# Human papillomavirus vaccine and pregnancy

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## Abstract

***Question*** A patient of mine who recently learned she was 6 weeks pregnant had received the recombinant human papillomavirus (HPV) quadrivalent vaccine at 4 weeks of gestation. She is quite worried about how this will affect her baby. What is known about the safety of the HPV vaccine during pregnancy?

***Answer*** The HPV vaccine is generally not recommended for use in pregnant women. However, theoretically, because it is not a live vaccine, it is not expected to be associated with an increased risk. Also, information from the manufacturer's pregnancy registry and phase 3 clinical trials does not indicate an increased risk of fetal malformations or other adverse effects due to the vaccine.

## Le vaccin contre le papillomavirus humain et la grossesse

## Résumé

***Question*** L'une de mes patientes vient d'apprendre qu'elle est enceinte de 6 semaines et elle a reçu le vaccin recombiné quadrivalent contre le papillomavirus humain (PVH) à 4 semaines de gestation. Elle s'inquiète maintenant des conséquences pour son bébé. Que sait-on de la sécurité du vaccin contre le PVH durant la grossesse?

***Réponse*** L'administration du vaccin contre le PVH n'est généralement pas recommandée chez les femmes enceintes. Par contre, théoriquement, parce que ce n'est pas un vaccin vivant, on ne s'attend pas à ce qu'il soit associé à un risque accru. De plus, les renseignements provenant du registre des grossesses et de la troisième phase des études cliniques du fabricant n'indiquent pas de risques accrus de malformations fœtales ni d'autres effets indésirables dus au vaccin.


Human papillomavirus (HPV) infection during pregnancy is not well studied; however, there has not been any association with an increased risk of birth defects. A case-control study detected HPV more frequently in placentas from preterm deliveries than in placentas of the women in the control group who delivered at term, suggesting a link between HPV infection and risk of preterm delivery.[1] The infection has also been associated with spontaneous abortion; however, this association has yet to be confirmed.[2] Human papillomavirus infection can be transmitted to the neonate during delivery and has been found in rare instances to result in laryngeal papillomatosis.[3]

## Safety of HPV vaccine during pregnancy

Currently there are 2 inactive recombinant HPV vaccines available in Canada: a quadrivalent vaccine, which provides protection against HPV types 6, 11, 16, and 18, and a bivalent vaccine, which provides protection against HPV types 16 and 18.

Although the National Advisory Committee on Immunization recommends not using the vaccine in pregnant women, inadvertent exposures during pregnancy do occur, especially as the vaccine is recommended for women of childbearing age.[4] Postmarketing pregnancy registries have been established by the manufacturers of both vaccines to evaluate pregnancy outcomes following immunization occurring within 1 month before the last menstrual period or at any time during pregnancy.

***Quadrivalent vaccine***. A combined analysis of 5 randomized controlled trials reported outcomes of 3620 women who, during phase 3 clinical trials, were inadvertently exposed to the quadrivalent HPV vaccine or placebo either during or just before pregnancy. Of these women, 1796 received the HPV vaccine and the remainder received placebo, resulting in 2008 and 2029 pregnancies, respectively, with known outcomes. No significant differences were noted overall for the proportions of pregnancies resulting in live birth, fetal loss, or spontaneous abortion. A total of 40 neonates (2.0%) born to vaccinated women and 30 neonates (1.5%) born to women given placebo had 1 or more congenital anomalies, which was not statistically significant ($P=.20$).[5]

As mentioned previously, the manufacturer has established a pregnancy registry for postmarketing

surveillance of the quadrivalent HPV vaccine. Data from the manufacturer's second report, which covered the first 2 years following licensure (from June 1, 2006, to May 31, 2008), were published in 2009.[6] The fourth and latest report, which is not yet published, covers the period from licensure up to May 31, 2010. In this report, outcomes are available for 1432 prospectively reported pregnancies, resulting in 1257 newborns. This report shows 27 major birth defects (2.3%, 95% CI 1.5 to 3.3) among the live births. The rates of spontaneous abortions, major malformations, and other pregnancy outcomes are comparable to those in the general population.[7]

