# Primary Ovarian Insufficiency and Adolescent Vaccination

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# Primary Ovarian Insufficiency and Adolescent Vaccination

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abstract

**BACKGROUND:** Published case series have suggested a potential association between human papillomavirus (HPV) vaccination and primary ovarian insufficiency (POI). We describe POI incidence and estimate POI risk after HPV; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap); inactivated influenza (II); and meningococcal conjugate (MenACWY) vaccination.

**METHODS:** We searched Kaiser Permanente Northwest electronic health records for outpatient diagnoses suggestive of POI in female patients aged 11 to 34 years between 2006 and 2014. We reviewed and adjudicated the medical record to confirm diagnoses and estimate symptom onset dates. We excluded cases with known causes and calculated the incidence of idiopathic POI. We estimated risk by calculating hazard ratios and 95% confidence intervals (CIs).

**RESULTS:** From a cohort of 199 078 female patients, we identified 120 with diagnoses suggestive of POI. After adjudication and exclusion of 26 POI cases with known causes, we confirmed 46 idiopathic POI cases. POI incidence was low in 11- to 14-year-olds (0.87 per 1 000 000 person-months) and increased with age. One confirmed case patient received the HPV vaccine 23 months before the first clinical evaluation for delayed menarche. The adjusted hazard ratio was 0.30 (95% CI: 0.07–1.36) after HPV, 0.88 (95% CI: 0.37–2.10) after Tdap, 1.42 (95% CI: 0.59–3.41) after II, and 0.94 (95% CI: 0.27–3.23) after MenACWY vaccination.

**CONCLUSIONS:** We did not find a statistically significant elevated risk of POI after HPV, Tdap, II, or MenACWY vaccination in this population-based retrospective cohort study. These findings should lessen concern about POI risk after adolescent vaccination.

*Naleway et al. Pediatrics. 2018;142(3). pii: e20180943.*

# Background

- **Primary Ovarian Insufficiency (POI):**
  - Premature menopause, premature ovarian failure
- **Characterized by the following before the age of 40 years:**
  - Dysfunction or depletion of ovarian follicles
  - Menopausal symptoms (e.g. amenorrhea, hot flashes)
  - Reduced fertility
- **Under age of 20, POI is uncommon**
  - Estimated prevalence is one case per 10,000 females
- **Known etiologies**
  - Turner syndrome, Fragile X syndrome, gonadotoxic cancer treatment
  - Most POI is idiopathic but may be associated with underlying autoimmune or infectious disease

# Background

- **Findings from over 12 years of post-licensure HPV vaccine safety studies are robust and reassuring:**
  - However, concerns surrounding association between POI and receipt of HPV vaccine from:
    - Published case series
    - Media attention
    - Social media and internet sites
- **Objective of study:**
  - Identify and describe characteristics of POI diagnosed in females 11-34 years
  - Describe prevalence and age-specific incidence of POI
  - Estimate the risk of idiopathic POI in females following 4vHPV vaccination and other adolescent vaccinations (Tdap, MenACWY, and IIV)*

*4vHPV- quadrivalent human papillomavirus vaccine; Tdap- tetanus, diphtheria, and acellular pertussis vaccine; MenACWY- meningococcal conjugate vaccine; IIV- inactivated influenza vaccine

# Methods

- **Study population:**
  - Females aged 11–34 years enrolled for at least 30 days at the Kaiser Permanente Northwest (KPNW) Vaccine Safety Datalink (VSD) site
- **Study period:**
  - August 1, 2006 through December 31, 2014

# Methods

- **Searched for select ICD-9 coded diagnoses in electronic health record databases**
  - 1st diagnosis in study period = index diagnosis
- **Chart review**
  - Information collected included:
    - Diagnostic testing (FSH, estradiol), karyotyping, adrenal antibodies, thyroid antibodies, anti-mullerian hormone, family history, cancer diagnoses/treatments, autoimmune diseases, vaccinations, symptom onset
- **Excluded non-cases and POI with a known cause**
  - Miscoded, ruled out diagnoses, or when medical record unavailable
  - Cancer diagnosis and treatment (radiation and/or chemotherapy), Surgical menopause, Turner syndrome, Fragile X, other sex chromosome disorder
- **OB/GYN clinician adjudication**

# Methods

- **Case definition:**
  - American College of Obstetrics and Gynecology (ACOG)
    - Menstrual irregularity for at least 3 consecutive months
    - Elevated follicle stimulating hormone (FSH) in the post-menopausal range and low estradiol levels on two separate occasions
- **Case confirmation:**
  - Probable POI:
    - there is strong evidence to support a diagnosis of POI and/or most or all of the case definition is met
  - Possible POI
    - there is some evidence to support a diagnosis of POI, but the case definition is not met
  - Not POI
    - the case clearly does not meet the case definition

