Primary Ovarian Insufficiency after Vaccination: Reports to the U.S. Vaccine Adverse Events Reporting System, 1990–2017

A. Patricia Wodi, MD[1]; Paige Marquez, MSPH[1]; Adamma Mba-Jonas, MD, MPH[2]; Faith Barash, MD, MPH[2]; Pedro L Moro, MD, MPH[1]

[1] Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA [2] Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD

Background

- Since 2012, six cases of primary ovarian insufficiency (POI) temporally associated with receipt of human papillomavirus (HPV) vaccine have been published in medical journals leading to questions about a potential causal association. A CDC Vaccine Safety Datalink study did not find an increased risk for POI after vaccination. To our knowledge, there are no published reports of POI temporally associated with receipt of non-HPV vaccines. We reviewed the Vaccine Adverse Event Reporting System (VAERS) to describe reports of POI after vaccination.
- Vaccine Adverse Events Reporting System (VAERS)
  - National, United States (U.S.) spontaneous reporting surveillance system operating since July 1990
  - Co-managed by CDC and FDA
  - Receives adverse event reports from manufacturers, medical providers, vaccine recipients, and the general public
  - Signs and symptoms in reports are coded using the Medical Dictionary for Regulatory Activities (MedDRA)
  - The information in each report and the assigned MedDRA codes are entered into the database.

Objective

To describe the characteristics of reports with a diagnosis of POI after vaccination in the Vaccine Adverse Event Reporting System.

Methods

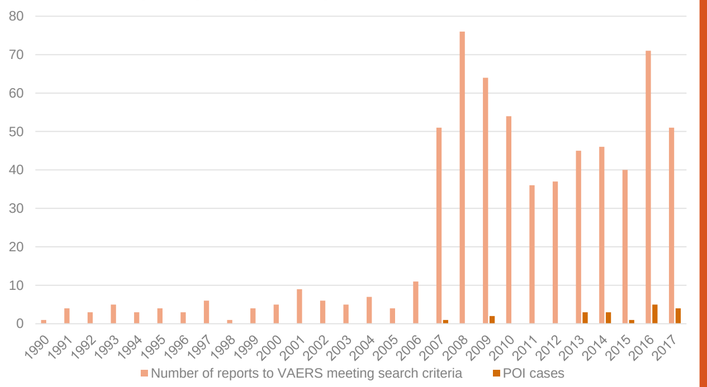
We searched VAERS to identify U.S. POI reports received from 01/01/1990 through 12/31/2017 after any vaccination. Two different search methods were used: (1) Medical Dictionary for Regulatory Activity Preferred Terms ("Premature Menopause", "Ovarian Disorder", "Ovarian Failure", "Amenorrhea", "Infertility", "Infertility Female", "Blood Follicle Stimulating Hormone Increased", "Oestradiol Decreased" and "Estradiol Decreased" and (2) text-based search ("Ovarian", "Amenorrhea" and "Premature Menopause"). Duplicate reports were identified and a final unique list was created. We reviewed each report and accompanying medical records (if available) to collect demographic and clinical information and then applied the American College of Obstetricians and Gynecologists (ACOG) guidelines for POI diagnosis i.e. presence of menstrual irregularity for at least 3 months, elevated follicle-stimulating hormone (FSH) in the postmenopausal range and low estradiol levels on 2 separate occasions.

Table 1: Characteristics of Primary Ovarian Insufficiency (POI) Reports in VAERS

Characteristics	Results N=19
Median age at vaccination[a]	14.5 years (range 10 -25 years)
Median age at POI diagnosis	18 years (range 15 -30 years)
Use of hormonal contraceptives	5 (26.3%)
POI etiology reported[b]	1 (5.3%)
Reporter	
Manufacturer	9 (47.4%)
Parent	8 (42.1%)
Healthcare provider	2 (10.5%)

[a] Age of 1st dose in report. Not reported=5
[b] 47XXX Chromosomal abnormality

Figure 1: Primary ovarian insufficiency (POI) after any vaccination reported to VAERS by year of report, Vaccine Adverse Event Reporting System (VAERS), January 1, 1990 – December 31, 2017



Results

Of 571,178 VAERS reports received during the study period, 652 unique reports met the search criteria. Clinical review identified 19 reports with a POI diagnosis (Table 1). Most reports (n=16) were received 2013 – 2017 (Fig 1) and median interval between vaccination and reporting was 36 months (range 0 – 132 months). Symptom onset was available for 2 reports (~2 and 10 months). Eleven reports documented irregular menses ≥3 months and 6 had ≥1 laboratory test result used to diagnose POI. Four reports met ACOG diagnostic guidelines. Eighteen of 19 reports described receipt of HPV vaccine with or without other vaccines. Other vaccines reported were meningococcal conjugate vaccine, hepatitis A, varicella and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis. Three reports described multiple vaccines.

Limitations

- Variable quality and completeness of VAERS reports including capture of clinical history and laboratory results
- VAERS not designed to assess if adverse event(s) is casually related to vaccine

Conclusion

POI is rarely reported to VAERS. Most reports contained limited clinical and diagnostic information and were submitted after published cases of POI following HPV vaccination. Results of our review do not suggest a safety concern.

References

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