Reviewer's report

Title: Human Papillomavirus (HPV) infection in pregnant women and mother-to-child transmission of genital HPV genotypes: a prospective study in Spain

Version: 2 Date: 2 October 2008

Reviewer: Anna Giuliano

Reviewer's report:

The authors have chosen an important problem to study – transmission of HPV from mothers to children, a topic that is grossly understudied. The methods are sound but a fuller and clearer description of the methods is needed prior to publication.

As stated in the introduction of the manuscript there is little known regarding vertical and horizontal transmission of HPV infection from mother to child. As such the manuscript submitted for review and publication by Castellsague and colleagues adds significantly to the literature. Because this is a difficult topic to study it is essential that the methods of the study design be carefully and clearly presented and the limitations of these methods, inherent to any transmission study, be presented.

Abstract:

It is essential that the final sample size used to estimate HPV prevalence among pregnant women and transmission (mother-child pairs) be written in the abstract. Also, ideally the timing of the HPV evaluation pre- and post-partum should be included in the abstract.

Methods:

It is difficult to follow the study design features of the study as written due to inconsistencies in reporting sample sizes in different sections of the manuscript. A paragraph that briefly describes and tracks the sample sizes would be most useful as an introduction. For example, the abstract lists that 943 pregnant women were screened for HPV prevalence but the Methods state that the first 115 women were excluded from prevalence analyses due to the fact that they were selected based on a high risk profile. The authors then state that all women from the pilot (n=115) were entered into the prospective part of the study but do not report the prevalence of HPV in this group or state why they chose this design element.

It would be useful to have a time frame for what is referred to as the “first or second obstetric visit”. When do these visits usually occur in the pregnancy – e.g., week 8, 12, 15? Was a full questionnaire administered to women at this time?
When was the “enrollment” visit to the prospective cohort study? As written it looks indistinguishable from the HPV prevalence screening portion of the study. State when in the pregnancy this enrollment visit occurred.

Clearly state what the final sample size of mother-child pairs was for the prospective study and state the distribution of HPV positivity among the 26 pairs that were dropped.

Adding a timeline (table or figure) of sampling mothers and children would be most helpful to clearly identify the time points and concordance of sampling between mother child pairs. For example, were mothers sampled at each of the same time points that the children were sampled?

There is a significant problem with the approach taken to examine factors associated with HPV prevalence in pregnant women. The authors specifically highlight their concern in including the 115 high risk pregnant women in an analysis of prevalence but then include all these women and HPV positive women from the general screened population for an analysis to determine factors associated with HPV infection in pregnancy. By design this group of 143 women are a biased sample. It would have been more appropriate to start with an examination of HPV prevalence and type distribution in the screened pregnant study population (n=828), describe the type distribution in this group and then go on to describe factors independently associated with infection. The number of pregnant women approached for this part of the study, the number consented, and enrolled, and the timeframe in which this occurred need to be reported. Tables 1 and 2 would then present the screened pregnant population characteristics and associations with HPV. The remaining tables would then focus on the 143 mother-child pairs.

A second related but separate part of the study is the prospective evaluation of transmission. A more careful description of how positive and negative pregnant women were selected for this part of the study, the sample size, exclusions, etc. should be reported. Were pregnant women told their HPV status prior to cohort enrollment?

Results:

As mentioned above the presentation of sample size is inconsistent. In the first paragraph 54 HPV positive women were reported from the 828 screened. In the next sentence a total of 82 HPV positives are reported with no description of where the remaining 28 HPV positive women were derived from.

Caution should be taken in reporting HPV prevalence estimates from a population of pregnant women specifically selected on HPV status. See comments above. I strongly suggest this analysis be replaced with one derived from the screened pregnant population of 828 women. Similarly, determinants of HPV status is more appropriately estimated form the screened pregnant population.
Please add the data for genotype specific concordance to Table 4.

Discussion:
Please add a limitations paragraph to the manuscript, especially for the transmission component of the study reported. For example how does acquisition of HPV post-partum influence HPV status of the child – can this be measured and assessed? What data are needed to more clearly distinguish vertical from horizontal transmission? Are there any available data to explain the HPV positivity among children born to HPV negative women? Also, add in citations to support statements regarding ease of transmission of genital compared with cutaneous infections and horizontal transmission.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests.