Merck Pregnancy Registry for qHPV Vaccine (Gardasil®): Exposure During Pregnancy June 1, 2006 through May 31, 2012

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Introduction

- Gardasil is not recommended for use during pregnancy
- Inadvertent exposures may occur
- All reports of exposure to vaccine during pregnancy are monitored closely by Merck
- The Pregnancy Registry for Gardasil has been one part of a multifaceted plan to monitor the safety in pregnancy from approval (2006). The Registry was part of regulatory commitments with the US FDA, the EMA, and Health Canada at the time of approval.

Methods

- Goals
  - Acquire information on pregnancy exposures/outcomes
  - Help identify safety signals
  - Provide information to providers, regulators and patients
- Data source
  - Pregnancy exposures spontaneously reported to Merck
- Enrollment criteria
  - Originate in U.S., Canada, or France
  - Unique patient identifier
  - HCP is identified
  - Received Gardasil within 1 month prior to the onset of the LMP or anytime during pregnancy

Methods

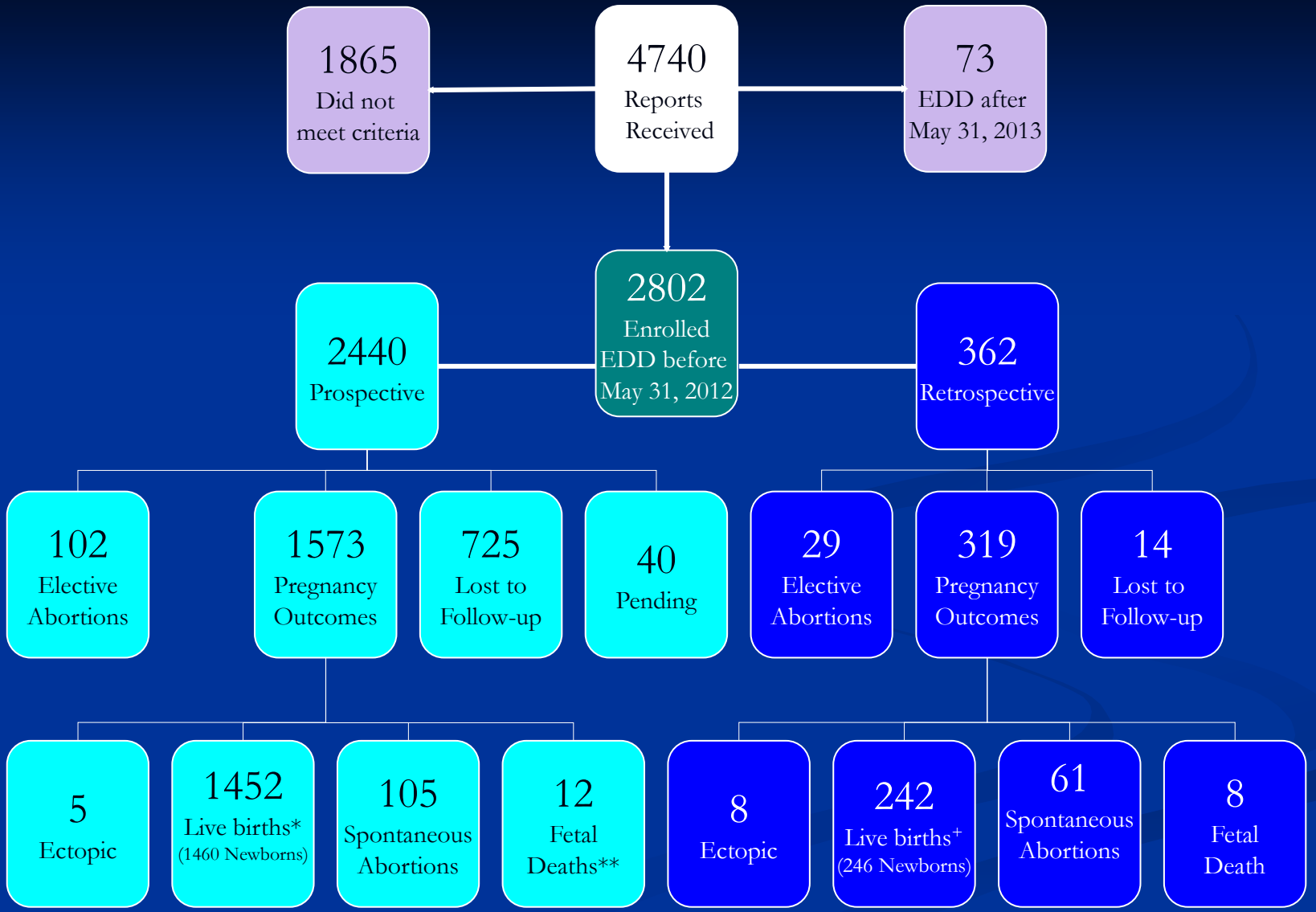
- Instructions about how to make a report into the pregnancy registry were described in the label and website (www.merckpregnancyregistry.com).
- The label and website also described the criteria for enrollment
- In summary, the data source for the registry consisted of:
  - Pregnancy exposures reported to Merck
    - Spontaneous and voluntary
    - From HCPs and vaccinees
- Pregnancy reports were monitored as they were received

