

Study of the association between the congenital uterine septum and Polycystic ovarian syndrome in infertility tertiary center in Iraq

Estudio de la asociación entre el tabique uterino congénito y el síndrome de ovario poliquístico en un centro terciario de infertilidad en Irak

Adnan A.H. Albdaire¹, <https://orcid.org/0000-0003-3645-6133>, Mohend A.N. Al-Shalah² <https://orcid.org/0000-0001-8550-0810>

¹MD-CABOG, Consultant infertility, Tiba Infertility Center, Hilla, Iraq. Email: dradnin5@gmail.com

²MRCS /Ireland -FRCS/ England, Consultant general surgery, Department of Surgery, College of Medicine, University of Babylon, Hilla, Iraq Email: mohend_alshalah2@uobabylon.edu.iq

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Abstract

Objective: The reproductive outcomes with patients who have both polycystic ovary syndrome (POC) and uterine anomalies are poor. The study aims is to assess the association between congenital uterine septum anomalies and PCOS in infertile patients.

Patients and Method: A retrospective case -control study on a cohort of 1374 consecutive patients seeking fertility advice at a tertiary specialized Tiba fertility Clinic, during the period of January 2015 to July 2019. The study depends on the Endocrine Society released practice guidelines for the diagnosis of PCOS. All women with suspected PCOS were screened for thyroid disease, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia. Gynecological examination, ultrasonography, hysterosalpingography (HSG), magnetic resonance imaging (MRI), and combined hysteroscopy and laparoscopy were all used as methods of diagnosis. Infertile patients are subdivided into two subgroups based on the presence or absence of associated congenital uterine anomalies. Patients diagnosed with PCOS were observed as a group. The in-

terrelationship between the congenital uterine anomalies subgroups was thoroughly studied in diagnosed patients with or without PCOS.

Results: There were no significant differences between means of age according to hysteroscopy results including (Septum or normal) P value 0.068. The percentage of infertile women with septum who had PCOS was (31.9%) which represents 219 women from a total 687 women. There was a significant association between hysteroscopy results and polycystic ovarian syndrome. A higher percentage of PCOS (31.9) was presented among patients with a septum in comparison to (24.0%) among those with normal hysteroscopy P-value 0.001.

Conclusions: There was an association between polycystic ovary syndrome (PCOS) and congenital uterine septum in infertile patients that might exist between the two reproductive health problems.

Keywords: Infertility, Uterine septum anomalies, PCOS.

Resumen

Objetivo: Los resultados reproductivos con pacientes que tienen síndrome de ovario poliquístico (POC) y anomalías uterinas son pobres. El objetivo del estudio es evaluar la asociación entre las anomalías congénitas del tabique uterino y el síndrome de ovario poliquístico en pacientes infértiles.

Pacientes y método: Un estudio retrospectivo de casos y controles en una cohorte de 1374 pacientes consecutivas que buscaron asesoramiento sobre fertilidad en una Clínica de fertilidad terciaria especializada en Tiba, durante el período de enero de 2015 a julio de 2019. El estudio depende de las guías de práctica publicadas por la Endocrine Society para el diagnóstico de SOP. Todas las mujeres con sospecha de síndrome de ovario poliquístico se sometieron a pruebas de detección de enfermedad tiroidea,

hiperprolactinemia e hiperplasia suprarrenal congénita no clásica. El examen ginecológico, la ecografía, la histerosalpingografía (HSG), la resonancia magnética (RM) y la histeroscopia y laparoscopia combinadas se utilizaron como métodos de diagnóstico. Las pacientes infértiles se subdividen en dos subgrupos según la presencia o ausencia de anomalías uterinas congénitas asociadas. Los pacientes diagnosticados con SOP se observaron como grupo. La interrelación entre los subgrupos de anomalías uterinas congénitas se estudió a fondo en pacientes diagnosticadas con o sin SOP.

Resultados: No hubo diferencias significativas entre las medias de edad según los resultados de la histeroscopia, incluido el valor de p (Septum o normal) de 0,068. El por-

centaje de mujeres infértiles con tabique que tenían SOP fue (31,9%), lo que representa 219 mujeres de un total de 687 mujeres. Hubo una asociación significativa entre los resultados de la histeroscopia y el síndrome de ovario poliquístico. Se presentó un mayor porcentaje de SOP (31,9) entre los pacientes con tabique en comparación con (24,0%) entre los que tenían un valor de p de histeroscopia normal 0,001.

