MÜLLERIAN ANOMALIES AND ENDOMETRIOSIS: POTENTIAL EXPLANATORY MODELS FOR THE METASTATIC AND THE EMBRYONIC/METAPLASTIC PATHOGENIC THEORIES. A SYSTEMATIC LITERATURE REVIEW

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ABSTRACT

We conducted a systematic literature review to verify whether endometriosis prevalence differed in patients with obstructive müllerian anomalies (OMA) versus those with nonobstructive müllerian anomalies (NOMA), and in patients with NOMA versus those without müllerian anomalies. The first comparison was aimed at evaluating if an association exists between the amount of retrograde menstruation (RM) and the risk of endometriosis development. This would confirm the metastatic theory of endometriosis. Instead, in the second comparison, a higher prevalence of endometriosis in the NOMA group than in the group without müllerian anomalies would support the embryonic cell rests/coelomic metaplasia hypothesis rather than the RM theory. Information was identified by searching the electronic PubMed and EMBASE databases in December 2023 using different strategies. Only comparative, full-length, English-language articles published in peer-reviewed journals between 1980 and 2023 were selected. Seven retrospective studies were eventually included. The overall mean estimate of the prevalence of endometriosis in patients with OMA was 47% (95% CI, 36% to 58%), and that in patients with NOMA was 19% (95% CI, 15% to 24%; *P*<.0001), with a common OR of 4.54 (95% CI, 2.53-8.15). The overall mean estimate of the prevalence of endometriosis in patients with NOMA was 23% (95% CI, 20% to 27%), and that in patients without müllerian anomalies was 21% (95% CI, 20% to 22%; *P*=.275) with a common OR of 0.95 (95% CI, 0.57–1.58). The quantitative synthesis of published data demonstrates a substantial increase in the risk of endometriosis in patients with OMA compared with those with NOMA, and a similar risk in patients with NOMA and those without müllerian anomalies. Thus, the metastatic theory only seems confirmed. However, methodological drawbacks and residual confounding impede definitive conclusions, and the findings on the association between different types of müllerian anomalies and endometriosis remain open to different interpretations.

KEYWORDS: müllerian anomalies; endometriosis; retrograde menstruation; embryonic cell rest theory; coelomic metaplasia; infertility; pathogenesis

INTRODUCTION

The association between congenital müllerian anomalies and endometriosis has been a topic of investigation and debate since the half of the past century, although scientific interest increased substantially during the eighties (Pitot *et al*., 2020).

The reason for such interest lies substantially in the search for evidence supporting or refuting two of the principal pathogenic theories underpinning endometriosis onset, i.e., i) the metastatic theory, favored by gynecologists, based on retrograde menstruation (RM) and implantation of originally eutopic endometrium at ectopic sites and ii) the metaplastic theory, preferred by pathologists, based on the development of endometrial tissue directly at ectopic sites from embryonic cell rest and/or coelomic metaplasia (i.e., coelomic epithelium-derived tissues differentiating into müllerian-oriented epithelium) (Lauchlan, 1972; Redwine, 1988; Fujii, 1991). This latter condition was originally ascribed by Sampson (1925) to "developmentally misplaced endometrial tissue".

The comparison of endometriosis prevalence in patients with obstructive müllerian anomalies (OMA) and those with nonobstructive müllerian anomalies (NOMA) could constitute an explanatory model based on the existence of a biological gradient between the amount of refluxed blood and endometrial fragments and the risk of developing endometriosis. In other words, women with OMA would constitute a natural "quasi-experimental" group with pathologically increased menstrual reflux, whereas patients with NOMA would constitute a control group characterized by a physiologic amount of menstrual reflux. The choice of women with NOMA as controls should limit confounding, as cases and controls are selected from basically the same population, i.e., women with a defect in the development, or in the process of descent, fusion, and medial resorption, of müllerian ducts during embryogenesis.

