HPV and Cervical Cancer: Current Practice Update

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Fertility and Reproductive Medicine Symposium

Disclosures

- None to declare
Objectives

- Review current HPV vaccination indications
- Update on challenges in rolling out new cervical cancer screening guidelines
- Review the role of HPV-testing within screening programs
- Understand implications for fertility treatments

Cervical Cancer Globally
HPV Vaccination Coverage

Epidemiology

• High-risk HPV (HR-HPV)
  o 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 68
  o Responsible for nearly all cervical and vaginal cancers
  o Large part of vulvar, anal, penile and oral cancers

• Low-risk HPV (LR-HPV)
  o 6, 11, 40, 42, 43, 44, 53, 53, 61, 72, 73, 81
  o Genital warts
  o Recurrent respiratory papillomatosis
  o Oral/conjunctival papillomas
Prevalence

- HPV is the most common STI
- Considered ubiquitous
  - Over 80% of men and women will be infected at some point in their life
  - Affect ~550,000 Canadians each year
- Vast majority will clear HPV within 24 months
- Persistent HPV infection results in dysplasia

Age matters!

Schiffman M et al. Cancer Epidemiol Biomarkers Prev 2013
Vaccines

• Bivalent (HPV2): 16, 18
  o Females aged 10-25
  o Cervarix (GSK)

• Quadrivalent (HPV4): 6, 11, 16, 18
  o Females aged 9-26
  o Males aged 9-26
  o Gardasil (Merck)

• Nonavalent (HPV 9): 6, 11, 16, 18, 31, 33, 45, 52, 58
  o Gardasil 9 (Merck)

Vaccine Programs (publically funded)

◦ Boys and girls in grade 6
  (started September 2017)
◦ Up to age 26
  • HIV positive
  • Transgender
  • MSM and questioning sexual orientation (sexually active or not)
  • Street involved youth
  • Up to age 18 in the care of MCFD
  • Youth in custody
Other Indications

**Human Papillomavirus (HPV) (HPV2, Cervarix®)**
- Women born in 1994 or later who are ≤ 26 years of age.
- Men ≤ 26 years of age with lifestyle or other risks.
- HIV positive individuals ≤ 26 years of age.
- Transgender individuals ≤ 26 years of age

**Recommended**
- Women ≤ 45 years of age.

**Available**
- Women 46 years of age and older.

**Human Papillomavirus (HPV) (HPV9, Gardasil®9)**

**Recommended**
- Women ≤ 45 years of age.
- Men ≤ 26 years of age.
- Men 27 years of age and older who have sex with men.

**Available**
- Women 46 years of age and older.
- Men 27 years of age and older.

Dosing Schedules

<table>
<thead>
<tr>
<th>Age at time of 1st dose</th>
<th>Doses Required</th>
<th>Schedule (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-14</td>
<td>2</td>
<td>0,6</td>
</tr>
<tr>
<td>≥ 15</td>
<td>3</td>
<td>0,2,6</td>
</tr>
</tbody>
</table>

➢ Three doses recommended if immunosuppressed
What about BC?

Efficacy and Safety

- HPV2 and HPV4 prevent 70% of cervical cancers
  - HPV 2 → 98.1% efficacy against CIN2+
  - HPV 4 → 98.2% efficacy against CIN 2+, AIS
- HPV9 prevent 90% of cervical cancer
  - 91% of anal cancers in women
  - 84% of anal cancers in men
- No abnormal clustering of adverse events
Barriers to Vaccination

- Common myths about the risk of the vaccine
- Cost!
  - Most expensive commercial vaccine ever developed
  - >$100/dose
  - Some compassionate coverage available

Does the vaccine change high risk sexual behaviour?

- Large Australian cohort using other STIs as indicators of sexual activity in vaccinated and unvaccinated groups did NOT show any difference in high risk sexual behaviours
- No difference between initiation of sexual activity, number of sexual partners or condom use in vaccinated and unvaccinated cohorts
- Some evidence of increased condom use in vaccinated populations
- Challenging discussion in a variety of cultural and religious settings
Why bother if I have already had an abnormal pap?

- Recommendation depends on age
- Protection from HPV type they have not yet been exposed to
- Evidence the vaccination facilitates clearance of acute HPV infections
  - Post-LEEP setting recommendations

Should I get the HPV9 if I have had the HPV4 in the past?

- No specific literature
- 70 versus 90% coverage however population tends to be over age 26
- Primary side effect is $$$
Why can’t my kid decide for themselves when they are 18?