# Methods

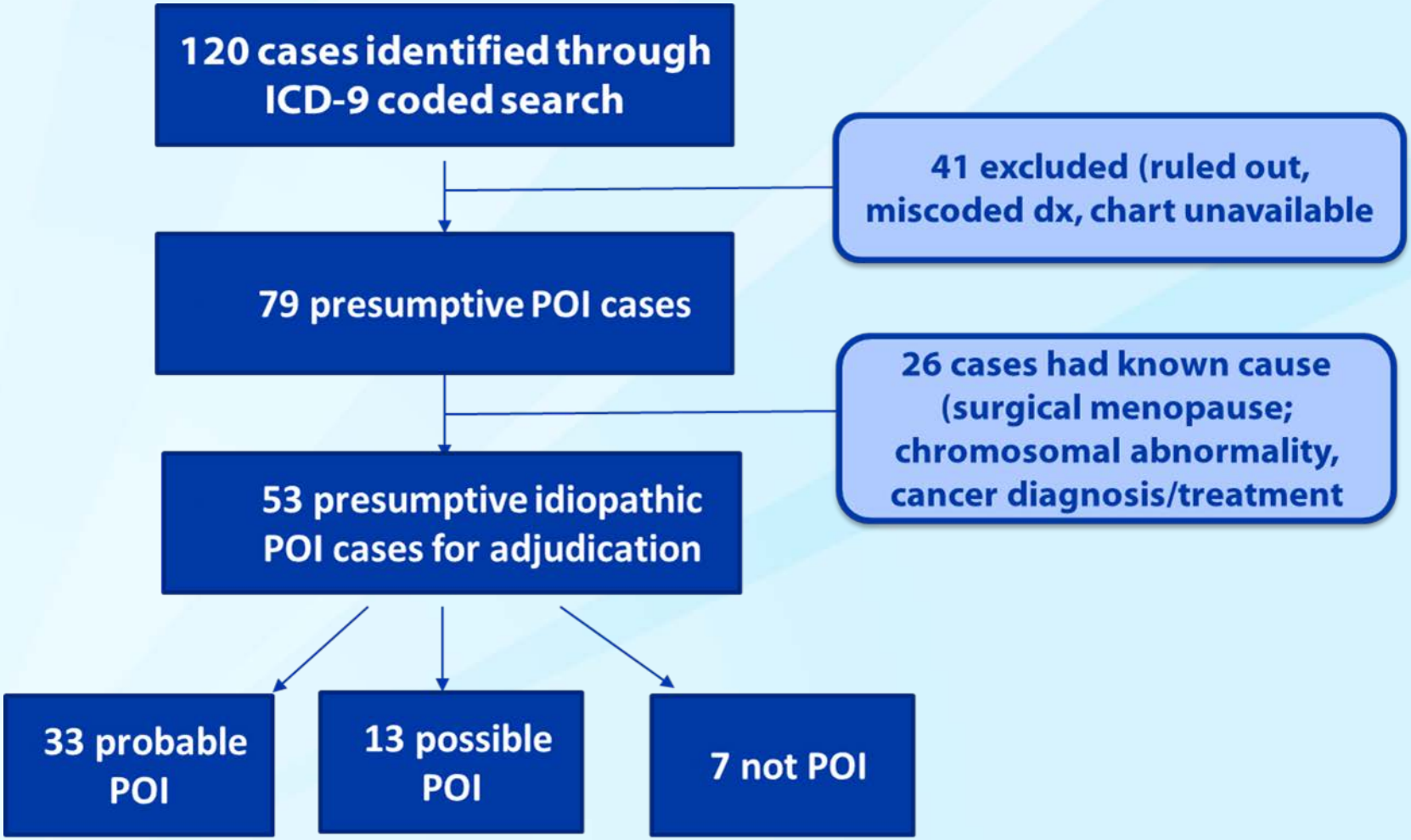
- **Symptom onset date**
  - Date of POI symptom onset in medical record
  - Estimated onset date:
    - Age of onset
    - Date of last menses
    - Earliest documented encounter for delayed menarche, amenorrhea, oligomenorrhea, or infertility evaluation
- **Among <u>probable</u> and <u>possible</u> POI cases:**
  - Conducted descriptive analyses
  - Calculated:
    - Prevalence and age specific incidence rates of idiopathic POI
    - Risk estimation
      - Hazard ratios, 95% CIs

