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Is administration of the HPV vaccine during pregnancy feasible in the future?

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Abstract

Despite the strong evidence supporting the efficacy of the HPV vaccine, the uptake rate remains low. One reason for this is that young females do not interact frequently with the health care system. In fact, pregnancy is often the first time young women experience multiple scheduled visits to a health provider. We review the data regarding safety of administering the HPV vaccine during pregnancy and consider the possibility of incorporating vaccination into prenatal care. Although the optimal time for vaccination is prior to sexual debut, this does not always occur. A broader approach to HPV vaccination may be necessary. Increasing the vaccine uptake rate among young women who did not initiate or complete the series earlier may significantly contribute to the decline in HPV associated diseases.

Keywords

HPV vaccine; vaccine administration; pregnancy; young women

In 2006, a non-infectious quadrivalent subunit vaccine based on virus-like particles was approved in the United States (US) for girls 9–26 years of age as a primary preventive strategy to reduce human papillomavirus (HPV)-related diseases and cancers [1]. In the following year, 80 additional countries made similar recommendations. By 2012, 19 out of 29 countries in the European Union (EU) had implemented HPV vaccination programs [201] Although the literature strongly demonstrates its efficacy [2], the uptake rate of this vaccine remains poor among most countries. In fact, only Portugal and the United Kingdom had three-dose uptake rates greater than 80% in 2010, while Australia, Denmark and Italy had rates between 50–60% and France, Luxembourg and Norway had rates less than 30% [201, 202]. The US had even lower uptake rates; only 28% of 11–17 year old girls had

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received at least 1 dose of the 3-dose series, and only 14% had completed all 3 doses by 2010 [3].

One of the common reasons cited for this universally low uptake rate is that young females do not interact frequently with the health care system. If they do see a provider for the initial immunization, they often fail to complete the series as this requires 2 additional visits over the next 6 months [4]. In an attempt to increase the uptake rate, Wright et al. investigated the feasibility of offering the vaccine to women postpartum [5]. This strategy was somewhat effective as a high percentage accepted the initial dose during their hospitalization. However, only 30% completed the entire series. Thus, the authors concluded that “novel strategies to promote vaccination are [still] needed”.

Currently, the HPV vaccine requires 3 doses to be administered over several months to mount a lasting immune response. The importance of receiving all 3 doses was recently demonstrated by a study that showed that the HPV-18 response 24 months after administration of the quadrivalent vaccine was not equal among girls given only 2 versus 3 doses [6]. One way to increase completion of all 3 doses would be to offer the vaccine during a time in a woman’s life when she is actively engaged with the health care system, such as during pregnancy. Currently, this is not possible as product labeling does not recommend administration of this vaccine to pregnant women. This policy may need to be reviewed, however, as both inactivated influenza and Tdap (tetanus toxoid, reduced diphtheria and acellular pertussis) vaccines are routinely given during pregnancy. In this article, we review data on vaccine administration during pregnancy, what is known about administering the HPV vaccine to pregnant women, and the potential benefits of administering this vaccine to pregnant women after 20 weeks gestation.

Vaccines Currently Administered During Pregnancy

Although several different vaccines are routinely administered to pregnant women, few are licensed for use during pregnancy. This is because manufacturers do not usually include pregnant women in clinical trials. Given that 15% of all pregnancies result in miscarriages, there is concern that such trials may result in associating the vaccine with fetal loss [7, 8]. As a result, most information on the effects of vaccination during pregnancy is obtained from vaccine registries, which collect information from women inadvertently vaccinated during pregnancy. These data, however, are rarely considered sufficient to recommend vaccination during pregnancy as they lack the rigorous standards of clinical trials.

In a few circumstances, guidelines have been adopted advising specific vaccinations during pregnancy in the absence of formal clinical trials. For example, a high rate of maternal deaths during the 2009 H1N1 pandemic led to a recommendation by the Advisory Committee of Immunization Practices (ACIP) of the Centers for Disease Control (CDC), and by the American College of Obstetrics and Gynecology (ACOG) that pregnant women should be immunized with the inactivated influenza vaccine [9]. Two studies support that this does not present a risk to the fetus. A study of 297 pregnant Danish women randomized to 4 arms, of which 3 received different compositions of the inactivated influenza A-H1N1 vaccine and a 4th received no vaccine, found no significant differences between groups in

the number of reported adverse events. Furthermore, no serious adverse events were observed in any group[10]. Only 6 adverse perinatal events were observed, none which were related to vaccination, in another randomized controlled trial of 340 pregnant women in Bangladesh who received either the inactivated influenza vaccine or the 23-valent pneumococcal polysaccharide vaccine [11].

