Clinical Paper

Is oral contraceptive associated with genital warts?

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Objective: To measure the association between oral contraceptive use and the prevalence of genital warts in women.

Methods: Cross sectional case control study comparing oral contraceptive use in women with and without genital warts attending a city centre genitourinary medicine clinic controlling for recent sexual activity, the presence of other sexually transmitted infections, socio-economic class and history of pregnancy using a multivariate logistic regression model.

Results: After controlling for potential confounding variables women with genital warts were significantly more likely to be current users of the oral contraceptive pill (OR 1.7, 95% CI 1.3-2.2).

Conclusion: The study suggests that women taking the oral contraceptive may be at increased risk of presenting with genital warts. Previously published papers provide some support for this hypothesis and potential biological mechanisms are discussed.

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Keywords: oral contraceptive pill; genital warts; human papillomavirus; STD; genitourinary medicine

Introduction

Genital warts are one of the commonest conditions diagnosed and treated in genitourinary medicine clinics and the prevalence of human papillomavirus (HPV) infection continues to increase in contrast to the decline in many bacterial sexually transmitted infections in the UK.¹ The association between certain subtypes of HPV and genital neoplasms, particularly cervical carcinoma, is a source of considerable confusion and worry to many patients particularly since current treatment options have limited value in clearing HPV from affected skin and are largely confined to cosmetic improvement. Preventive measures, such as the use of barrier contraception, are also of limited efficacy since HPV infection is often present in adjacent apparently normal skin and asymptomatic viral carriage is likely.²

Thus at present there is a rising prevalence of genital warts, with lack of an effective cure, concerns about the long-term consequences of infection and often frequent recurrences despite therapy. In addition, the clinical impression of a heterogeneous response of patients to treatment suggests that other independent factors may influence the severity and duration of infection with a small subgroup of patients having a prolonged and recurrent course of infection despite therapy.

A number of studies have suggested that use of the combined oral contraceptive pill (OCP), particularly after prolonged exposure, is associated with an increased risk of cervical dysplasia and cervical carcinoma.³⁻⁶ If certain HPV types increase the risk of cervical dysplasia⁷ is it possible that steroid hormones in the OCP increase the acquisition and/or expression of HPV leading to cervical dysplasia? Support for this hypothesis is provided by studies suggesting that increasing oestrogen levels are associated with reduced cell mediated immunity^{8,9} and that the transforming ability of certain HPV types may be enhanced by glucocorticoids.¹⁰

This cross sectional case control study

assessed whether there was an association between oral contraceptives and the presence of genital warts by comparing the prevalence of OCP use in women with and without genital warts attending a genitourinary medicine clinic whilst controlling for potential confounding variables.

Methods

All women who presented with a diagnosis of first episode genital warts between the January and 31 December 1994 at the Department of Genitourinary Medicine, Edinburgh Royal Infirmary over the age of 15 years and not known to be HIV positive were allocated to the study group. The control group was comprised of a randomly selected group of women who attended over the same time period and who were also over the age of 15, not known to be HIV positive, not attending solely for an HIV antibody test (unless also screened for sexually transmitted diseases [STDs]) and not known to have a past history of genital warts.

Information was collected from the patients' casenotes on age, the presence of specific infections likely to have been acquired sexually (gonorrhoea, chlamydia, syphilis, pubic lice and first episode genital herpes), a past history of pregnancy, the number of sexual partners within the past 3 months, the socio-economic class of the patient (based on occupation) and whether the patient was currently taking oral contraceptives. This information was routinely recorded on a proforma within the notes of each patient at the first visit.

An initial power analysis showed that 842 patients would be required to have an 80% chance of detecting a 1.5 fold difference in the use of oral contraceptive between patients with and without warts, with 95% confidence. A multivariate logistic regression model was used to compare the use of oral contraceptives in patients with and without genital warts controlling for sexual activity, age, presence of

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Distribution of STDs in patients with warts and in control groups.

other sexually transmitted diseases, socioeconomic class and past history of pregnancy. The data were entered onto the dBase database package (Borland) and exploratory analysis carried out using the EpiInfo package (WHO Public Domain). Logistic regression analysis was performed using the SPSS statistical package (SPSS Inc.).

Results

Over the one year study period 2489 female patients attended with a total of 2785 diagnostic episodes. Four hundred and twenty nine women had a first episode of genital warts and were allocated to the study group while 418 of the remaining women were assigned to the control group. The presence of STDs in each group is shown in the figure. Significantly more patients in the control group had a diagnosis of first episode genital herpes (odds ratio 10.9, 95% CI 3.9–42.4). On initial univariate comparison significantly more women with genital warts were

current users of the oral contraceptive pill (204/429 [48%]) compared with the control women who had no clinical evidence of HPV infection (153/418 [37%]) (odds ratio 1.6, 95% CI 1.2–2.1). The results of multivariate analysis controlling for the other measured variables are shown in the table. Genital warts were more common in patients aged between 21–25 years compared with older or younger age groups. Individuals with warts were also less likely to admit to having a sexual partner within the previous 3 months and were half as likely to have a concurrent STD. Current OCP use remained significantly associated with a clinical presentation with genital warts after multivariate analysis.

Owing to the larger number of patients with herpes in the control group the analysis was repeated controlling for herpes as a separate variable. OCP use remained a significantly associated with genital warts (odds ratio 1.7, 95% CI 1.3–2.1).

