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

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Objective: The reproductive outcomes with patients who have both polycystic ovary syndrome (POC) and uterine anomalies are poor. The study aims 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 interrelationship 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 periodo 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 hysterosalpingografía (HSG), la resonancia magnética (RM) y la histeroscopia y laparoscopia combinadas se utilizaron como métodos de diagnóstico. Las pacientes infértiles se sub-
dividen 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 porcentaje 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.

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Introduction

Infertility is the inability to become pregnant after one year of intercourse without contraception involving a male and female partner. 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 patients. 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 function. 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 syndrome. 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 Gynaecologists (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).

In 2001, Grimbizis and colleagues reported that the mean incidence of uterine malformations was 4.3% for the general population and/or for fertile women. 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.

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 tissue. Numerous septal variations exist. The complete septum extends from the fundal area to the internal os (interimal orifice of the cervix uteri) and divides the endometrial cavity into 2 components. This anomaly is rarely associated with a longitudinal vaginal septum. The partial septum does not extend to the os. Some septa may be segmental, permitting partial communication between the endometrial cavities.
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.

Results

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 hysteroscopy results

<table>
<thead>
<tr>
<th>Study variable</th>
<th>Hysteroscopy results</th>
<th>N</th>
<th>Mean ± SD</th>
<th>t-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Septum</td>
<td>687</td>
<td>32.43 ± 6.97</td>
<td>1.827</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>687</td>
<td>31.73 ± 7.17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

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

<table>
<thead>
<tr>
<th>Study variables</th>
<th>Hysteroscopy results</th>
<th>x^2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>Septum</td>
<td>Normal</td>
<td>10.53</td>
</tr>
<tr>
<td>Positive</td>
<td>219 (31.9)</td>
<td>165 (24.0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>468 (68.1)</td>
<td>522 (76.0)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>687 (100.0)</td>
<td>687 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

*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 POCS.

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.

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.

Discussion

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