# Results

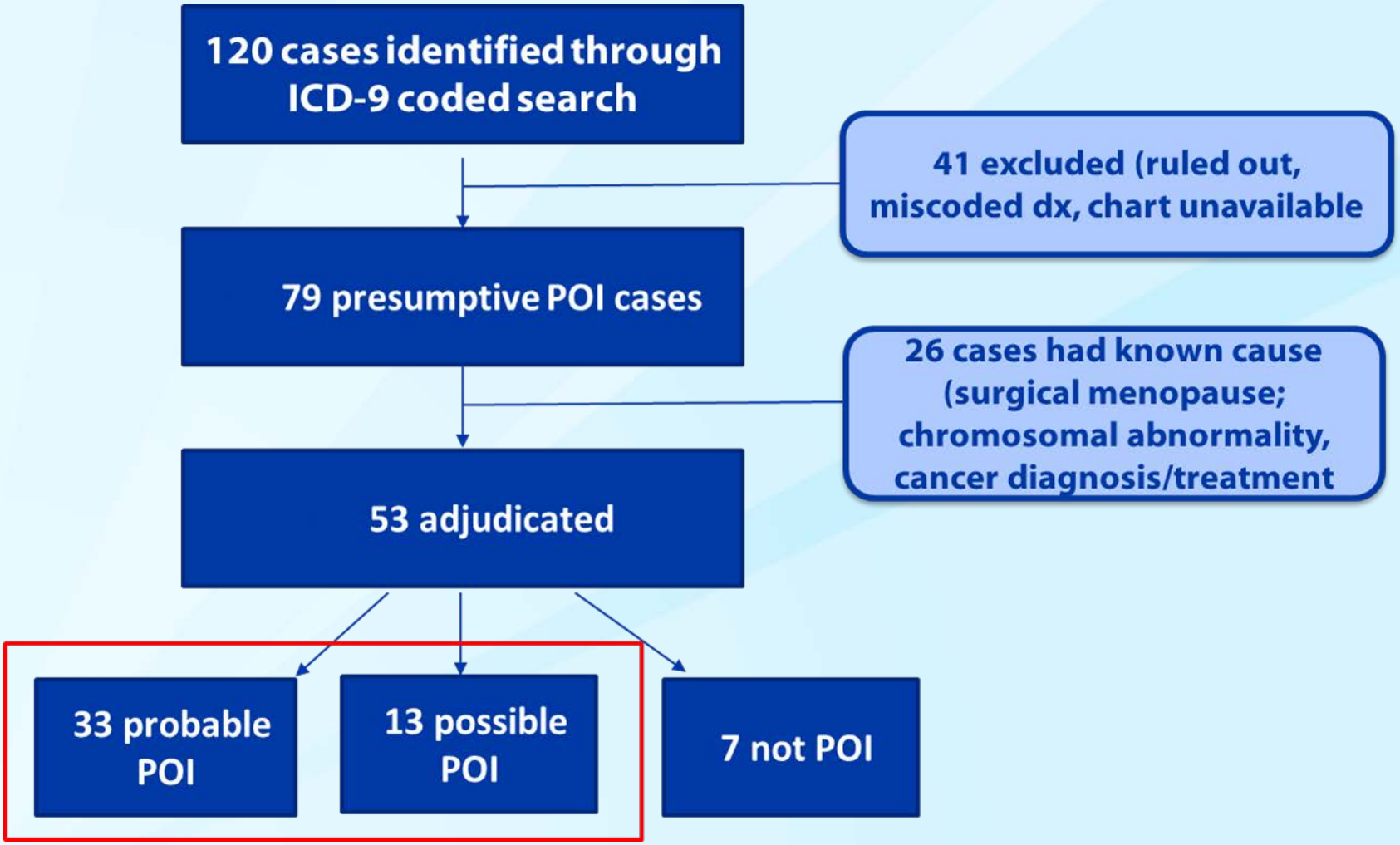
- **199,078 11-34 year old females enrolled at KPNW during study period**
  - 58,871 received 4vHPV (at least one dose)
  - 119,078 received Tdap
  - 46,231 received MenACWY
  - 84,783 received IIV

4vHPV- quadrivalent human papillomavirus vaccine; Tdap- tetanus, diphtheria, and acellular pertussis vaccine; MenACWY- meningococcal conjugate vaccine; IIV- inactivated influenza vaccine

# Results


120 cases identified through ICD-9 coded search
41 excluded (ruled out, miscoded dx, chart unavailable
79 presumptive POI cases
26 cases had known cause (surgical menopause; chromosomal abnormality, cancer diagnosis/treatment
53 presumptive idiopathic POI cases for adjudication
33 probable POI
13 possible POI
7 not POI

# Results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# Results: Descriptive analysis among 46 probable and possible idiopathic POI cases

| Characteristic | N (%) |
|---|---|
| Race | |
| White | 28 (61) |
| Non-white | 5 (11) |
| Unknown | 13 (28) |
| Ethnicity | |
| Latina/Hispanic | 7 (15) |
| Non-Latina/Non-Hispanic | 31 (67) |
| Unknown | 8 (17) |
| Met ACOG definition | 9 (20) |
| Autoimmune comorbid diagnosis | 8 (17) |
| Primary amenorrhea | 6 (13) |
| Family history of POI | 4 (9) |

Primary amenorrhea is defined as the absence of menses at age 15 years in the presence of normal growth and secondary sexual characteristics.