Conclusiones: Hubo una asociación entre el síndrome de ovario poliquístico (SOP) y el tabique uterino congénito en pacientes infértiles que podría existir entre los dos problemas de salud reproductiva.

Palabras clave: Anomalías del tabique uterino, SOP.

Infertility is the inability to become pregnant after one year of intercourse without contraception involving a male and female partner¹. Women with the polycystic ovarian syndrome (PCOS) have abnormalities in the metabolism of androgens and estrogen and the control of androgen production. High serum concentrations of androgenic hormones, such as testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS), may be encountered in these patients². A proposed mechanism for anovulation and elevated androgen levels suggests that, under the increased stimulatory effect of luteinizing hormone (LH) secreted by the anterior pituitary, stimulation of the ovarian theca cells is increased. These cells, in turn, increase the production of androgens (e.g., testosterone, androstenedione). Because of a decreased level of follicle-stimulating hormone (FSH) relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens, which leads to decreased estrogen levels and consequent anovulation. Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) may also augment the effect on ovarian function³. Polycystic ovaries are enlarged bilaterally and have a smooth, thickened capsule that is avascular.

The most striking ovarian feature of PCOS is hyperplasia of the theca stromal cells surrounding arrested follicles. On microscopic examination, luteinized theca cells are seen. The diagnosis of the polycystic ovarian syndrome (PCOS) requires the exclusion of all other disorders that can result in menstrual irregularity and hyperandrogenism, including adrenal or ovarian tumors, thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinemia, acromegaly, and Cushing syndrome⁴⁻⁶. Biochemical and/or imaging studies must be done to rule out these other possible disorders and ascertain the diagnosis. A karyotype usually excludes mosaic Turner syndrome as a cause of the primary amenorrhea.

The Royal College of Obstetricians and Gynecologists (RCOG) recommends the following baseline screening

tests for women with the suspected polycystic ovarian syndrome (PCOS): thyroid function tests, serum prolactin levels, and a free androgen index (defined as total testosterone divided by sex hormone-binding globulin [SHBG] × 100, to give a calculated free testosterone level)⁶.

The uterus, tubes, and upper vagina develop from the Müllerian ducts in the absence of anti Müllerian hormone. This development requires the prior existence of mesonephric ducts that will give rise to the renal system. The fusion of the Müllerian ducts will form the tubes, uterus, and upper vagina around the tenth week of gestation. Subsequent canalization will form the cavity, and the absorption of the dividing septum will result in the final, normal anatomy by midgestation⁷. The mechanism by which a uterine septum regress may be mediated through the mechanism of apoptosis, which is regulated by the Bcl-2 gene. Sonographic incidence of polycystic ovaries in a gynecological population. Ultrasound Obstet Gynecol 6:182-185). By week 12, the fundus rises, and the uterus assumes its mature morphological shape. Abnormalities in the formation, fusion or disappearance of the Müllerian ducts can result in a variety of anomalies.

In 2001, Grimbizis and colleagues reported that the mean incidence of uterine malformations was 4.3% for the general population and/or for fertile women⁸. This rate was determined by reviewing data compiled from 5 studies that included approximately 3000 women with uterine malformations. In women with fertility problems, the incidence of Müllerian duct anomalies is slightly higher at 3-6%. In general, women with recurrent abortions have an incidence of 5-10%, with the highest incidence of Müllerian defects occurring in patients having third-trimester miscarriages^{9,10}.

Septate uterus is the most common structural abnormality of all Müllerian duct defects. It results from incomplete resorption of the medial septum after complete fusion of the Müllerian ducts has occurred. The septum, located in the midline fundal region, is composed of poorly vascularized fibromuscular tissue¹¹. Numerous septal variations exist. The complete septum extends from the fundal area to the internal os (internal orifice of the cervix uteri) and divides the endometrial cavity into 2 components. This anomaly is rarely associated with a longitudinal vaginal septum¹². The partial septum does not extend to the os. Some septa may be segmental, permitting partial communication between the endometrial cavities¹³. The poor reproductive outcomes associated with both PCOS and uterine anomalies have led some researchers to investigate a possible association between both conditions.

The aim of the study to find the association between PCOS and congenital uterine septum in infertile patients to unveil a common player that might exist between the two reproductive health problems.

