Check for updates

Pre-Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
0(0) 1–7
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0300060519893497
journals.sagepub.com/home/imr
SAGE

Effect of the anterior uterocervical angle in unexplained infertility: a prospective cohort study

Ilknur Col Madendag[1], Mefkure Eraslan Sahin[1], Yusuf Madendag[2], Erdem Sahin[2], Mustafa Bertan Demir[1], Fatma Ozdemir[2], Gokhan Acmaz[2] and Iptisam Ipek Muderris[2]

Abstract

Objective: The present study aimed to evaluate an anatomical region, the anterior uterocervical angle (UCA), to determine whether it plays a role in unexplained infertility.

Methods: In this prospective, cross-sectional study, unexplained infertile and healthy fertile (controls) women were compared. The longitudinal and transverse axes of the uterine cervix and uterine corpus were measured by transvaginal ultrasonography. The UCA was determined as the angle between two lines. One line was drawn between the internal and the external os, and the other was drawn through the internal cervical os and was parallel to the lower side of the front part of the uterine wall in the internal os. Demographic characteristics and uterocervical ultrasonographic measurements were compared between the two groups.

Results: Eighty participants, aged from 20 to 35 years, were enrolled (unexplained infertile [n = 30] and healthy fertile women [n = 50)]. The mean lengths of the uterine corpus longitudinal axis, uterine corpus transverse axis, and uterine cervix longitudinal axis were similar between the groups. The mean UCA was significantly higher in healthy fertile women (131.9 ± 22.9 degrees) than in women with unexplained infertility (114.2 ± 17.3 degrees).

Conclusion: The present study shows that a narrow anterior UCA is associated with unexplained infertility.

[1]Department of Obstetrics and Gynecology, Kayseri City Hospital, Kayseri, Turkey
[2]Department of Obstetrics and Gynecology, Erciyes University Medicine Faculty, Kayseri, Turkey

Corresponding author:
Ilknur Col Madendag, Department of Obstetrics and Gynecology, Kayseri City Hospital, Erciyes University Medicine Faculty, Şeker Neighborhood, Molu/Kocasinan/ Kayseri, Turkey.
Email: ilknurmadendag@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Keywords
Anterior uterocervical angle, unexplained infertility, uterine cervix, cervical os, transvaginal ultrasonography, pregnancy

Date received: 12 July 2019; accepted: 15 November 2019

Introduction

A large percentage of female infertility is unexplained because such women have normal hormonal profiles and ovulatory cycles, without any other clear reason for their infertility.[1,2] Despite improved diagnostic methods and new research in reproductive medicine, infertility remains unexplained in approximately one quarter of cases.[3] Various critical points in the fertility process cannot be fully investigated.[4] The cervix plays an important role in the storage of spermatozoa and in permitting their passage through the cervical os. However, there are no standard examination methods available to determine if the cervix has a normal function.[5]

The uterocervical angle (UCA), which is between the cervical canal and the uterine frontal wall, is a newly investigated ultrasonographic parameter. Some studies have suggested that measurement of the cervical length and the UCA by ultrasound are helpful for determining if the cervix is functioning well.[5,6] A large UCA might be associated with the contents of the uterus being moved toward the cervix.[6] According to Sahin et al.,[7] primary dysmenorrhea is more severe with a narrower size of the UCA. Dziadosz et al.[6] reported that the UCA in pregnant women is a useful ultrasonographic marker that may be used as a screening tool for spontaneous preterm birth. Additionally, Knight et al.[8] stated that UCA measurement was useful in predicting preterm delivery in twin pregnancies. All of these studies show that cervical anatomy has a clinical function. To the best of our knowledge, there are no data on cervical anatomical angles in women with unexplained infertility.

There is the hypothesis that if the UCA is narrow, spermatozoa will have difficulty in ascending. The presence of a narrow UCA may lead to unexplained infertility. Therefore, this study aimed to determine the role of the anterior UCA in unexplained infertility.

Patients and methods

This cross-sectional study was conducted at Kayseri City Hospital in Turkey. The study was approved by the Ethics Committee of Erciyes University (decision number: 2019/314) according to the Declaration of Helsinki. Written informed consent for the study was obtained, as well as for publication. Study participants included women aged 20 to 35 years who were referred to the infertility clinic for complaints of infertility.