In 2011, the ACIP and ACOG also began recommending the Tdap (tetanus toxoid, reduced diphtheria and acellular pertussis) vaccine for pregnant women after 20 weeks gestation stating that “the benefits of non-live vaccines outweigh any unproven potential concerns” [12]. This recommendation primarily was made to minimize the consequences of neonatal tetanus, which may occur in low income countries as a result of unhygienic birth practices [7, 13]. In the absence of maternal vaccination, newborns are vulnerable to these diseases as they are not vaccinated until 2 months of age and cannot form their own antibodies until 6 months of age. Thus, national organizations investigated other novel strategies to protect neonates, resulting in the recommendation of vaccinating pregnant women.

Several other vaccines that are not routinely given during pregnancy are recommended for high risk women. These include hepatitis A, hepatitis B, meningococcal, and pneumococcal vaccines, which are all either inactivated or subunit vaccines [14]. In addition, current research efforts are being focused on antenatal vaccines against respiratory syncytial virus and group B streptococcus [15–17]. Thus, the concept of vaccination in pregnancy is now gaining momentum and being approached with less hesitancy.

Administration of the HPV vaccine during pregnancy

No clinical trials have been conducted to specifically assess the safety of administering the HPV vaccine during pregnancy. However, data are available from other sources. For example, a manufacturer-established HPV registry from the first 2 years after vaccine licensure [18] reported prospective data on 517 women and retrospective data on 76 women inadvertently vaccinated during pregnancy. Of the live births in the prospective cohort, 97% of the neonates had no reported complications. Ten neonates had major birth defects, which is consistent with the rate of major birth defects reported in the literature. Of the 90 women who reported receiving the HPV vaccination within 30 days of their last menstrual period, 84 had live births, 3 had spontaneous abortions, 2 had elective abortions, and 1 experienced a fetal death. Of the 76 women retrospectively observed, 44 had live births, 19 had spontaneous miscarriages, 7 had elective abortions, 2 had fetal deaths, and 2 had ectopic pregnancies. Based on these data, the authors concluded that “the evaluation of pregnancy outcomes among women exposed to HPV 6/11/16/18 during pregnancy has generated no safety concerns after 2 years”.

In a pooled analysis of 11 clinical trials, which included pregnant women who received the Cervarix vaccine (n=870), pregnancy outcomes were similar for the vaccination and placebo groups, with the exception that the spontaneous abortion rate was slightly higher among vaccinated women [19]. The authors noted that this rate fell within the expected range for spontaneous abortions in the US. Another study by Wacholder et al on 3599 women with intrauterine pregnancies who received the HPV vaccine after conception also failed to

demonstrate any increased risk from the HPV vaccine as compared to the inactivated hepatitis A vaccine [20]. Overall, they observed that 92% of women who received the HPV vaccine had a term birth, 10% had a miscarriage and 0.8% had a stillbirth. No significant difference in total live births was observed between the HPV and the hepatitis A vaccine groups (p=0.23). In addition, they found no difference between the 2 vaccines in the miscarriage rate for those pregnancies conceived within 3 months of vaccination.

Safety of the quadrivalent HPV vaccine in pregnancy was further evaluated by a combined analysis of 5 phase III clinical trials [21]. A total of 1,824 women in the placebo group and 1,796 women in the quadrivalent HPV vaccine group became pregnant. No significant differences were observed in rates of spontaneous miscarriage (19.5% for the placebo group and 18.2% for the vaccine group; p=0.96) or fetal anomalies (1.5% for the placebo group and 2% for the vaccine group; p=0.20) between the 2 groups. With regards to early pregnancy exposure, 138 women in the placebo group and 128 women in the vaccine group became pregnant within 30 days of intervention. Congenital malformations were uncommon, occurring in 1 placebo and 5 vaccine cases. The authors noted that the congenital anomalies in these 6 cases were “relatively common and pathogenetically unrelated, suggesting a variety of causes”. The rate of spontaneous miscarriage among these women was also similar: 21% for the placebo group versus 18% for the vaccine group.