We conducted this retrospective case-control study on a cohort of 1374 consecutive patients seeking fertility advice at a tertiary specialized Tiba fertility clinic, from January 2015 to July 2019. All patients signed a full informed consent before being enrolled in the study. The Ethical Committee Board at the Babylon Health Directorate approved the research plan. Physical examination was done for all cases on the first visit. In our study, we depend on the Endocrine Society released practice guidelines for the diagnosis of PCOS conclude the use the Rotterdam criteria for diagnosing PCOS (presence of 2 of the following: androgen excess, ovulatory dysfunction, or polycystic ovaries)¹⁴.

All women diagnosed with PCOS were screened for metabolic abnormalities (e.g., type 2 diabetes mellitus, dyslipidemia, hypertension), regardless of body mass index¹⁵⁻¹⁷.

All women with suspected PCOS should be screened for thyroid disease, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia¹⁵. Gynecological examination, ultrasonography, hysterosalpingography (HSG), magnetic resonance imaging (MRI), and combined hysteroscopy and laparoscopy were all used as methods of diagnosis.

The main modality for diagnosis for both PCOS and uterine anomalies was ultrasonographic scans done for all patients by the same investigator using transvaginal Probe. For hormonal assessment TOSOH Automated Immunoassay Analyzer (AIA360) were used.

Infertile patients were subdivided into two subgroups based on the presence or absence of associated congenital uterine anomalies. Patients diagnosed with PCOS were observed as a group.

The interrelationship between the congenital uterine anomalies subgroups was thoroughly studied in diagnosed patients with or without PCOS.

Data Analysis

Statistical analysis was carried out using SPSS version 20. Categorical variables were presented as frequencies and percentages. A p-value of ≤ 0.05 was considered as significant.

Table 1 shows mean differences of age (years) according to hysteroscopy results including (Septum or normal). There were no significant differences between means of age according to hysteroscopy results.

Table 1: The mean differences of age according to hystoscopic results

Study variable	Hysteroscopy results	N	Mean \pm SD	t-test	P-value
Age (years)	Septum	687	32.43 \pm 6.97	1.827	0.068
	Normal	687	31.73 \pm 7.17		

Figure 1 shows the distribution of patients with septum according to the history of the polycystic ovarian syndrome including (positive or negative). The percentage of infertile women with septum who had PCOS was (31.9%) which represents 219 women from a total 687 women.

Figure 1: Distribution of patients with septum according to polycystic ovarian syndrome

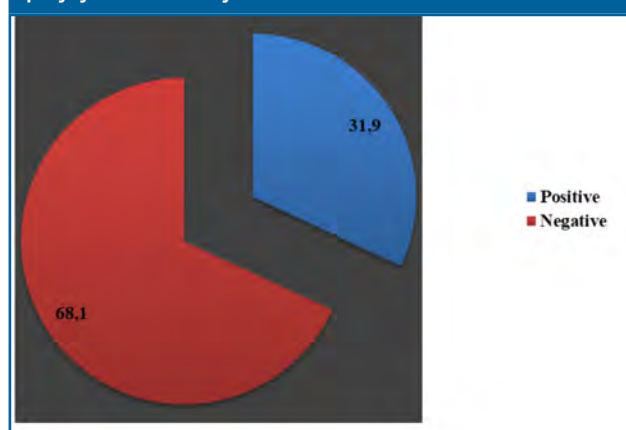


Table 2 shows the association between hysteroscopy results including (Septum or normal) and polycystic ovarian syndrome including (positive or negative). There was a significant association between hysteroscopy results and polycystic ovarian syndrome. The higher percentage of PCOS (31.9%) was presented among patients with septum in comparison to (24.0%) among those with normal hysteroscopy.

Table 2: Association between hysteroscopy results and polycystic ovarian syndrome

Study variables	Hysteroscopy results		X ²	P-value
	Septum	Normal		
Polycystic ovarian syndrome				
Positive	219 (31.9)	165 (24.0)	10.53	0.001 *
Negative	468 (68.1)	522 (76.0)		
Total	687 (100.0)	687 (100.0)		

*P -value ≤ 0.05 was significant.

Congenital uterine anomalies can be detected in about 5% of women. The rate is lower in the general population, higher among infertile women, and the highest in women with recurrent pregnancy losses (10%)⁹.