The definition of unexplained infertility was a lack of a definite reason for inability of a couple to conceive within 1 year of trying to do so, even after a complete medical workup.[9] Nulliparous volunteers aged between 20 and 35 years were divided into two groups on the basis of their fertility as follows: (1) control group and (2) unexplained infertility group. We selected women who were known to be fertile as the control group. Women with fertility were defined as those who had not given birth previously and in whom the beta-human chorionic gonadotropin (Bhcg) level had recently become positive

(Bhcg level ≤ 100 mIU/ml). Pregnancy changes uterine blood flow, and the anatomical position of the uterus and cervix. Therefore, to exclude these factors, we preferred women who were positive for Bhcg at an early stage. Patients were excluded from the study if there was a known cause of infertility, a retroverted uterus, a history of uterine and cervical surgery, advanced age, type 1 or type 2 diabetes, systemic disease, presence of a known malignancy, or a history of chemotherapy or radiotherapy.

The preovulatory phase was preferred for evaluation of all ultrasonographic parameters. The longitudinal and transverse axes of the uterine cervix and uterine corpus were measured by transvaginal ultrasonography by the same specialized person (ICM). The uterine cervical longitudinal axis was measured when at least three of the following five recognition points on the plane were clearly visible: (1) the external cervical os, (2) the internal cervical os, (3) the cervical canal, (4) the cervical/vaginal interface, and (5) the cervical corpus.[7] To standardize measurement of the UCA, especially in problematic cases, measurement was performed on three of these five parameters and the UCA was accepted as the mean of three measurements for all volunteers. In some cases, we could not measure a straight line between the internal and external cervical os because the cervical canal was curved. In these participants, we measured several shorter linear distances, added them together, and considered this sum to be the longitudinal diameter of the uterine cervix. We measured the longitudinal axis of the uterine corpus starting at the site where the endometrium projected on to the uterine corpus all the way to the internal cervical os. This was the location of the longest visible distance from the endometrium to the internal cervical os. At the widest point of the uterine corpus, we measured the uterine corpus transverse axis, which was perpendicular to the longitudinal axis of the uterine corpus. We defined the UCA as the angle between two lines. The first line was drawn between the internal and the external os. The second line was drawn through the internal cervical os and was parallel to the lower side of the front part of the uterine wall in the internal os.[7] We used only one sonographer (ICM) to minimalize intra- and interobserver variation. We also used only one ultrasound device (Philips ClearVue 550 Ultrasound System, 2D-Clearvue 550 device; Milan, Italy) and a 3.5-MHz abdominal probe for all measurements (Figure 1).

To determine the appropriate number of patients to be evaluated in our study, we referred to a study conducted by Sahin et al.[7] Statistical analysis was performed with PASW Statistics 18 (SPSS version 18, Inc., 2009, Chicago, IL, USA). The Shapiro–Wilk test was used to determine normality of the data and Levene's test was used to test the assumption of homogeneity of variance. Values are expressed as mean $\pm$ standard deviation. Parametric comparisons were performed using the t-test and non-parametric comparisons were performed using the Mann–Whitney U test. A two-sided P value of <0.05 was considered statistically significant.

Results

Of the 80 volunteers enrolled in the study, 30 had unexplained infertility and 50 were healthy fertile women. Demographic characteristics were compared and are shown in Table 1. Age, body mass index, education levels, smoking rate, alcohol use rate, age at menarche, and length of the menstrual cycle were similar between the groups.