A comparison between patients with NOMA and those without müllerian anomalies is aimed, on one hand, at validating a causal relation between RM and endometriosis. A strong positive association would partially argue against such a causal relation and instead support the

embryonic cell remnants/coelomic metaplasia hypothesis. If genetic derangements or abnormal intrauterine environmental exposures cause both uterine malformations and endometriosis, a higher prevalence of endometriosis would be observed in the NOMA group than in the group without müllerian anomalies. In this case, endometriosis could originate from vestigial müllerian cells embedded in the coelomic mesothelium during the organogenetic derailment (Fedele *et al*., 1992). This condition has also been termed mülleriosis (Redwine, 1988). Conversely, if the same prevalence were observed in individuals with NOMA and those without genital anomalies, the hypothesis of an embryologic etiology of endometriosis would lose credibility.

Finally, if the natural OMA experimental model is biologically valid, correction of outflow obstruction without destruction of endometriotic lesions should be followed by the usual course of endometriosis observed in patients without müllerian anomalies, e.g., high pain and lesion recurrence rates in the absence of postoperative hormonal suppression. Instead, prompt spontaneous endometriosis resolution without the need for surgical or medical interventions after obstruction removal would support the hypothesis that the pathogenesis of such "secondary" endometriosis may differ from that of the classic disease, and would scale back the importance of the amount of RM in spontaneous "primary" forms, thus emphasizing the role of additional promoting factors.

To try to partly disentangle the above uncertainties, we reviewed the literature data on the prevalence of endometriosis in women with müllerian anomalies published since 1980. In particular, we aimed at pooling the available evidence on the prevalence of endometriosis in patients with OMA versus NOMA, as well as in individuals with NOMA versus those without müllerian anomalies.

EVIDENCE ACQUISITION

This review was restricted to full-length, English-language articles published in peer-reviewed journals between 1st January 1980 and 1st December 2023. Studies were selected in which the prevalence of surgically confirmed endometriosis was compared in 1) individuals with obstructive

(OMA) versus those with non-obstructive müllerian anomalies (NOMA), and 2) in patients with NOMA versus those without müllerian anomalies. Information was identified by searching the electronic PubMed and EMBASE databases in December 2023 using the keyword 'endometriosis' in combination with 'müllerian anomalies', 'obstructive müllerian anomalies', 'female genital malformations', 'retrograde menstruation', 'infertility', 'pelvic pain', and 'classification'. References from relevant publications were systematically screened and further articles were searched using PubMed's "similar articles" and "cited by" functions.

Noncomparative studies and studies not investigating the presence or absence of endometriosis (e.g., Rock *et al*., 1980; Rock et al., 1984; Rock and Jones 2010; Song *et al*., 2016), not reporting both the numerator (subjects with endometriosis) and the denominator (total number of individuals with müllerian anomalies or with other gynecological conditions), those reporting exclusively data on patients with absent or uncertain menstrual function (e.g., complete müllerian agenesis category, Mayer-Rokitanksy-Küster-Hauser (MRKH) syndrome), or those with imperforate hymen who generally do not undergo abdominal exploration, and those describing patients included in a subsequent larger series (e.g., Fedele *et al*. 1989) were excluded. When the series included patients with and without abdominal exploration, only the former subgroup was considered. Reviews, case reports, and abstracts presented at meetings were not included.

Two observers independently evaluated all retrieved articles and extracted the year of publication, country of origin, malformation category, number of patients with endometriosis, and, when available, disease stage.

For each study, a 2×2 table was generated that included the number of patients with and without endometriosis in the two considered study groups (OMA vs NOMA; NOMA vs patients without müllerian anomalies), and odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. For each meta-analysis, the summary OR estimate was calculated using the Mantel–Haenszel (1959) or the DerSimonian and Laird method (1986 and 2007) for, respectively, fixed- and random-effects models, as appropriate. The I^2 statistics, which describe the proportion of the

total variation of estimates across studies due to heterogeneity rather than chance (Higgins *et al*., 2003), were then calculated. Negative values of I^2 are set equal to zero so that I^2 lies between 0 and 100%. A value of 0% indicates no observed heterogeneity, whereas I^2 values of 25, 50, and 75% indicate low, moderate, and high heterogeneity, respectively (Higgins *et al*., 2003). Random-effect models were applied in the case of I^2 >50%. Small study effect bias was tested using the Egger's test (Egger et al., 1997). All analyses were performed using Stata software, version 17.0 (StataCorp., 2022).