Methods

- Prospective reports are those received before the outcome of the pregnancy is known
  - Primary cohort for rate calculations
- Retrospective reports are those received after the outcome is known
- Primary outcomes of interest:
  - Pregnancy outcomes: Elective abortions, Spontaneous abortions (prior to week 20), Fetal deaths (≥week 20), Live births
  - Infant outcomes (Congenital anomalies)
  - Medical Records were requested for up to 2 years
- Birth defect frequencies calculated on prospective reports using MACDP* methodology
  - # affected (live born, fetal deaths, terminations ≥20 weeks) per 100 live born infants
- Appropriate experts were consulted as needed

*MACDP= Metropolitan Atlanta Congenital Defects Program

Results as of May 31, 2012



* Includes 8 sets of twins

** One twin pregnancy resulted in 2 different outcomes (late fetal death and live birth), therefore outcome is counted twice.

\+ Includes 4 sets of twins and 1 single twin

Prospective Reports (Primary Analysis Population)

- Report disposition (n=2440), 30% lost to FU, <2% pending, 69% (n=1,675) had outcomes available
- Age range 11 to 42 years (mean 20 years)
- ~91% of exposures were prior to the end of the 1st trimester
- 102 elective abortions* (1 associated with anencephaly and hypoplastic heart)
- 105 spontaneous abortions (Includes 1 triplet pregnancy and one with chromosomal anomaly)
- Infant Outcomes=1460 newborns
  - 1381 normal infants (95%)
  - 34 infants with major congenital anomalies as defined by MACDP and 45 had minor congenital anomalies

*4 elective abortions involved a double first trimester exposure; 2 elective abortions involved 1st and 2nd trimester exposures

Prospective Reports

- Rate of spontaneous abortions: 6.7/100 outcomes (95% CI 5.5, 8.2)
  - Background rate among clinically recognized pregnancies is 15%[1]
- Rate of fetal deaths: 0.8 per 100 outcomes (live births + fetal deaths) (95% CI 0.4, 1.4)
  - Background rate 0.62 to 1 per 100 [2-3]
- Overall rate of major congenital anomalies: 2.5 per 100 live born infants (95%CI 1.7, 3.4)
  - Background rate 2.67 per 100 live born infants[4]

1. Scott JR. *Danforth's Obstetrics and Gynecology*. Lippincott Williams & Wilkins. 1999: 143-53.
2. Fox R et al. *Br J Obstet Gynaecol*; 104:4-10, 1997
3. MMWR 56(49);1293, Dec 14, 2007
4. Correa et al, Birth Defects Research, Part A: Clinical and Molecular Teratology. 79(2): February, 2007.

Retrospective Registry Reports

- 362 retrospective reports
- 25 infants with major congenital anomalies
  - 13 isolated congenital anomaly
  - 4 with 2 anomalies each
  - 3 multiple anomalies
  - 2 multiple anomalies as part of chromosomal abnormality

Rationale for Registry Discontinuation

- Registry has fulfilled its regulatory obligation of 5 years
- The largest vaccine pregnancy registry to date
- There was no clustering of malformations in a specific SOC
- There was no identified pattern in terms of birth defects
- Overall rates of spontaneous abortions, fetal deaths and congenital anomalies were at or below background rates
- Continuation of the registry will not significantly increase the power to detect adverse pregnancy outcomes.

Ongoing and Future Activities

- Routine pharmacovigilance activities will continue for all exposures during pregnancy including:
  - Cases are reviewed in real time
  - Follow-up attempts on all cases
  - Periodic aggregate analysis
  - Case reports and analysis routinely submitted to agencies
- Merck has updated the website with text noting the discontinuation of the registry, and the Company's continued interest in receiving reports of exposure during pregnancy.
- A summary of the overall results of the pregnancy registry will be added to the label.
- Merck will prepare a final Registry Report with all the data and publish the final data in a peer review journal

Summary

- Data from the registry are reassuring with respect to safety after pregnancy exposures
  - Rates of spontaneous abortions, fetal deaths, and overall congenital anomalies compare favorably to background rates
- Rate of congenital anomalies appears consistent with background rates
  - Reported anomalies are varied in type, etiology, and gestational age
- This review does not support a causal relationship between qHPV vaccine and the birth defects reported to the pregnancy registry.
- Merck has monitored the safety of Gardasil for >6 years including reports of exposure during pregnancy.
- The FDA, EMA and Health Canada considered Merck's regulatory commitment for the pregnancy registry fulfilled as of April 2013.