PCOS is a genetically heterogeneous syndrome in which the genetic contributions remain incompletely described¹⁸. Some evidence suggests that patients have a functional abnormality of cytochrome P450c17, the 17-hydroxylase, which is the rate-limiting enzyme in androgen biosynthesis¹⁹. Studies of family members with PCOS indicate that an autosomal dominant mode of inheritance occurs for many families with this disease. The fathers of women with PCOS can be abnormally hairy; female siblings may have hirsutism and oligomenorrhea, and mothers may have oligomenorrhea²⁰. In addition, a Dutch twin-family study showed a PCOS heritability of 0.71 in monozygotic twin sisters, versus 0.38 in dizygotic twins and other sisters²¹.

The ovaries and the uterus have different embryonic origins; it is thus expected for a woman with Müllerian anomalies to have an undisturbed ovarian function or at the very least a coincidental occurrence of the ovarian disorder, and a congenital uterine anomaly should not be a common finding.

We investigated a possible association between PCOS and uterine anomalies in a cohort of patients attending a fertility clinic. This case-control study was one of the very few reports in the literature on this issue. There were no significant differences between means of age according to hysteroscopy results including (Septum or normal). The percentage of infertile women with septum which had PCOS was (31.9%) who represents 219 women from total 687 women. There was a significant association between hysteroscopy results and polycystic ovarian syndrome (Septum or normal) and polycystic ovarian syndrome including (positive or negative) P-value 0.001. The higher percentage of PCOS (31.9) was presented among patients with septum in comparison to (24.0%) among those with normal hysteroscopy.

Our work demonstrated a significant association between PCOS and uterine septum anomaly; in other words, this should alert gynecologists to suspect patient with POC to have uterine anomalies and vice versa, focusing more on those presenting with uterine anomalies with suspicion for presence of PCOS.

In agreement with our results, Appleman et al.²² conducted a case-control study of 214 cases and suggested an association between polycystic ovaries and a high rate of uterine Müllerian anomalies.

Another retrospective study follow-up of 74 consecutive women with PCOS who underwent ovarian drilling, together with hysteroscopy surgery indicated Hysteroscopy detected and simultaneously treated a uterine anomaly in 18 of 74 patients: uterine septum (n=10, 13%) and conclude the high rate of associated uterine anomalies justifies simultaneous hysteroscopy surgery²³.

Several studies demonstrate that PCOS is significantly associated with elevated serum Anti-Müllerian Hormone (AMH), which could be linked to the coexisting uterine anomalies, which highlight biochemical factors as pathogenesis of both conditions²⁴⁻²⁶.

Well-known factors, such as intrauterine and extrauterine elements, genetics, and teratogens (eg, diethylstilbestrol [DES], thalidomide), have been associated with Müllerian duct anomalies²⁷. On the other hand, previous reports by Ugur et al²⁸. suggested a developmental defect to have a role in the etiology of PCOS and primary disorder within the ovary.

However, other studies suggest a genetic rather than a developmental defect to be a possible common player for the development of both PCOS and uterine anomalies. This possible single / multiple gene defect (s) may explain the high prevalence of PCOS in patient with uterine anomalies and vice versa, which would look rather strange on a developmental or local basis knowing the different embryological origin for the ovaries and the uterus. One-third (n = 149, 31.4 %) had uterine anomalies, while in patients with confirmed uterine anomalies, almost three-fourths (n = 149, 73 %) had PCOS²⁹.

Conclusions

There was an association between polycystic ovary syndrome (PCOS) and congenital uterine septum in infertile patients that might exist between the two reproductive health problems.

Conflict of interest there has been no conflict of interest of any kind with the authors of this work.

Ethical standard: The study was formally approved by the research plan by the Ethical Committee Board at the Babylon Health Directorate.

References

1. Chowdhury SH, Cozma AI, Chowdhury JH. Infertility. Essentials for the Canadian Medical Licensing Exam: Review and Prep for MCCQE Part I. 2nd edition. Wolters Kluwer. Hong Kong. 2017.
2. Macarena Alpañés, Elena Fernández-Durán & Héctor F Escobar-Morale (2012) Androgens and polycystic ovary syndrome, Expert Review of Endocrinology & Metabolism, 7:1, 91-102, DOI: 10.1586/eem.11.