The present literature overview was exempt from Institutional Review Board approval as exclusively published, de-identified data were used.

EVIDENCE APPRAISAL

The flow diagram of the literature search results is shown in Supplementary Figure 1. Seven comparative studies published between 1986 and 2014 were eventually selected for the assessment of endometriosis prevalence in patients with OMA versus those with NOMA (Acien, 1986; Olive and Henderson, 1987; Ugur *et al*., 1995; Tong *et al*., 2014), and in those with NOMA versus those without müllerian anomalies (Fedele *et al*., 1992; Ugur *et al*., 1995; Nawroth *et al*., 2006; Demir *et al*., 2011). One study recruited the three types of patients (OMA, NOMA, and no müllerian anomalies) at the same time (Ugur *et al*., 1995). Consequently, this study has been included in both the preplanned comparisons. All studies were retrospective reviews of case series. A total of 76 patients had OMA, 668 had NOMA, and 4462 various non-müllerian gynecologic conditions. The characteristics and the results of studies selected for the two comparisons are shown in Tables 1 and 2.

Two additional studies addressed the frequency of NOMA in patients with or without endometriosis (Matalliotakis *et al*., 2010; LaMonica *et al*., 2016), whereas another study (Boujenah *et al*., 2017) investigated the effect of concomitant infertility on frequency and severity of endometriosis in a population of individuals with müllerian anomalies. Owing to the different

designs, these reports could not be included in the quantitative synthesis concerning the two comparisons that are the objective of this review, but were nonetheless retained for completeness and are here briefly narratively synthesized.

Obstructive versus nonobstructive müllerian anomalies

Acien (1986) described the surgical findings in 46 patients with various genital anomalies. Excluding four cases of gonadal dysgenesis and three cases of MRKH syndrome, endometriosis was detected in 5/39 (13%) cases, 1/10 (10%) in the obstructive anomalies group, and 4/29 (14%) in the nonobstructive anomalies group (P=1.00). Endometriosis was not found in two patients with transverse vaginal septum.

Olive and Henderson (1987) observed endometriosis in 10/13 (77%) women with OMA versus 16/43 (37%) of those with NOMA (P<.01). Eight of nine patients with hematocolpos or hematometra had endometriosis.

In the series of Ugur *et al*. (1995), endometriosis was detected in 15/26 (58%) patients with outflow obstruction versus 21/119 (18%) of those with NOMA (P<.001). Endometriosis was in minimal or mild forms, except for four cases of moderate disease, all in the obstructive anomalies group.

Tong *et al*., (2014) diagnosed endometriosis in 18/94 (19%) young women who underwent surgery for obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome. The prevalence of endometriosis was significantly higher in patients with complete hemivaginal outflow obstruction (10/27, 37%) than in those with incomplete obstruction (8/67, 12%; P=.012). In 14 individuals an endometrioma was present in the ovary ipsilateral to the hemivaginal obstruction.

Among the above four comparative studies, the overall mean estimate of the prevalence of endometriosis in patients with OMA was 47% (95% CI, 36% to 58%), and that in patients with NOMA was 19% (95% CI, 15% to 24%; P<.0001).

The OR of endometriosis ranged from 0.69 (Acien, 1986) to 6.36 (Ugur *et al*., 1995). Pooling of the results derived from the included reports yielded a common OR of 4.54 (95% CI,

2.53–8.15), demonstrating a substantial increase in the risk of endometriosis in patients with OMA compared with those with NOMA (Figure 1).

