x, indexed in Pubmed: 21699671.
4. Li J, Yang Lu, Pu C, et al. The role of duloxetine in stress urinary incontinence: a systematic review and meta-analysis. Int Urol Nephrol. 2013; 45(3): 679–686, doi: 10.1007/s11255-013-0410-6, indexed in Pubmed: 23504618.
5. Basu M, Duckett JRA. Update on duloxetine for the management of stress urinary incontinence. Clin Interv Aging. 2009; 4: 25–30, indexed in Pubmed: 19503763.
6. Athanasopoulos A, Perimenis P, Giannitsas K, et al. The relationship between the perineal length measurements and the urodynamic stress incontinence. Int Urol Nephrol. 2005; 37(4): 701–705, doi: 10.1007/s11255-005-0252-y, indexed in Pubmed: 16362583.
7. Shin YuS, You JH, On JiW, et al. Clinical significance of anatomical urethral length on stress urinary incontinence women. Int J Womens Health. 2018; 10: 337–340, doi: 10.2147/IJWH.S161672, indexed in Pubmed: 30013403.
8. Sánchez-Ferrer ML, Prieto-Sánchez MT, Moya-Jiménez C, et al. Anogenital distance and perineal measurements of the pelvic organ prolapse (POP) quantification system. J Vis Exp. 2018(139), doi: 10.3791/57912, indexed in Pubmed: 30295651.

9. Ekmez M, Ekmez F. Effect of anogenital distance on stress urinary incontinence. African J Urol. 2021; 27: 1–5, doi: 10.1186/s12301-021-00247-6.
10. Thankamony A, Ong KK, Dunger DB, et al. Anogenital distance from birth to 2 years: a population study. Environ Health Perspect. 2009; 117(11): 1786–1790, doi: 10.1289/ehp.0900881, indexed in Pubmed: 20049133.
11. Sathyanarayana S, Beard L, Zhou C, et al. Measurement and correlates of ano-genital distance in healthy, newborn infants. Int J Androl. 2010; 33(2): 317–323, doi: 10.1111/j.1365-2605.2009.01044.x, indexed in Pubmed: 20132349.
12. Suzuki Y, Yoshinaga J, Mizumoto Y, et al. Foetal exposure to phthalate esters and anogenital distance in male newborns. Int J Androl. 2012; 35(3): 236–244, doi: 10.1111/j.1365-2605.2011.01190.x, indexed in Pubmed: 21696396.
13. Jones K, Yang L, Lowder JL, et al. Effect of pessary use on genital hiatus measurements in women with pelvic organ prolapse. Obstet Gynecol. 2008; 112(3): 630–636, doi: 10.1097/AOG.0b013e318181879f, indexed in Pubmed: 18757662.
14. Vakili B, Zheng YT, Loesch H, et al. Levator contraction strength and genital hiatus as risk factors for recurrent pelvic organ prolapse. Am J Obstet Gynecol. 2005; 192(5): 1592–1598, doi: 10.1016/j.ajog.2004.11.022, indexed in Pubmed: 15902163.
15. Han MOk, Lee NY, Park HS. Abdominal obesity is associated with stress urinary incontinence in Korean women. Int Urogynecol J Pelvic Floor Dysfunct. 2006; 17(1): 35–39, doi: 10.1007/s00192-005-1356-8, indexed in Pubmed: 16021328.
16. Schwertner-Tiepelmann N, Schwab F, Tunn R. Do predictive parameters exist for therapy with duloxetine in women with stress urinary incontinence? Int Urogynecol J. 2014; 25(8): 1071–1079, doi: 10.1007/s00192-014-2358-1, indexed in Pubmed: 24604277.
17. Viktrup L, Yalcin I. Duloxetine treatment of stress urinary incontinence in women: effects of demographics, obesity, chronic lung disease, hypoestrogenism, diabetes mellitus, and depression on efficacy. Eur J Obstet Gynecol Reprod Biol. 2007; 133(1): 105–113, doi: 10.1016/j.ejogrb.2006.05.003, indexed in Pubmed: 16769171.

Table 1. Demographic data for all patients

	n — 178
Age (years)*	56.8 ± 9.3
BMI (kg/m²)*	27.9 ± 5.6
Diabetes mellitus	40 (22.5%)
Parity n (%)	

Nulliparous	38 (21.4%)
Parity ≥ 1	140 (78.6%)
Duration of SUI	2.9 ± 1.8
AGD_{AF} (mm)*	24.0 ± 5.5
AGD_{AC} (mm)*	74.4 ± 11.1
GH (mm)*	24.0 ± 7.8
POP Q stage	
0	119 (66.8%)
1	41 (23.0%)
2	18 (10.2%)

*mean ± standard deviation; AGD_{AC} — anogenital distance from the anus to the clitoris; AGD_{AF} — anogenital distance from the anus to the fourchette; BMI — body mass index; GH — genital hiatus; POP Q — Pelvic Organ Prolapse Quantifications System; SUI — stress urinary incontinence

Table 2. Comparison of demographic data and anogenital distance parameters according to treatment success

	Treatment failed (n — 82)	Treated (n — 96)	p value
Age (years)*	57.6 ± 9.1	56.2 ± 9.5	0.312
BMI (kg/m^2)*	29.4 ± 5.8	26.7 ± 5.2	0.001
Diabetes mellitus	21 (25.6%)	19 (19.8%)	0.354
Parity n (%)			0.043
Nulliparous	12 (14.6%)	26 (27.1%)	
Parity ≥ 1	70 (85.4%)	70 (72.9%)	
Duration of SUI	2.9 ± 1.8	2.8 ± 1.8	0.665
AGD_{AF} (mm)*	23.4 ± 5.9	24.5 ± 5.2	0.194
AGD_{AC} (mm)*	77.9 ± 9.4	71.4 ± 11.6	0.001
GH (mm)*	26.7 ± 7.8	21.7 ± 7.2	0.001
Pop Q stage			0.946
0	54 (65.9%)	65 (67.7%)	
1	19 (23.2%)	22 (22.9%)	
2	9 (11.0%)	9 (9.4%)	

AGD_{AC} — anogenital distance from the anus to the clitoris; AGD_{AF} — anogenital distance from the anus to the fourchette; BMI — body mass index; GH — genital hiatus; POP Q — Pelvic Organ Prolapse Quantifications System; SUI — stress urinary incontinence

Table 3. Logistic regression analysis of factors affecting the success of duloxetine in stress urinary incontinence treatment

	Odds ratio	95% CI	p value

BMI (< 30 kg/m² vs ≥ 30 kg/m²)	2.092	1.047–4.182	0.037
Parity (nulliparous vs parity ≥ 1)	1.629	0.720–3.688	0.241
GH (mm)	1.055	1.003–1.110	0.039
AGD_{AC} (mm)	1.038	1.002–1.074	0.036

BMI — body mass index; AGD_{AC} — anogenital distance from the anus to the clitoris; GH — genital hiatus

Figure 1. A. Receiver operator characteristic curve analysis of genital hiatus for prediction of treatment success for stress urinary incontinence; **B.** receiver operator characteristic curve analysis of anogenital distance from the anus to the clitoris for prediction of treatment success for stress urinary incontinence