***Bivalent vaccine***. The manufacturer of the bivalent vaccine reported on known outcomes of women who, during clinical trials, received either the bivalent vaccine or a control (hepatitis A) vaccine. In a subanalysis of 761 women who were exposed to either vaccine from 45 days before to 30 days following their last menstrual period, there was no difference in major malformations or preterm delivery when compared with controls. However, spontaneous abortion occurred in a higher proportion of women who received the bivalent vaccine (13.6%) compared with a control group (9.6%). However, it is not known if this increased risk is due to the vaccine or chance.[8]

Further evidence is available from a pooled analysis of 2 multicentre, phase 3 blinded trials of women aged 15 to 25 years who were randomly assigned to receive 3 doses of bivalent HPV (types 16 and 18) vaccine (n = 13 075) or hepatitis A vaccine as a control (n = 13 055). Out of the 3599 pregnant women eligible for analysis, 1786 of whom received the HPV vaccine, the estimated rate of miscarriage was 11.5% in the HPV arm and 10.2% in the control arm (1-sided *P* value = .16). Thus, overall, there was no significant increase in the miscarriage rate among women assigned to the HPV vaccine arm.[9]

## Conclusion

According to clinical trial and registry data, the HPV vaccine, when administered during pregnancy, has not been associated with adverse pregnancy outcomes, including major malformations. If the vaccine is administered inadvertently during pregnancy, it is not necessary to become unduly concerned or to consider termination of pregnancy; however, the remaining doses should probably be delayed until completion of the pregnancy.[4] If a woman has received an HPV vaccine and is planning to become pregnant, there is no need to delay pregnancy, as the HPV vaccines are inactive.

If any of your patients have been exposed to one of the HPV vaccines before or during pregnancy, please have them call our Motherisk line at 877 439-2744.

**Competing interests**
None declared

**References**

1. Gomez LM, Ma Y, Ho C, McGrath CM, Nelson DB, Parry S. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. *Hum Reprod* 2008;23(3):709-15. Epub 2008 Jan 8.
2. Hermonat PL, Kechelava S, Lowery CL, Korourian S. Trophoblasts are the preferential target for human papilloma virus infection in spontaneously aborted products of conception. *Hum Pathol* 1998;29(2):170-4.
3. Puranen M, Yliskoski M, Saarikoski S, Syrjanen K, Syrjanen S. Vertical transmission of human papillomavirus from infected mothers to their newborn babies and persistence of the virus in childhood. *Am J Obstet Gynecol* 1996;174(2):694-9.
4. Public Health Agency of Canada [website]. *Statement on human papillomavirus vaccine*. Ottawa, ON: Public Health Agency of Canada; 2007. Available from: **www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-02/index-eng.php**. Accessed 2011 Oct 4.
5. Garland SM, Ault KA, Gall SA, Paavonen J, Sings HL, Ciprero KL, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol* 2009;114(6):1179-88.
6. Dana A, Buchanan KM, Goss MA, Seminack MM, Shields KE, Korn S, et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine. *Obstet Gynecol* 2009;114(6):1170-8.
7. Merck & Co. *Merck pregnancy registry program. Fourth annual report on exposure during pregnancy from the Merck pregnancy registry for quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine [GARDASIL/SILGARD] covering the period from first approval (June 1, 2006) through May 31, 2010*. North Wales, PA: Merck & Co. In press.
8. *Cervarix* [product monograph]. Mississauga, ON: GlaxoSmithKline; 2011.
9. Wacholder S, Chen BE, Wilcox A, Macones G, Gonzalez P, Befano B, et al. Risk of miscarriage with bivalent vaccine against human papillomavirus (HPV) types 16 and 18: pooled analysis of two randomised controlled trials. *BMJ* 2010;340:c712. DOI: 10.1136/bmj.c712.

MOTHERISK Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Ms Narducci** was a doctoral candidate in the Faculty of Pharmacy at the University of Toronto when this update was written. **Ms Einarson** is a consultant for the Motherisk Program. **Ms Bozzo** is Assistant Director of the Motherisk Program.

Do you have questions about the effects of drugs, chemicals, radiation, or infections in women who are pregnant or breastfeeding? We invite you to submit them to the Motherisk Program by fax at 416 813-7562; they will be addressed in future **Motherisk Updates**.

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