Nonobstructive müllerian anomalies versus no müllerian anomalies

Fedele *et al*. (1992) detected endometriosis in 61/198 (31%) patients with NOMA and 210/545 (39%) of those without müllerian anomalies (*P*=.209), who all underwent laparoscopy for infertility. The prevalence of endometriosis was significantly higher in individuals with unicornuate uterus (55%) compared with those with other malformation classes (28%; *P*<.05), but not compared with the control group without anomalies.

In the large cohort of Ugur *et al*. (1995), endometriosis was detected in 21/119 (18%) of patients with NOMA and 619/3,240 (19%) of those without müllerian anomalies (*P*>.05).

In the study by Nawroth *et al*. (2006), the prevalence of endometriosis was significantly higher in patients with subseptate uterus (31/120; 26%) than in those undergoing laparoscopy for infertility (74/486; 15%; *P*=.006).

Demir *et al*. (2011) observed endometriosis in 9/92 (10%) patients with complete or partial septate uterus compared with 30/191 (16%) patients with a normal uterus and who underwent laparoscopy for primary or secondary infertility (*P*=.39).

Among the above four comparative studies, the overall mean estimate of the prevalence of endometriosis in patients with NOMA was 23% (95% CI, 20% to 27%), and that in patients without müllerian anomalies was 21% (95% CI, 20% to 22%; *P*=.275).

The OR of endometriosis ranged from 0.58 (Demir *et al*., 2011) to 1.94 (Nawroth *et al*., 2006), with significant heterogeneity among studies (I^2=76.5%; *P*=.005). Therefore, the DerSimonian–Laird random-effects model was used to compute the overall OR. Pooling of the results derived from the included reports yielded a common OR of 0.95 (95% CI, 0.57–1.58), demonstrating no significant difference in risk of endometriosis in patients with NOMA compared with those without müllerian anomalies (Figure 2).

Nonobstructive müllerian anomalies in patients with and without endometriosis

A different approach to studying the association between NOMA and endometriosis has been adopted by some investigators who, instead of evaluating the prevalence of endometriosis in individuals with and without NOMA, assessed the prevalence of NOMA in patients with and without endometriosis.

Matalliotakis *et al*. (2010) retrospectively reviewed the diagnoses of 625 patients who underwent hysteroscopy and laparoscopy or laparotomy for primary or secondary infertility, 425 of whom had endometriosis and 200 did not. A total of 13 cases of NOMA (mostly septate uteri) were observed in the endometriosis group (3%) and a single case of septate uterus (0.5%) in the non-endometriosis group (P=.045).

LaMonica *et al*. (2016) evaluated prospectively a series of 343 women undergoing laparoscopy and hysteroscopy because of infertility, pelvic pain, or abnormal uterine bleeding, to compare the prevalence of septate uterus in participants with and without endometriosis. Endometriosis was visually diagnosed and histologically confirmed in 228 (66%) patients. The remaining 115 patients constituted the comparison group. The prevalence of septate uterus was 37% in the endometriosis group and 27% in the non-endometriosis group (P=.046). The highest prevalence of septate uterus (41%) was found in the severe (stage IV) endometriosis subgroup.

Endometriosis severity in infertile and fertile patients with müllerian anomalies

Boujenah *et al*. (2017) retrospectively assessed whether infertile patients with müllerian anomalies have more frequent and more severe endometriosis compared with fertile women with similar müllerian anomalies. The prevalence of endometriosis was higher in the former (18/41, 44%) than in the latter (3/11, 27%) group, although not significantly so. However, ovarian endometriomas (n=6) and deep infiltrating lesions (n=6) were observed in the infertile group only, whereas exclusively superficial peritoneal implants were detected in the fertile group.

Effect of correcting outflow obstruction in OMA on the course of endometriosis

We could not identify any controlled case series on the outcome of endometriosis in patients

with OMA after surgical correction of outflow obstruction with versus without concomitant laparoscopic eradication of endometriotic lesions. In addition, no studies are available comparing pain recurrence, lesions recurrence, or fertility in individuals with OMA who underwent surgical destruction of endometriotic foci in addition to correction of outflow obstruction, versus matched patients without OMA who underwent surgical treatment for similar type and extent of endometriotic lesions.

