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Smoking habits and endometriosis risk among infertile women: results from a case control study

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ABSTRACT

Some studies have suggested that tobacco smoking may affect the risk of endometriosis, but published data are controversial.

We conducted a case control study on the association between smoking and endometriosis risk Cases of endometriosis included 90 women (median age 35, range 19-49) with incident, i.e. laparoscopically diagnosed within the year before interview, histologically confirmed endometriosis.

Controls were 90 women (median age 35.5, range 17-76) admitted for a wide spectrum of acute conditions unrelated to known potential risk factors for endometriosis. Compared with never smokers the OR of endometriosis was 2.36 (95% CI 1.04-5.35) in ever smokers. These findings were largely consistent in strata of age and education. Considering separately nulliparous and parous women the estimated OR of endometriosis in ever smokers were 1.51 (95%CI 0.26-11.36) and 2.52. In conclusion despite the limitations of this study the present analysis suggest that smoking may increase the risk of endometriosis in nulliparae women attending an infertility clinic: this finding may at least in part due to the effect of smoking on infertility.

Key words: risk factor smoking endometriosis

SOMMARIO

Alcuni studi hanno suggerito che il fumo di tabacco può influenzare il rischio di endometriosi, ma i dati pubblicati sono controversi. Abbiamo condotto uno studio caso-controllo sull'associazione tra fumo ed endometriosi che ha incluso 90 casi di endometriosi (età mediana 35 anni) istologicamente 90 donne controllo (età mediana 35,5) ricoverate in ospedale per un ampio spettro di condizioni acute non correlate a fattori di rischio potenziali per l'endometriosi. Rispetto ai non fumatori il odds ratio (OR) di endometriosi era nei fumatori pari a 2,36 (Limiti di confidenza (LC) al 95% 1,04-5,35). Questi risultati erano coerenti negli strati di età e l'istruzione. Considerando le donne nullipare e pluripare separatamente l'OR stimato di endometriosi in mai fumatori erano 1,51 (non significativo) e 2,52. In conclusione nonostante le limitazioni di questo studio la presente analisi suggeriscono che il fumo può aumentare il rischio di endometriosi in nullipara donne che assistono ad una clinica di infertilità: ciò che trova potrebbe almeno in parte a causa dell'effetto del fumo sulla sterilità.

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INTRODUCTION

Endometriosis is a common gynecological condition, affecting women during their reproductive years.

The pathogenesis of endometriosis is not completely understood [1]: altered hormonal milieu including estrogen dependence and progesterone resistance, inflammation, evasion from immune clearance [2], endometrial cell attachment and invasion of peritoneal tissues [3], neo angiogenesis [4,5], have been shown to play a role in the development of endometriosis. More recently overexpression of cell-cycle regulatory gene products such as p16–cyclin D1–pRb and CDKs which has been investigated in various gynecologic malignancies [6] have been also suggested to play a role in the regulation of cell growth in adenomyosis and ovarian endometriotic cysts [7].

From an epidemiological point of view, the main reported risk factors are regular menstrual cycles and nulliparity [8]. Further, familiarity (a risk factor for several gynecological diseases [9-11] is considered a main risk factor for the disease [12].

Among the other risk factors investigated, some studies have examined the role of tobacco smoking, Smoke compounds disrupt steroidogenesis, leading to impairment of E2 synthesis [13,14] and progesterone synthesis deficiency [15-17].

Moreover, smoking has a strong effect on inflammatory mediators in both the pulmonary and extra-pulmonary environments and can further trigger inflammation associated with the disease resulting in pro-inflammatory gene overexpression [18]. Published studies however have generally shown controversial results [19-29]. In this paper we have analysed the association between smoking and endometriosis risk using data of a case control study conducted in Milan [30,31].

MATERIALS AND METHODS

The general methods of this study have been published [30,31].

Subjects were enrolled in a case-control study of endometriosis conducted at the S Raffaele Hospital and Policlinico of Milan. Cases of endometriosis included 90 women (median age 35, range 19-49) with incident, i.e. laparoscopically diagnosed within the year before interview, histologically confirmed endometriosis.

Controls were 90 women (median age 35.5, range 17-76) admitted for a wide spectrum of acute conditions unrelated to known potential risk factors for endometriosis. Of these, 7.8% had traumatic or non-traumatic orthopaedic conditions, 6.7% acute surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia), 47.8% gynaecological benign conditions, and 11.1% ear, nose, throat conditions and 26.6% miscellaneous other illnesses (such as eye and dental disorders). Less than 4% of cases and controls approached for interview refused to participate and the response rates did not vary across cases and controls.

All interviews were conducted in hospital using a structured questionnaire which assessed personal characteristics and habits, anthropometric variables, education and other socio-economic factors, general lifestyle habits, such as smoking, alcohol, coffee consumption and medical history.

The study was approved by the Hospital Institutional Review Boards.

Odds ratios (ORs) for endometriosis, and the corresponding 95% confidence intervals (CI) for smoking habits. Furthermore, in order to take into account potential confounding factors, ORs were also computed using unconditional multiple logistic regression, fitted by the method of maximum likelihood [32]. The factors included in the model were age and factors found to be associated with endometriosis risk in the crude analysis.