3. Dunaif A, Wu X, Lee A, Diamanti-Kandarakis E. Defects in insulin receptor signaling in vivo in the polycystic ovary syndrome (PCOS). *Am J Physiol Endocrinol Metab*. 2001 Aug. 281(2):E392-9.
4. Vause TD, Cheung AP, Sierra S, et al. Ovulation induction in polycystic ovary syndrome. *J Obstet Gynaecol Can*. 2010 May. 32(5):495-502.
5. American College of Obstetricians and Gynecologists. Polycystic ovary syndrome. Washington, DC: American College of Obstetricians and Gynecologists; 2009. ACOG practice bulletin; no. 108.
6. Royal College of Obstetricians and Gynaecologists. Long-term consequences of polycystic ovary syndrome. London, UK: Royal College of Obstetricians and Gynaecologists; 2007. Green-top guideline; no. 33.
7. Acien P. Embryological observations on the female genital tract. *Hum Reprod*. 1992;7:437-445.
8. Grimbizis GF, Camus M, Tarlatzis BC, Bontis JN, Devroey P. Clinical implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update*. 2001 Mar-Apr. 7(2):161-74.
9. Acien P. Incidence of Müllerian defects in fertile and infertile women. *Hum Reprod*. 1997 Jul. 12(7):1372-6.
10. Raga F, Bauset C, Remohi J, Bonilla-Musoles F, Simon C, Pellicer A. Reproductive impact of congenital Müllerian anomalies. *Hum Reprod*. 1997 Oct. 12(10):2277-81.
11. Raga F, Bauset C, Remohi J, Bonilla-Musoles F, Simon C, Pellicer A. Reproductive impact of congenital Müllerian anomalies. *Hum Reprod*. 1997 Oct. 12(10):2277-81.
12. Heinonen PK, Saarikoski S, Pystynen P. Reproductive performance of women with uterine anomalies. An evaluation of 182 cases. *Acta Obstet Gynecol Scand*. 1982. 61(2):157-62.
13. Candiani GB, Fedele L, Zamberletti D, De Virgiliis D, Carinelli S. Endometrial patterns in malformed uteri. *Acta Eur Fertil*. 1983 Sep-Oct. 14(5):311-8.
14. [Guideline] Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013 Oct 22.
15. Legro RS, Arslanian SA, Ehrmann DA, et al.; Endocrine Society. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2013;98(12):4565-4592.
16. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab*. 2007;92(12):4546-4556.
17. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. *Obstet Gynecol*. 2009;114(4):936-949.
18. Barber TM, Franks S. Genetic basis of polycystic ovary syndrome. *Expert Review of Endocrinology & Metabolism*. 2010. 5(4):549-61.
19. Toulis KA, Goulis DG, Farmakiotis D, et al. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. *Hum Reprod Update*. 2009 May-Jun. 15(3):297-307.
20. Ehrmann DA, Kasza K, Azziz R, Legro RS, Ghaziz MN. Effects of race and family history of type 2 diabetes on metabolic status of women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2005 Jan. 90(1):66-71.
21. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. *J Clin Endocrinol Metab*. 2006 Jun. 91(6):2100-4.
22. Appelman Z, Hazan y, Hagay Z (2003). High prevalence of müllerian anomalies diagnosed by ultrasound in women with polycystic ovaries. *J reprod Med* 48(5):362–364.
23. Olivier Poujade, Amélie Gervaise, Erika Faivre, Xavier Deffieux, Hervé Fernández. Surgical management of infertility due to polycystic ovarian syndrome after failure of medical management. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. Volume 158, Issue 2, October 2011, Pages 242-247.
24. Casadei L, Madrigale A, Puca F, et al. The role of serum anti-müllerian hormone (AMH) in the hormonal diagnosis of polycystic ovary syndrome. *Gynecol Endocrinol* 2013; 29:545–550
25. Sahmay S, Aydin Y, Oncul M, Senturk LM. Diagnosis of polycystic ovary syndrome: AMH in combination with clinical symptoms. *J Assist Reprod Genet* 2014; 31:213–220
26. Homburg R, Ray A, Bhide P, et al. The relationship of serum anti-müllerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study. *Hum Reprod* 2013; 28:1077–1083
27. Golan A, Langer R, Bukovsky I, Caspi E. Congenital anomalies of the müllerian system. *Fertil Steril*. 1989 May. 51(5):747-55.
28. ugur M, Karakaya S, Zorlu G, Arslan S, Gülerman c, Kükner S, Gökmen O (1995) polycystic ovaries in association with Müllerian anomalies. *eur J Obstet Gynecol reprod Biol* 62(1):57–59.
29. Hisham Ali Saleh, Fady M. Shawky Moiety. Polycystic ovarian syndrome and congenital uterine anomalies: the hidden common player. *Arch Gynecol Obstet* (2014) 290: Issue 2, pp 355–360.