DISCUSSION

The findings of the present systematic review confirm that the prevalence of endometriosis is substantially and significantly higher in patients with OMA compared with that in patients with NOMA. The magnitude of the association is high (>4). This suggests a causal relationship rather than being explained by confounders (Grimes and Schulz, 2012). This appears to support the RM hypothesis of a positive association between the amount of transtubal reflux and the risk of endometriosis.

However, the interpretation of the evidence is not straightforward because, if on one side a biological gradient based on the amount of RM as a determinant of endometriosis onset seems established, on the other side such an amount can be considered quantitatively massive and non-physiologic. In other words, endometriosis could affect individuals with OMA regardless of the presence of other biological mechanisms that generally favor the development of the disease in women without uterine malformations. These patients may not necessarily be also biologically predisposed to the development of spontaneous, non-obstructive endometriosis. Thus, it can be questioned whether data observed in these “quasi-experimental”, though natural, conditions are generalizable to the entire endometriosis population, presumably composed mainly of biologically predisposed subjects that develop the disease in the absence of chronic cryptomenorrhea. In addition, the characteristics of the patients with OMA or NOMA are not comparable, as the former

are generally much younger and with a different surgical indication (postmenarcheal acute colicky pain) compared with the latter individuals.

Overall, less than half of patients with OMA had coexistent endometriosis. This percentage might appear too low to support RM as the exclusive pathogenic factor, otherwise, almost all patients with OMA should have developed endometriosis. However, in most patients the outflow obstruction was surgically corrected soon after the onset of symptoms (Tong *et al*., 2014) and, theoretically, there might have not been enough menstrual episodes to systematically induce endometriosis development (Sanfilippo *et al*., 1986). As an example, in the study by Tong *et al*. (2014), the mean age at diagnosis of endometriosis and of OHVIRA syndrome was, respectively, 13.7 and 14.8 years in those with complete obstruction and 19.7 and 21.5 years in those with incomplete obstruction. Moreover, the mean time between menarche and the diagnosis of endometriosis was 2.5 years in the former group and 8 years in the latter ($P<.05$ for all comparisons). Of relevance here, Song *et al*. (2016) reported that, in a large series of adolescents with cervical atresia and functioning endometrium, the only variable significantly associated with the presence of pelvic endometriosis was the extent of the delay from symptom onset to surgery. The prevalence of endometriosis was 30% (7/23) in patients with a delay of one year or less, and 63% (45/71) in those with a delay of more than 1 year ($P=.006$).

Furthermore, according to Rock *et al*. (1982), the lower the obstruction, such as in cases of transverse septum of the middle third of the vaginal canal or low-lying obstructed hemivaginas, the better the possibility to accommodate large amounts of trapped menstrual debris in the developing hematocolpos before hematometra and hematosalpinx ensue with the resulting aberrant pelvic reflux. Unfortunately, data are too small and/or unclear to permit reliable subgroup analyses based on the level of the outlet obstruction. Finally, histological demonstration of endometriosis was not always reported and supposedly biopsies were not systematically performed at laparoscopy. Therefore, it may not be excluded that some cases of presumed peritoneal endometriosis in patients with OMA were mere hemosiderin deposits (Fedele *et al*., 1992).

Regardless of statistical significance, one out of five patients with NOMA had endometriosis, and such a high prevalence is probably even more unexpected than the relatively limited estimate found in patients with OMA. Selection biases in the recruitment of subjects in the included studies may explain this finding. Moreover, it may not be excluded that some müllerian anomalies, although classified as nonobstructive, may create a partial and subclinical obstacle to menstrual efflux. In this case, stronger myometrial contractions would be needed to generate a pressure gradient between the uterine cavity and the vaginal canal sufficient to prompt a transcervical flow (e.g., a single sub-stenotic cervical canal in patients with didelphys uteri, bicornuate uteri with double cervix, or completely septate uteri with a septate cervix). The retrograde flow would thus also augment, increasing the likelihood of endometriosis onset that would explain the unusually high prevalence estimates reported. In addition, the same embryologic disorder that results in aberrant development of müllerian ducts hypothetically may also determine a myometrial dysfunction leading to loss or partial reversal of the physiologic fundo-cervical uterine contraction polarity during menses (uterine dysperistalsis) that would favor RM and increase the risk of endometriosis.