RESULTS

Table 1 shows the distribution of cases and the controls according to age and selected factors. As expected, women with endometriosis were more educated (P=0.0005) and less frequently parous than controls (P<0.0001).

In our sample, irregular menstrual cycle, days of bleeding and oral contraceptive use were not significantly related to endometriosis, as well as alcohol drinking.

Table 2 shows the distribution of cases and controls with corresponding multivariate ORs in relation to smoking habits in the whole series and in strata of selected factors. Compared with never smokers the OR of endometriosis was 2.36 (95% CI 1.04-5.35) in ever smokers. These findings were largely consistent in strata of age and education. Considering separately nulliparous and parous women the estimated OR of endometriosis in ever smokers were 1.51 (95%CI 0.26-11.36) and 2.52.

Considering separately current smokers no risk emerged with endometriosis in the whole series (OR current vs never smokers 1.10 (95%CI 0.38.-3.00) and in strata of age education and parity (data not shown).

Table 1.
Distribution of 90 cases of endometriosis and 90 controls, according to selected factors.

	Cases No. (%)	Controls No. (%)	AOR (95% CI)
Age (years)			
<30	24 (27.8)	18 (20.4)	1
31-35	22 (25.3)	26 (29.6)	0.70 (0.26-1.85)
36-40	28 (32.2)	18 (20.4)	0.84 (0.31-2.30)
≥41	13 (14.9)	26 (29.6)	0.33 (0.11-0.99)
Education (years)			
3-8	8 (9.0)	22 (25.9)	1
9-13	37 (41.6)	39 (45.9)	2.13 (0.75-2.05)
≥14	44 (49.4)	24 (28.2)	5.65 (1.86-17.16)
Parity			
0	80 (88.9)	53 (58.9)	1
1	5 (5.6)	20 (22.2)	0.14 (0.04-0.50)
≥2	5 (5.6)	17 (18.9)	0.25 (0.06-1.01)
Menstrual cycles			
Regular	83 (92.2)	86 (95.6)	1
Irregular	7 (7.8)	4 (4.4)	0.88 (0.20-2.00)
Duration of menstrual cycles (days)			
1-3	11 (14.7)	4 (6.1)	1.69 (0.40-7.08)
4-6	51 (68.0)	51 (77.3)	1
≥7	13 (14.3)	11 (16.7)	1.27 (0.44-3.67)
Oral contraceptive use			
No	51 (56.7)	57 (63.3)	1
Yes	39 (43.3)	33 (36.7)	1.20 (0.58-2.46)
Alchool intake			
No	37(46.2)	49(54,4)	1
Yes<=1 per day	43(53.8)	41(45.6)	1.45(0.69-2.79)

Table 2.
Adjusted odds ratios (AORs) and 95% confidence intervals (95% CI) of endometriosis of ever, current and former smoking, according to selected covariates.

	Cases	Controls	AOR (95% CI) Ever smoking (ref=Never)
Whole sample	33 (37.9)	28 (31.8)	2.36 (1.04-5.35)
Age			
≤35	13 (28.9)	14 (32.6)	1.07 (0.36-3.16)
≥36	19 (47.5)	12 (27.9)	4.48 (1.14-17.71)
Education			
<14	20 (45.4)	22 (37.3)	2.25 (0.84-6.04)
≥14	13 (30.2)	4 (16.7)	3.58 (0.8-18.70)
Parity			
Nulliparae	30 (38.0)	17 (32.7)	2.42 (0.95-6.17)
Parae	3 (37.5)	11 (30.6)	1.71 (0.26-11.36)

COMMENT

The results of this study shows an increased risk of endometriosis among ever smokers This effect was however present among nulliparae but not parous women. No association emerged between current smoking and risk of endometriosis: this finding is explainable by the fact that the cases were identified in a fertility clinics and women are currently invited to quit smoking before pregnancy. Before discussing these results potential limitations of the study should be considered.

The potential confounding effect of alcohol intake (and habits commonly associated with smoking) was allowed for in the analysis, but there was no material modification in the pattern of risk estimates. Socio-economic status and body weight are associated with smoking and endometriosis: however, to take into account these factors into the analysis does not affect the general results of the study. With regard to recall bias, there is no reason to assume different recall on the basis of the disease status, as the association between endometriosis risk and smoking is not a matter of public knowledge in Italy.

The participation of cases and controls was almost complete. Controls were not examined by laparoscopy, so we cannot exclude that some may have had undiagnosed endometriosis. This can be considered a limitation of this study, but the potential misclassification should only underestimate any difference between cases and controls. Exclusion of controls with gynaecological conditions or reporting one or more birth from the analysis did not modify the risk estimates.

Some previous studies have shown controversial results on the effect of smoking on endometriosis risk. A recent meta analysis [29], however, suggests that smoking did not affect the risk of endometriosis.

Our data, however, show an increased risk of endometrosis among nulliparae but not parous women. The effect of smoking on infertility is well recognized [33]. thus this association may be at least in part due to residual confounding effect of infertility.

In conclusion despite the limitations of this study the present analysis suggest that smoking may increase the risk of endometriosis in nulliparae women attending an infertility clinic: this finding may at least in part due to the effect of smoking on infertility.

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