Table 2 shows comparison of ultrasonographic measurements between the groups. The mean lengths of the uterine corpus longitudinal axis and uterine corpus transverse axis were similar in both groups. Additionally, the mean length of the uterine

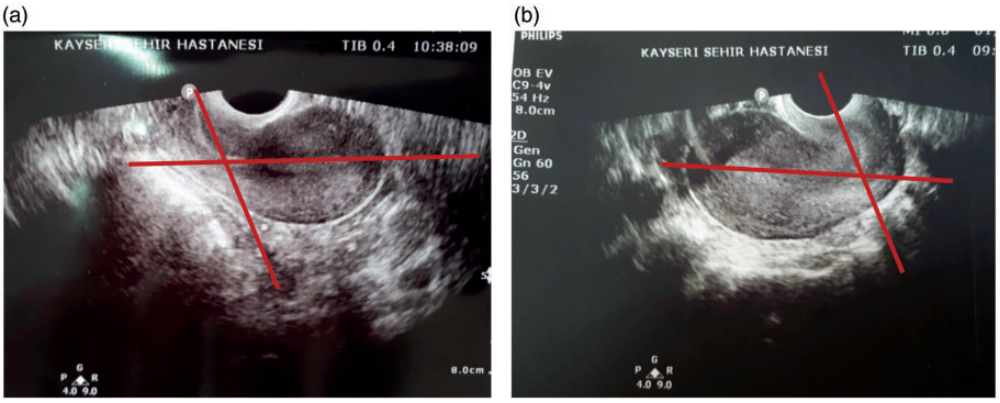


Figure 1. Ultrasonographic measurements of the anterior uterocervical angle. (a) An example of a wide uterocervical angle. (b) An example of a narrow uterocervical angle in a patient with unexplained infertility.

Table 1. Comparison of demographic characteristics between the groups.

	Unexplained infertility group (n = 30)	Control group (n = 50)	*P* value
Age (years)	29.9 ± 1.9	29.6 ± 1.6	0.421
BMI (kg/m^2)	24.8 ± 1.4	25.0 ± 1.6	0.620
Education (high school graduate), n (%)	21 (70)	37 (74)	0.840
Smoking, n (%)	5 (16.6)	9 (18)	0.720
Alcohol use, n (%)	2 (6.6)	3(6)	0.940
Age at menarche (years)	12.6 ± 0.8	12.8 ± 0.8	0.451
Length of menstrual cycles (days)	28.22 ± 1.27	28.44 ± 1.18	0.740

Values are presented as mean ± standard deviation or (n%). BMI, body mass index.

Table 2. Comparison of ultrasonographic measurements between the groups.

	Unexplained infertility group (n = 30)	Control group (n = 50)	*P* value
Uterine corpus longitudinal axis (mm)	46.8 ± 3.2	46.0 ± 2.6	0.440
Uterine corpus transverse axis (mm)	32.9 ± 2.5	33.3 ± 2.1	0.390
Uterine cervix longitudinal axis (mm)	31.7 ± 2.0	31. 9 ± 1.5	0.731
Anterior uterocervical angle (degrees)	114.2 ± 17.3	131.9 ± 22.9	0.001

Values are presented as mean ± standard deviation.

cervix longitudinal axis was similar between the groups. The mean UCA was significantly higher in the control group than in the unexplained infertility group ($P = 0.001$).

Discussion

When a complete medical workup does not show any cause for infertility, the situation is usually diagnosed as unexplained

infertility. There are many possible explanations for such unexplained infertility. One category of potential explanations is abnormal cervical causes. In the present study, we aimed to determine the role of the anterior UCA in unexplained infertility. We found that the UCA was significantly narrower in women with unexplained infertility compared with fertile women. The UCA appears to an anatomical factor involved in the etiopathogenesis of unexplained infertility.

Many authors have suggested possible reasons for unexplained infertility.[10–16] The cervix plays an important role in reproduction because it is the site where spermatozoa are stored before they ascend into the uterus. However, even though this role is important, the function of the cervix cannot be tested clinically with currently available techniques.[5] Numerous studies have focused on disease treatment,[2] but only a few have assessed the association of cervical anatomy and physiology with unexplained infertility. Martyn et al.[5] showed that the cervical and vaginal ecosystems, cervical mucus, the sperm–cervical-mucus interaction, and many cervical inflammatory and immunological factors have important roles in fertility. However, the anatomical position of the cervix has not been investigated yet.