Concerning the second preplanned comparison, no significant difference was observed in the prevalence of endometriosis among patients with NOMA and those without müllerian anomalies. Thus, at *prima facie*, it is tempting to reject the hypothesis of a common embryologic pathogenic pathway leading to both müllerian anomalies and endometriosis (Redwine, 1988), because, if this was the case, a significantly higher prevalence of endometriosis would have been expected in the former group (Fedele *et al*., 1992).

However, the comparison between patients with NOMA and those without müllerian anomalies is also not straightforward. Patients with anovulation and tubal factors were not always excluded from the NOMA group, thus potentially reducing the real prevalence of endometriosis in this specific subpopulation. In addition, the considered study period was not always the same for

cases and controls (e.g., Nawroth *et al*., 2006), and surgeon awareness, diagnostic abilities, and accuracy in reporting early endometriotic lesions may have changed over time.

Moreover, the 21% mean prevalence of endometriosis in the no müllerian anomalies group obtained by pooling the individual estimates of the selected studies was substantially higher than the 3%-5% observed in the general female population of reproductive age (Ghiasi *et al*., 2020; Parazzini *et al*., 2020; Sarria-Santamera *et al*., 2021). Removal from the analysis of a single very large series (Ugur *et al*., 1995) did not substantially change the result.

Indeed, the so-called control group may not be representative of the general female population. The indications for surgery in patients with NOMA and those without müllerian anomalies differed and some conditions strictly associated with endometriosis (e.g., infertility) sometimes were unevenly distributed (Demir *et al*., 2011). As an example, in the series published by Fedele *et al*. (1992), primary infertility was the surgical indication for laparoscopy in 23% of patients with NOMA and 69% of those without müllerian anomalies ($P<.0001$). Conversely, the proportion of women with a history of repeated abortion was 52% and 4%, respectively ($P<.0001$). It might be argued that the frequency of endometriosis in individuals with primary infertility and few previous conceptions is expected a priori to be high, thus spuriously nullifying a potentially significant difference with patients with NOMA. More in general, NOMA may interfere with the pregnancy course, but rarely impede conception, and do not cause pelvic pain. Thus, comparing two groups with different surgical indications introduces confounding, as most individuals in the control group underwent laparoscopy precisely because of the two conditions, i.e., infertility and pelvic pain, most strongly associated with endometriosis.

The only data that would reliably answer the question of whether an excess in the prevalence of endometriosis exists in patients with NOMA would be a comparison with the prevalence observed in the general population in individuals without surgical indications. This is impossible, especially if one aims at including also superficial peritoneal implants because these lesions cannot be detected without direct visualization.

Concerning the third question that prompted our review, that is, does secondary, obstructive endometriosis promptly resolve once the outflow obstruction is removed or, instead, does it share the same disease course, in terms of pain, infertility, lesion recurrences, need for medical treatments, and reoperations, of primary, spontaneous endometriosis caused by classic RM (Mulchahey, 2002)? Unfortunately, no conclusions can be drawn regarding the effect of outlet obstruction correction, as the popular wisdom that restoring a normal menstrual efflux is followed by endometriosis resolution (Sanfilippo *et al*., 1986) is based on very few anecdotal cases. Indeed, in several, although much less emphasized, instances this has not occurred, as second-line laparoscopy for recurrent pain revealed persistence or recurrence of endometriosis six months to two years after the successful removal of outflow obstruction (Pinsonneault and Goldstein, 1985; Taylor and McComb, 2007; Silveira *et al*., 2013).