# Results: Descriptive analysis among 46 probable and possible idiopathic POI cases

| Age (years) | Symptom Onset N(%): | Diagnosis N(%): |
|---|---|---|
| 11-14 | 6 (13) | 1 (2) |
| 15-18 | 9 (20) | 5 (11) |
| 19-22 | 5 (11) | 4 (9) |
| 23-26 | 11 (24) | 7 (15) |
| 27-30 | 10 (22) | 13 (28) |
| 31-34 | 5 (11) | 16 (35) |

Median time from sx onset to diagnosis ~3 years (range: 75 days-16 years)

# Results

- Prevalence of idiopathic POI in the study period 2.31 per 10,000 females

**Age specific incidence of diagnosed POI:**

| Age at initial diagnosis (years) | Cases | Person-months | Incidence per million person months (95% CI) |
|---|---|---|---|
| 11-14 | 1 | 1,151,805 | 0.87 (0.12-6.16) |
| 15-18 | 5 | 1,226,602 | 4.08 (1.70-9.79) |
| 19-22 | 4 | 1,109,535 | 3.61 (1.35-9.61) |
| 23-26 | 7 | 1,059,109 | 6.61 (3.15-13.86) |
| 27-30 | 13 | 1,151,201 | 11.29(6.56-19.45) |
| 31-34 | 16 | 1,245,185 | 12.85 (7.87-20.97) |

# Results

- **Among 46 probable and possible idiopathic POI cases:**
  - 18 confirmed cases (39%) had symptom onset prior to August 1, 2006
  - Leaving 28 confirmed cases of idiopathic POI
- **Exposure status of 28 confirmed cases of idiopathic POI*†,**

| Vaccine type** | Cases vaccinatedprior to symptom onset |
|---|---|
| 4vHPV | 1 |
| Tdap | 6 |
| MenACWY | 3 |
| IIV | 11 |

*Some had more than one vaccine exposure

†15/28 no documentation of exposure to these vaccines in the medical record

** 4vHPV- quadrivalent human papillomavirus vaccine; Tdap- tetanus, diphtheria, and acellular pertussis vaccine; MenACWY- meningococcal conjugate vaccine; IIV- inactivated influenza vaccine

# Results

- **4vHPV vaccinated case:**
  - 16 yearsold at time of diagnosis
  - Received 3rd 4vHPVdose approximately 23 months prior to symptom onset date
    - In this case, symptom onset date was estimated as the first encounter for delayed menarche
  - Negative for autoantibodies, normal karyotype, no autoimmune diagnoses

# Results

## POI incidence in vaccinated and unvaccinated and associated age-adjusted hazard ratios (HRs) with 95% CIs

| Vaccine type* | Cases vaccinated prior to symptom onset | Unexposed cases | Age-adjusted HR (95% CI) |
|---|---|---|---|
| 4vHPV | 1 | 27 | 0.30 (0.071.36) |
| Tdap | 6 | 22 | 0.88 (0.372.10) |
| MenACWY | 3 | 25 | 0.94 (0.273.23) |
| IIV | 11 | 17 | 1.42 (0.593.41) |

* 4vHPV- quadrivalent human papillomavirus vaccine; Tdap- tetanus, diphtheria, and acellular pertussis vaccine; MenACWY- meningococcal conjugate vaccine; IIV- inactivated influenza vaccine

# Challenges and Limitations

- **Time from symptom onset to diagnosis may be variable or long**
  - Median time from symptom onset to POI diagnosis was 3 years
  - Potential for misclassification was minimal, as 81% of our cohort were enrolled in health plan for > 24 months
- **Patients did not undergo all the diagnostic testing required to meet the ACOG definition**
  - 9 out of 46 probable/possible cases met the ACOG definition
- **Hormonal contraceptive use may mask POI symptoms and onset of POI**
  - Unable to collect hormonal contraceptive use
  - Studies show that potential for misclassification would be non-differential
    - No difference in use among vaccinated as compared to unvaccinated

# Conclusion

**In this study of nearly 200,000 young women, we observed no evidence of increased risk of POI following HPV vaccination or other routine adolescent exposures.**

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- Kathleen Mittendorf PhD
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# Thank you!

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