In this study, we found that unexplained infertility was associated with a less wide UCA. After deposition of semen in the vagina, sperm must ascend through the barrier of the cervix before entering the uterus. Sahin et al.[7] reported that a narrow UCA increases resistance to ejection of menstrual blood from the uterine cavity in patients with virginal primary dysmenorrhea. If a narrow UCA blocks the flow of blood downwards, such a narrow UCA may also increase resistance to the flow of semen upwards. The relationship between resistance and flow can be explained by the Navier–Stokes equation, which is the basic motion equation for a viscous fluid. This equation considers the unit volume of fluid, mass conversion, Newton's second law, energy conversion, and the second law of thermodynamics.[17]

As of 2013, the UK National Institute for Health and Care Excellence (NICE) issued a statement opposing the practice of providing couples who have unexplained infertility the option of intrauterine insemination, regardless of whether ovarian stimulation is included. The NICE further stated that if a couple could not conceive in 2 years with expectant management (EM), *in vitro* fertilization would be acceptable.[18] EM resulted in a pregnancy rate of 27% in a randomized, clinical trial of 253 patients with unexplained infertility.[19] In a more challenging patient population consisting of patients with 2 years or more of unexplained low fertility, as many as 13% of patients became pregnant spontaneously while waiting for *in vitro* fertilization.[20] However, a similar study reported a pregnancy rate of only a 5.9% in 1 year.[21] Treatments that result in pregnancy rates comparable with those of EM include clomiphene, timed intercourse, and intrauterine insemination, according to one systematic review.[22] However, some published data have suggested that repeating intrauterine insemination for three cycles along with ovarian stimulation results in a rate of live births three times as high as that found with EM over the same time frame.[23]

There are some limitations and clinical significance of our study. First, the cross-sectional design and small sample size are possible limitations of this study. Second, we included women who had not given birth previously and in whom the Bhcg level had recently become positive to verify that the control group was fertile. Pregnancy changes uterine blood flow, and the anatomical position of the uterus and cervix. Therefore, to exclude these factors, we preferred to study Bhcg-positive

women as early as possible before pregnancy. The best way to achieve this state is to measure this parameter during the preconceptional period in nulligravid women. These patients can then be divided into those who could achieve pregnancy (fertile) and those who could not (infertile), after 1 year of unprotected regular vaginal intercourse. Further prospective studies that use this method are required to clarify the importance of the UCA. Third, in routine clinical practice when choosing a treatment plan, induction of ovulation and intrauterine insemination may be recommended, rather than EM, in patients with a narrow UCA. Of course, the choice of these methods will bypass cervical factors. Therefore, even though a narrow UCA may be a factor in the etiopathogenesis of unexplained infertility, it is not a parameter that affects treatment. Finally, further prospective studies may clarify the clinical importance of the UCA. An example of such a study is that evaluation of the association between the UCA and spontaneous pregnancy rates in EM women with unexplained infertility may be helpful to clarify the clinical importance of the UCA.

Conclusion

The present study shows that a narrow anterior UCA is associated with unexplained infertility. Further prospective studies with a greater number of patients are required to substantiate our results.

Availability of data and materials

The dataset used and analyzed during the current study is available from the corresponding author on reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

ICM, ES, YM: conception and design of the study; ICM, MES: data collection and analysis of the data; ES, MES: manuscript writing and design of the study; and MBD, FO, GA, and IIM: editing of the manuscript and interpretation of the manuscript. All authors read and approved the final manuscript.

ORCID iDs

Ilknur Col Madendag https://orcid.org/0000-0001-6700-2236
Yusuf Madendag https://orcid.org/0000-0002-7622-2991

References

1. Manohar M, Khan H, Sirohi VK, et al. Alteration in endometrial proteins during early- and mid-secretory phases of the cycle in women with unexplained infertility. *PLoS One* 2014; 9: e111687. DOI: 10.1371/journal.pone.0111687.
2. Ray A, Shah A, Gudi A, et al. Unexplained infertility: an update and review of practice. *Reprod Biomed Online* 2012; 24: 591–602. DOI: 10.1016/j.rbmo.2012.02.021.
3. Somigliana E, Paffoni A, Busnelli A, et al. Age-related infertility and unexplained infertility: an intricate clinical dilemma. *Hum Reprod* 2016; 31: 1390–1396. DOI: 10.1093/humrep/dew066.
4. Diagnostic evaluation of the infertile female: a committee opinion. *Fertil Steril* 2015; 103: e44–e50. DOI: 10.1016/j.fertnstert.2015.03.019.
5. Martyn F, McAuliffe FM and Wingfield M. The role of the cervix in fertility: is it time for a reappraisal? *Hum Reprod* 2014; 29: 2092–2098. DOI: 10.1093/humrep/deu195.
6. Dziadosz M, Bennett TA, Dolin C, et al. Uterocervical angle: a novel ultrasound screening tool to predict spontaneous preterm birth. *Am J Obstet Gynecol* 2016; 215: 376.e1-7. DOI: 10.1016/j.ajog.2016.03.033.