- Increased vaccine effectiveness if given prior to exposure to HPV
- Young immune systems react differently to vaccines
  - More robust immunogenic response
  - Immune quiescence as we age

Secondary Prevention – BC Guidelines

- Pap update in BC 67-69%
  - Slight decrease in update in women under 30
- Starting at age 25 or 3 years after first sexual activity \textit{whichever is later}
- Until age 69
- Interval is now every 3 years
- Decrease to 12 months the length of time we follow low-grade changes conservatively
Won’t we miss cases in younger women?

- 15 – 19 year olds
  - 3/1,000,000
  - Rate unchanged since centralized screening programs began in 1970s
- 20 – 24 year olds
  - 1.35/100,000
  - No change in mortality since screening programs began

Harms of Over-Screening

- Invasiveness of a pelvic exam
- FURTHER invasiveness of a colposcopic exam which involves a cervical biopsy
- Discomfort of a LEEP
- Implications for future pregnancies
  - Preterm labour (<37 weeks)
  - Second trimester loss
Adverse Pregnancy Outcomes

<table>
<thead>
<tr>
<th>Outcome (# of studies)</th>
<th>Cases</th>
<th>Controls</th>
<th>Pooled Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd trimester loss (4)</td>
<td>1.6%</td>
<td>0.4%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Preterm birth &lt; 34 weeks (5)</td>
<td>48/1,670 (2.9%)</td>
<td>6,053/267,889 (2.3%)</td>
<td>48/1,670 (2.9%)</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes (6)</td>
<td>108/2,102 (5.1%)</td>
<td>7,940/314,891 (2.5%)</td>
<td>108/2,102 (5.1%)</td>
</tr>
<tr>
<td>Preterm birth &lt; 37 weeks</td>
<td>473/5,457 (8.6%)</td>
<td>54,036/1,172,059 (4.6%)</td>
<td>473/5,457 (8.6%)</td>
</tr>
<tr>
<td>vs. no dysplasia (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vs. dysplasia untreated</td>
<td>109/1,092 (10.0%)</td>
<td>17,696/242,946 (7.2%)</td>
<td>109/1,092 (10.0%)</td>
</tr>
</tbody>
</table>


Exceptions to the Rules?

- Provider autonomy
- Early age of first sexual activity
- Multiple sexual partners
- Smoking
- Immune status – HIV (guidelines in the works)
- Term pregnancy as an adolescent
HPV Primary Screening

- HPV has a higher sensitivity (over 90%) than pap smears (65-70%)
- Testing for the virus that causes the abnormal cells instead of detecting the dysplastic cells themselves
- The interval between HPV testing can therefore be longer at 5 years

Private Pay HPV Testing

- Problematic as no current algorithm within provincial screening program
- Cost of around $90
- Clinician collected specimen
Gaps in Screening

- Immigrant and refugee populations
- First Nations, Inuit and Metis women
- Underserviced/rural geographies
- Women with disabilities
- LGBTQ+ populations
HPV Self-collection in BC

Implications for Fertility Treatments

- More likely to engage in screening prior to fertility treatments
- Consider age and ovarian reserve when considering any delay in fertility treatments based on abnormal cervical cytology
Recommendations for AIS

- Adenocarcinoma in situ
  - Screening challenging due to skip lesions
- Definitive treatment is hysterectomy if childbearing complete
- Alternatively followed for 5-years with colposcopy q6months

Common HPV Questions

- Do I need to tell my partner I have HPV?
  - Personal decision
  - The more you know about HPV the less worry both you and your partner will have
  - If you are monogamous you and your partner likely share the same strain of HPV
  - Most common STI, most sexually active people have been exposed
  - Not possible to determine who gave you HPV
  - If you partner is male, serious HPV related health problems are rare
What do women want to hear?

- De-stigmatize HPV/Emphasize prevalence
- Taking time with women to address their questions and concerns
- Consistent, easy to understand messaging
- Using a variety of methods to convey information (pamphlets/web-based/verbal)

Smith LW and Ogilvie GS

Take Home Messages

- Remember that over-screening causes harm!
- HPV vaccination is safe, its very effective and we need to improve coverage
- We have significant gaps in screening in BC and globally
- Need to de-stigmatize HPV
Useful References

- www.bccancer.bc.ca/HPVFOCAL
- http://www.bccancer.bc.ca/screening/health-professionals/cervix
- http://www.immunizebc.ca/diseases-vaccinations/hpv
- http://hpvinfo.ca/

Questions

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Vaccine Safety

- Rates of most adverse events are no higher than other vaccines
- Report peaked in 2008 and have since declined
- Adverse events with significantly higher rates
  - Syncope: 8.2/100,000
  - Venous thromboembolic events: 0.2/100,000
  - Headache, dizziness, nausea, injection site reaction, allergic reaction

www.cdc.gov/vaccinesafety/vaccines/hpv