Pregnancy as a Period of Active Engagement with the Health Care System

Pregnancy may be the first opportunity to vaccinate some women, as a significant number of adolescents do not routinely seek out preventative healthcare services. In an attempt to increase vaccination rates, ACOG recently published a committee opinion that “obstetrician-gynecologists should embrace immunizations as an integral part of their women’s health care practice”[22]. Although HPV vaccination during pregnancy was not recommended, this approach should be considered. The first dose could be given at 20 weeks gestation, which would avoid exposing the fetus to the vaccine during the first trimester. ACIP recommends that the HPV vaccine be administered at 0, 2, and 6 months, but allows the second dose to be given as early as 4 weeks after the first dose and the third dose within 12 weeks of the second [203]. Thus, injections could be given at 20, 24, and 36 weeks gestation which would allow completion of all 3 doses prior to delivery and at a time when the woman is actively interacting with her physician [4].

Potential Benefits to the Neonate

Vaccination during pregnancy may also provide a potential benefit for the neonate. Although rare, vertical transmission of HPV has been documented in the literature and been proposed as a source of neonatal infections [23–30].This may occur as the infant passes through an infected birth canal or through an ascending infection after premature rupture of membranes, as demonstrated by the detection of HPV DNA in placental trophoblastic cells, fetal membranes, and amniotic fluid [23, 29–31]. In addition, HPV DNA has been detected in peripheral blood mononuclear cells of pregnant women, suggesting maternal blood as a possible source of fetal HPV exposure [28]. Finally, evidence suggests that HPV may be

transferred through sexual intercourse during pregnancy, possibly leading to fetal transmission [32–34].

Transmission of HPV to the fetus can result in anogenital warts, conjuctival papillomas, or laryngeal papillomas [35–38]. The latter is an exceedingly rare disease, with reported rates of 1/10,000 to 1/100,000 live births. However, in severe cases it can lead to juvenile onset recurrent respiratory papillomatosis (JO-RRP) which may cause aphonia or even respiratory obstruction and distress in young children [37, 39–44]. This is typically caused by an infection with HPV types 6 or 11 and is thought to be due to exposure to the virus in the birth canal, as vaginal deliveries and longer delivery times have been associated with development of JO-RRP [37, 45–48]. In their retrospective study of 1.2 million live births obtained from Danish registries, Silverberg et al. identified 57 cases of respiratory papillomatosis. Their analysis showed that maternal genital warts in pregnancy conferred a 231 times higher risk of disease relative to births without a maternal history of genital warts during pregnancy [37]. Futhermore, malignant transformation of respiratory papillomatosis occurs in less than 5% of cases and extralaryngeal spread occurs in approximately 30% of cases [49]. With widespread HPV vaccination, the elimination of JORRP is theoretically possible [44]. However, further research is needed as recent studies suggest that the HPV types that the vaccine protects against may not be involved in vertical transmission [50, 51].

With regard to childhood anogenital warts, evidence suggests that in addition to transmission via other sources, these infections may also be transmitted perinatally [52–56]. Studies suggest that at least 20% of anogenital warts occur because of perinatal transmission [57], and that 75% are caused by genotypes 6 and 11 [54, 56, 58, 59].

Although little research has been undertaken on the transmission of anti-HPV antibodies to infants of mothers who inadvertently received the vaccine during pregnancy, one recent study has shown that women who receive HPV vaccination prior to pregnancy are able to transfer such antibodies to their infants [60, 61]. Thus, as newborn infants are unable to produce antibodies to fight off infections during the first 6 months of life, the potential transfer of maternal anti-HPV antibodies to infants may serve as an added benefit of HPV vaccination during pregnancy.

Nevertheless, it is important to consider the rarity of vertical transmission prior to determining if pregnant women should be vaccinated against HPV. In their study of 574 pregnant women and corresponding newborns, Smith et al. found that only 1.6% of newborns tested positive for HPV DNA [40]. In addition, 5 of 6 infants showed discordant types to those of their mothers, suggesting another source of contamination such as caregivers who are in close contact with the infant [40]. A more recent study in Spain found that although risk of vertical transmission was low, the infants of mothers who were HPV-positive at the postpartum visit were 5 times more likely to test HPV-positive when compared to infants of HPV-negative mothers [42]. However, Syrjanen and others note that the frequency of vertical HPV infection remains controversial [41, 43, 51]. A careful analysis of current data and further studies are warranted to determine if it is truly efficacious to target pregnant women in order to prevent rare cases of vertical transmission.