7. Sahin ME, Sahin E, Madendag Y, et al. The effect of anterior uterocervical angle on primary dysmenorrhea and disease severity. *Pain Res Manag* 2018; 2018: 9819402. DOI: 10.1155/2018/9819402.
8. Knight JC, Tenbrink E, Onslow M, et al. Uterocervical angle measurement improves prediction of preterm birth in twin gestation. *Am J Perinatol* 2018; 35: 648–654. DOI: 10.1055/s-0037-1608877.
9. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* 2008; 90: S60. DOI: 10.1016/j.fertnstert.2008.08.065.
10. Blacker CM, Ginsburg KA, Leach RE, et al. Unexplained infertility: evaluation of the luteal phase; results of the National Center for Infertility Research at Michigan. *Fertil Steril* 1997; 67: 437–442.
11. Leach RE, Moghissi KS, Randolph JF, et al. Intensive hormone monitoring in women with unexplained infertility: evidence for subtle abnormalities suggestive of diminished ovarian reserve. *Fertil Steril* 1997; 68: 413–420.
12. Guzick DS, Carson SA, Coutifaris C, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. National Cooperative Reproductive Medicine Network. *N Engl J Med* 1999; 340: 177–183. DOI: 10.1056/NEJM199901213400302.
13. Pandian Z, Bhattacharya S, Vale L, et al. In vitro fertilisation for unexplained subfertility. *Cochrane Database Syst Rev* 2005; 2002(2): CD003357. DOI: 10.1002/14651858.CD003357.pub2.
14. Lyons RA, Saridogan E and Djahanbakhch O. The reproductive significance of human Fallopian tube cilia. *Hum Reprod Update* 2006; 12: 363–372. DOI: 10.1093/humupd/dml012.
15. Cakmak H and Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. *Hum Reprod Update* 2011; 17: 242–253. DOI: 10.1093/humupd/dmq037.
16. Wang C and Swerdloff RS. Limitations of semen analysis as a test of male fertility and anticipated needs from newer tests. *Fertil Steril* 2014; 102: 1502–1507. DOI: 10.1016/j.fertnstert.2014.10.021.
17. Chavez ML and DeKorte CJ. Valdecoxib: a review. *Clin Ther* 2003; 25: 817–851.
18. National Collaborating Centre for Ws and Children's H. National Institute for Health and Clinical Excellence: Guidance. *Fertility: assessment and treatment for people with fertility problems*. London: Royal College of Obstetricians & Gynaecologists National Collaborating Centre for Women's and Children's Health, 2013.
19. Steures P, van der Steeg JW, Hompes PG, et al. Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial. *Lancet* 2006; 368: 216–221. DOI: 10.1016/S0140-6736(06)69042-9.
20. Donderwinkel PF, van der Vaart H, Wolters VM, et al. Treatment of patients with longstanding unexplained subfertility with in vitro fertilization. *Fertil Steril* 2000; 73: 334–337.
21. Evers JL, de Haas HW, Land JA, et al. Treatment-independent pregnancy rate in patients with severe reproductive disorders. *Hum Reprod* 1998; 13: 1206–1209. DOI: 10.1093/humrep/13.5.1206.
22. Gunn DD and Bates GW. Evidence-based approach to unexplained infertility: a systematic review. *Fertil Steril* 2016; 105: 1566–1574.e1. DOI: 10.1016/j.fertnstert.2016.02.001.
23. Farquhar CM, Liu E, Armstrong S, et al. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. *Lancet* 2018; 391: 441–450. DOI: 10.1016/S0140-6736(17)32406-6.