Human papillomavirus infection and use of oral contraceptives

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CRD summary
This review assessed the relationship between oral contraceptives and genital human papillomavirus (HPV) infection. The authors concluded that there was no evidence of a strong positive or negative relationship between detectable HPV and ever or long-term use of oral contraceptives, but that the evidence was limited. These conclusions are appropriately cautious given the limitations of the data presented.

Authors' objectives
To assess the relationship between oral contraceptives and genital human papillomavirus (HPV) infection using evidence from epidemiological studies.

Searching
MEDLINE was searched from 1966 to August 2002 for studies published in any language; the search terms were stated. The references in identified studies were also checked. The review also included two ‘in press’ studies from groups that presented data at the International Papillomavirus Conferences (2000 to 2002).

Study selection
Study designs of evaluations included in the review
Epidemiological studies with at least 200 participants were eligible for inclusion. The studies had to report the relative risk for HPV positivity (i.e. detectable HPV) for oral contraceptive users compared with never users, with the estimates adjusted for age or estimated for age-matched or age-restricted women. The included studies were either cross-sectional studies (all but one) or case-control studies.

Specific interventions included in the review
Studies that reported information on oral contraceptive use were eligible for inclusion. In most of the included studies, the term 'oral contraceptives' covered any dose and formulation and studies did not distinguish between combined or progesterone-only oral contraceptives.

The review classified duration of contraceptive use as short (less than 5 years), medium (5 to 9 years) or long (longer than 9 years). The review defined 'current contraceptive use' as current or use within previous year, and 'past use' as past use that stopped more than 12 months ago.

Participants included in the review
Studies of women with normal cervical cytology, or studies of women with a mix of normal and abnormal cytology who were at relatively low risk of cervical abnormality, were eligible for inclusion. Studies of women attending colposcopy clinics were excluded, as were studies of women with conditions leading to an increased risk of cervical abnormality. In the review, high risk was used as defined in the individual studies. All of the included studies classified HPV types 16 and 18 as high risk and types 6 and 11 as low risk. The number and classification of other HPV types varied among the studies. Most of the women in the included studies had normal cytology; the rates of normal cytology ranged from 89 to 100% among the studies. The studies recruited women from the general population, colleges or clinics.

Outcomes assessed in the review
Studies that assessed genital HPV infections using any method were eligible for inclusion. All but one of the included studies detected HPV in cervical specimens on the basis of the polymerase chain reaction (PCR) or hybridisation methods. One study and part of a second study detected HPV using serology. All of the included studies assessed HPV prevalence and did not distinguish between recent and persistent infection.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

**Assessment of study quality**
The authors did not state that they assessed validity.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The percentages of HPV positives for each study were tabulated. Relative risks and 95% confidence intervals for HPV positivity were presented for 'contraceptive users' compared with 'never users' for each study.

**Methods of synthesis**
How were the studies combined?
The relative risks and 95% confidence intervals were presented in forest plots. A meta-analysis was not considered appropriate.

How were differences between studies investigated?
Statistical heterogeneity was tested using the weighted least-squares method described by Cox and Snell. Separate analyses for each type of HPV (any type, high-risk and low-risk) and for different durations of contraceptive use (short-, medium- and long-term) were conducted. Results from studies that used PCR to detect the presence of HPV were analysed separately for different HPV types. Studies that adjusted for the lifetime number of sexual partners were also analysed separately.

**Results of the review**
Nineteen studies (20,509) women were included in the review.

HPV positivity and ever contraceptive use (7 studies): the studies showed no evidence of a strong positive or negative relationship between ever users and never users of contraceptives. Considerable variation in the results among studies precluded a meta-analysis.

Duration of contraceptive use (8 studies): the studies showed no consistent relationship between HPV positivity and the duration of contraceptive use. Variability of the results among studies and a lack of data on long-term use precluded a meta-analysis.

Current versus past contraceptive use: the studies showed no evidence of a strong positive or negative relationship between ever users and never users of contraceptives. Considerable variation in the results among studies precluded a meta-analysis.

Studies detecting HPV using PCR (15 studies): the studies showed similar results to an analysis of all studies. Statistical heterogeneity was less among studies using PCR. There were too few studies that did not use PCR to compare with studies using PCR.

When the analysis was restricted to studies that adjusted for lifetime number of sexual partners (10 studies), the findings were similar and the variability among studies remained.

It was not possible to assess the influence of other factors such as type of population (normal or mixed cytology), or the use of an adjustment for socioeconomic, smoking and reproductive factors, owing to the lack of data.

**Authors' conclusions**
There was no evidence of a strong positive or negative relationship between HPV positivity and ever or long-term use of oral contraceptives. The authors also stated that the evidence was limited by the paucity of data, variability among studies, and the potential for bias and confounding in the data.
CRD commentary
The review question was clear in terms of the intervention, participants and outcomes. The inclusion criteria were broadly defined in terms of the study design. Only one database was searched, which might have resulted in the omission of other relevant studies. The methods used to select the studies and extract the data were not described; hence, any efforts made to reduce errors and bias cannot be judged. Some information was presented in tabular format, while additional information was reported in the text of the review. Statistical heterogeneity was tested and illustrated graphically with forest plots. As the authors correctly stated, the variability of the results among studies indicated that the use of a meta-analysis to produce summary statistics would not be appropriate. The authors explored the influence of various factors on the results and highlighted the limitations of the evidence. The authors were appropriately cautious with their conclusions given the limitations of the data presented.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further studies are required to confirm the study findings and to investigate possible associations between oral contraceptive use and the persistence and detectability of cervical HPV infection.

Bibliographic details
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