HPV Vaccination after Sexual Debut

The major goal of vaccination of adolescents is to immunize them prior to initiating sexual activity. Since pregnant women have engaged in sexual activity and may already be infected with HPV, some may consider that vaccination will provide little benefit. However, the literature suggests women who were not vaccinated prior to sexual activity can still benefit from later vaccination, even if they have been exposed to HPV. In a retrospective analysis of 2 large double blinded, placebo controlled, randomized trials of the quadrivalent vaccine (FUTURE I and FUTURE II trials) [62, 63], the authors found that women who were PCR positive or seropositive for at least 1 HPV vaccine type at enrollment [64] that were vaccinated were less likely to develop CIN 1 or high grade dysplasia (CIN2 or worse) than those who received placebo. With regards to anovaginal dysplasia, vaccinated women were less likely to develop HPV-related external anogenital/vaginal lesions, condyloma, low grade lower genital tract dysplasia (VIN1 or VaIN1), or high grade lower genital tract dysplasia (VIN2/3 or VaIN 2/3) than those who received placebo. Based on these results, the authors concluded that despite prior exposure to HPV, subsequent vaccination afforded protection against precancerous cervical, vaginal, and vulvar lesions.

A more recent retrospective analysis of these same 2 randomized trials focused on women who had received treatment for HPV-related cervical dysplasia after intervention (i.e. HPV vaccine or placebo). In their analysis of 587 women who received the HPV vaccine and 763 women who received the placebo, the authors found that women who had received the HPV vaccine were significantly less likely to be diagnosed with HPV-related dysplasia after treatment than women who had received placebo [65]. In addition, vaccinated women were less likely to have subsequent high grade cervical dysplasia after treatment than women who received placebo. With regards to vaginal disease, women who were vaccinated were less likely to have recurrent HPV-related genital warts or vaginal dysplasia after initial treatment than women who received placebo.

Similar findings were observed in a pooled analysis of 2,617 women from 3 randomized, controlled clinical trials [62, 63, 66] of women who were HPV seropositive at enrollment [67]. None of the women who received vaccination (n=1243) developed HPV-related cervical or external genital disease, whereas 7 women who received placebo (n=1283) developed HPV-related cervical disease and 8 women developed HPV-related anogenital disease. Although randomized controlled trials are lacking, these observational studies suggest that women who have already been exposed to HPV may still benefit from vaccination.

Despite this evidence, we must remember that HPV vaccination is still most effective when administered prior to sexual debut [68]. In an ideal world, all females would receive this vaccination prior to exposure to the virus. However, given that not all young women receive the HPV vaccination during this critical time period, targeting unvaccinated women during pregnancy would be a good opportunity for “catch-up” vaccination. Given the limited funding for HPV vaccination programs, further studies are needed to determine the cost-effectiveness of such a catch-up strategy for vaccinating young pregnant females.

Expert commentary

The HPV vaccine has already had a significant impact on HPV prevalence in the US in the few years since its approval [2]. Increasing the vaccine uptake rate would increase this decline in the prevalence of HPV and diseases associated with this virus. HPV vaccination during pregnancy could provide an additional opportunity to reach women not previously vaccinated and achieve herd immunity. In fact, pregnancy may be the best opportunity to complete this multi-dose regimen due to the frequent interactions during pregnancy between women and their healthcare providers. Although data from randomized trials are not available, a review of the current literature suggests that administering the vaccine during pregnancy is not associated with adverse outcomes. Further research is needed to assess the safety of the HPV vaccine during pregnancy and the potential benefits vaccination may have on the mother and her newborn.

Five-year view

Only 14% of U.S. girls, 11–17 years of age, completed the 3-dose HPV vaccine series during 2006–2010. Similarly, low rates are evident in countries where the series is not mandated and in developing countries where vaccine supplies are limited. Thus, broader strategies are needed to promote improvement in HPV vaccination rates. We have seen an evolution from focusing only on vaccination of younger adolescent girls to the current recommendation that boys and young men should also receive the vaccine. The authors believe that in the next 5 years the value of “catch up” vaccinations will be recognized as an equally important approach in cancer prevention. Further studies will establish HPV vaccination during pregnancy as an acceptable standard of care.

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Key issues

- Vaccinations for Tdap, influenza, hepatitis A & B, meningitis, and pneumonia are administered routinely to pregnant women.
- The prenatal care period provides an excellent opportunity to begin or to “catch up” the HPV vaccination series in young women who did not initiate or complete the regime during adolescence.
- Administration of the HPV vaccine during pregnancy demonstrated pregnancy outcomes (birth defects, miscarriages, stillbirths) similar to expected ranges in the general population.
- Recent studies indicate possibility of vertical transmission of HPV antibodies to infants of mothers who received the HPV vaccine.