Finally, in the two studies investigating the prevalence of NOMA in patients with and without endometriosis (Matalliotakis *et al*., 2010; LaMonica *et al*., 2016), the reported estimates were completely inconsistent, being 3% in the former study and 37% in the latter, even though the sample size was fairly large in both series (n = 625 and n = 343, respectively), and the proportion of women with endometriosis similar (68% and 66%, respectively). Both studies highlighted a higher prevalence of NOMA in the endometriosis group. However, the magnitude of the association was modest and the statistical significance was marginal, thus making confounders the most plausible explanation. Though any inference seems unwarranted, these data appear to confirm an absence of a strong association between endometriosis and septate uteri. Indeed, endometriosis was associated with infertility rather than with NOMA (Boujenah *et al*., 2017).

CONCLUSION

In conclusion, the difference in the prevalence of endometriosis in patients with OMA compared with those with NOMA supports the validity of the RM theory but, in our opinion, cannot definitively rule out alternative hypotheses, as less than half of women with obstructed outlet had

the disease and the magnitude of the difference was less than expected if RM was the only determinant of endometriosis. However, the presence of endometriosis was assessed at a much younger age in patients with OMA compared with those with NOMA, and the obstruction was generally corrected after a limited number of ovulatory menses. Moreover, it cannot be excluded that some NOMA subtypes also create a partial obstacle to menstrual efflux and/or generate dysfunctional myometrial contractions that favor transtubal reflux, thus increasing the risk of endometriosis and limiting the difference between OMA and NOMA.

The embryonic müllerian rests hypothesis also cannot be reasonably rejected merely based on a lack of a significant difference in endometriosis prevalence between patients with NOMA and those with infertility and or pelvic pain, as these latter conditions are strongly associated with the outcome of interest, and women with these symptoms cannot be considered proper controls. Thus, confounding by indication could explain the findings. In addition, endometriosis has been reported in premenarcheal girls without OMA (Marsh and Laufer, 2005).

The results of our appraisal of the available evidence on the association between different types of müllerian anomalies and endometriosis remain open to different interpretations and the long-lasting debate (Redwine, 1988) that prompted this systematic review seems unsettled. Whereas the causal relation between OMA and endometriosis is indisputable, several collateral but important questions remain unanswered. Unfortunately, the methodological limitations that here prevent definitive conclusions appear difficult to circumvent even in future studies.

CONFLICT OF INTEREST

P.Ve. is a member of the Editorial Board of the Journal of Obstetrics and Gynaecology Canada and of the International Editorial Board of Acta Obstetricia et Gynecologica Scandinavica; has received royalties from Wolters Kluwer for chapters on endometriosis management in the clinical decision support resource UpToDate; and maintains both a public and private gynaecological practice. E.S. discloses payments from Ferring for research grants and honoraria from Merck-Serono for lectures. All other authors declare they have no conflict of interest.

AUTHORS' ROLES

P.Ve. conceived the study and drafted the original version of the article. M.P., F.C. and P.Ve. contributed to acquisition of the data and drafting of the manuscript. E.S. and P.Vi. participated in conceiving and drafting part of the article and critically revising the paper. S.D.M. processed and analysed the data. All authors revised critically the drafts of the manuscript and approved its final version. All authors agree to be accountable for all aspects of the work.

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The data included in this article were extracted as published in the available original articles. No new data were generated or analysed to support this paper.

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LEGENDS TO FIGURES

FIGURE 1. Results of studies comparing the prevalence of endometriosis in patients with obstructive müllerian anomalies (OMA) and those with non-obstructive müllerian anomalies (NOMA). Horizontal lines indicate 95% confidence interval (CI); boxes show the study-specific weight; the rhombus represents combined effect size; and the dashed line indicates the overall estimate.

FIGURE 2. Results of studies comparing the prevalence of endometriosis in patients with non-obstructive müllerian anomalies (NOMA) and those without müllerian anomalies (Controls). Horizontal lines indicate 95% confidence interval (CI); boxes show the study-specific weight; the rhombus represents combined effect size; and the dashed line indicates the overall estimate.