Discussion

In women attending a city centre genitourinary medicine clinic who presented with clinically apparent genital warts a significantly larger proportion were taking the oral contraceptive pill after controlling for recent sexual activity, age, the presence of other STDs, socio-economic class and history of pregnancy (OR 1.7, 95% CI 1.3–2.2). Thus if there were a causal relationship between the OCP and genital warts the proportion of warts attributable to the OCP would be 41% (attributable risk % = relative risk – 1/relative risk × 100). Women with warts were more likely to be aged in their early 20s and were less likely to have had a recent sexual partner or concurrent STD than the control group.

There are various mechanisms by which oestrogen and progesterone may affect the immune system and increase susceptibility to viral infection. Glucocorticoid hormones may enhance the transcription of HPV in vivo and in vitro^{10 12} and women on the OCP may have a higher prevalence of HPV.¹³ Immunity to viral infection may also be reduced by elevated oestrogen levels inhibiting natural killer cell activity.⁸ Cellular immunity, as assessed by phytohaemagglutinin induced lymphocyte transformation, is reduced in OCP users and this effect is independent of the length of exposure to OCP or the brand of OCP.⁹ The latter study suggested that OCP use had little effect on the humeral immune system although there is some evidence that oestrogens may stimulate humeral immunity and antibody production via the inhibition of suppressor T cells.¹⁴

Three recent studies have used polymerase chain reaction to detect HPV in the genital tract of women in high and low risk groups in different geographical areas^{15 17} and have then related their findings to OCP use in addition to other potential confounding variables. Although there was a trend favouring an association between OCP use and HPV detection, particularly when oral contraception was used

Multivariate analysis comparing oral contraceptive use in patients with and without genital warts

Variable	Patients without warts	Patients with warts	OR (95% CI)
Age group (years):			
16–20	63	134	1
21–25	129	154	1.2 (1–1.6)
26–30	111	73	0.7 (0.5–0.97)*
31–35	46	25	0.6 (0.4–0.99)*
over 35	69	43	0.7 (0.5–0.97)*
STD:			
yes	91	38	0.5 (0.4–0.6)*
no	327	391	1
Socio-economic class:			
1–2	38	30	1 (0.7–1.5)*
3–5	190	193	1
unknown	190	206	1 (0.7–1.2)
History of pregnancy:			
yes	182	136	0.9 (0.7–1.4)
no	189	258	1
unknown	47	35	0.8 (0.4–1.6)
Partners within past 3 months:			
none	20	55	2.5 (1.5–4.2)*
1	334	316	1
more than 1	24	28	0.8 (0.5–1.3)
unknown	40	30	0.8 (0.4–1.7)
Current OCP use:			
yes	153	204	1.7 (1.3–2.2)*
no	184	196	1
unknown	81	29	0.4 (0.3–0.6)*

*p < 0.05.

over prolonged periods, this failed to reach statistical significance. However, the presence of clinically apparent warts was significantly associated with long-term (over 5 years) OCP use in a case control study from Washington.¹⁸ There has also been an anecdotal report of recalcitrant genital warts which regressed after the withdrawal of oral contraceptives.¹⁹ The role of the OCP in genital cancers is controversial but may be protective for ovarian and endometrial tumours^{20,21} but increase the risk of cervical dysplasia (particularly high grade changes) and possibly cancer.²²⁻²⁶

Therefore despite the cross sectional design of our study, which presents difficulties in establishing a cause and effect relationship, there is a biological basis for oral contraceptives increasing the prevalence of clinically apparent genital warts (via depressed cellular immunity) and a possible dose response effect with some studies suggesting that prolonged exposure is required before an effect is apparent.

It was not possible to control for all potential confounding factors owing to the retrospective study design. Although the length of time that each patient had been sexually active was not known the patient's age may have provided an indirect assessment of this. Age at first intercourse and lifetime number of partners could also not be compared in the study and control groups. The oestrogen dose in different preparations of OCP may be relevant to the risk of genital warts, as may the total length of time on the OCP and neither of these could be assessed accurately from the present study design. Another potential confounder is condom use since those using the OCP are less likely to use barrier protection and any effect seen may reflect the lack of a condom rather than the use of the OCP. Unfortunately this information was not reliably collected in the casenotes.

In restricting the analysis to genitourinary medicine clinic attenders there is also a potential recruitment bias in those studied. Thus it is possible that clinic attenders with genital warts may differ from other patients in the community with warts who do not attend a GU clinic for treatment. There is increasing evidence, however, that sexual behaviour patterns and STD rates differ little between patients attending genitourinary clinics, family planning clinics and in general practice.²⁷⁻²⁹

Patients with genital warts were twice as likely not to admit to having had a sexual partner within the preceding 3 months. This may have been the result of embarrassment associated with having visible signs of a sexually transmitted infection inhibiting the formation of new relationships. The present study also suggests that once warts present clinically patients are no more, and possibly less, sexually active than those attending the clinic without warts, even before being provided with health education and advice. The low prevalence of concurrent STDs in patients with warts compared to genitourinary medicine clinic attenders without warts also suggests that this group may be less sexually active or

using additional barrier methods of contraception.

The relatively few studies that have assessed the association between genital warts and oral contraceptive use have generally done so in a family planning or colposcopy setting and although there is limited evidence for the asymptomatic detection of HPV being associated with taking the OCP, the evidence from this and other studies supports a limited role for oral contraceptives in the prevalence of clinical condylomata acuminatum. The major problem in interpreting these studies is the large number of other factors which may influence the prevalence of genital warts and which may act as confounders for OCP use. Thus a prospective trial using the published studies as a basis for the trial design and permitting the inclusion of these confounding factors is required to strengthen the hypothetical link between oral contraceptives and genital warts.

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