Report on Human Papillomavirus Vaccine safety research regarding the ovary.

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HUMAN PAPILLOMAVIRUS VACCINE and the OVARY: the NEED FOR RESEARCH

Author and affiliation
Deirdre Little dradford@wirefree.net.au
Department of General Practice North Bellingen Medical Services, Bellingen, NSW Australia.
Visiting Medical Officer Bellinger River District Hospital, NSW, Australia

Summary
New onset of menstrual disturbance and oligomenorrhoea commencing four months after quadrivalent human papillomavirus vaccine (HPV4) and proceeding to premature ovarian failure over the next twenty four months occurred in a well 16-year-old girl. Exclusion of metabolic, other endocrine, genetic and overt auto-immune causes left unknown causation as it does in 90% of cases. Enquiry of vaccine animal testing found no research reports were available of ovarian histology or of ongoing ovarian function in vaccine tested rats. Histology reports were available of vaccine tested rat testes and epididymides. Pre-clinical studies did not consider the duration or capacity of the reproductive life-span. Subsequent phase II and phase III clinical studies before vaccine licensing have lacked the capacity to attest to ovarian function due to weaknesses in study design and hormonal contraceptive usage. Studies since licensing lack capacity to evaluate ovarian function due to focus on emergency department presentations, and definitional limitations. Vaccine adverse event notifications of amenorrhoea are poorly investigated and followed up. Other documented published cases of premature menopause following HPV4 vaccination indicate the need for further research of the ovary after HPV4 vaccination. In the interests of women’s reproductive health and egg-bearing capacity, this issue needs to be resolved prior to the implementation of universal vaccination programmes.

Keywords: HPV4 (Gardasil™) oligomenorrhoea periods ovarian failure menopause

INTRODUCTION
A 16-year-old girl presented with secondary amenorrhoea following 12 months of oligomenorrhoea after HPV4 vaccinations, completed in August 2008. Menarche had occurred at age 13 and a regular monthly pattern had established. Menses became irregular in early 2009 and scant and infrequent by 2010. Menstruation ceased in January 2011 and hot flushes commenced. The oral contraceptive pill (OCP) was prescribed, which she declined, preferring further assessment for continuing amenorrhoea at which
premature ovarian failure (POF) was diagnosed [1]. Amenorrhea and POF after HPV4 in young teens have been notified as vaccine adverse events to safety surveillance programmes such as the Vaccine Adverse Event Reporting System (VAERS) [2] in the USA. Cases of secondary amenorrhea in very young teens following HPV4 administration and subsequently diagnosed as premature ovarian failure have recently been published [3]. The incidence of POF between ages 15 to 29 years has been reported as 10/100,000 person-years [4] but the prevalence of idiopathic POF in very early to mid-teen age groups is uncertain. Research on ovarian health and safety in early teens after HPV4 was sought.

MATERIAL AND METHODS

Pre-clinical toxicology studies, clinical pre-licensing studies and post-licensing research and surveillance were reviewed. Request was made to the TGA for a histology report of the vaccine tested rodent ovary and for data concerning tested rats’ subsequent litters and numbers of pups therein. Clinical studies which had been identified by the Vaccine and Related Biological Products Advisory Committee [5] (VRBPAC) as HPV4 pre-licensing safety studies were reviewed for evidence of ongoing ovarian safety after HPV4. Post-licensing studies were reviewed for their capacity to detect safety signals for ovarian malfunction. VAERS database case histories (August 10th 2013) were searched for notifications indicating possible deterioration in ovarian function following HPV4.

RESULTS

Pre-clinical studies  The TGA agreed to a ‘freedom of information’ request (FOI 001-1112) for a histology report of the vaccine-tested rat ovary and numbers of subsequent pups and litters produced by vaccine-tested rats. No histology report of vaccine-tested rat ovaries was available. No research was available concerning ongoing rat reproductive function and subsequent fecundity. Tested rats conceived once at the onset of sexual maturity and evaluation of the ovary at post-weaning euthanasia recorded only a numbering of corpora lutea present. No record of ovarian cellular integrity was available [6]. A histology report of testes and epididymides is included in The TGA Public Assessment Report for HPV Vaccine February 2011 [7]. Pre-clinical studies to evaluate the safety profile and biological activities of vaccines inform subsequent clinical trials.

Clinical Pre-licensing Safety Studies  Pre-licensing studies of HPV4 which were identified by the VRBPAC [5] to the Food and Drug Administration as safety studies were Phase II study protocols V501: 007 [8], 016 [9], and 018 [10] and phase III protocols 013 (‘Future I’) [11] and 015 (‘Future II’) [12]. Of these safety studies, only phase II protocols 016 and 018 studied adolescents under 16 years. A vaccine report card recorded temperatures and adverse events occurring within 2 weeks of each vaccination and prompted for recording of local site reactions.

Protocol 016 [9] studied 506 healthy girls aged 10 to 15 years. Only 240 girls, 47.4%, completed the planned 12 month follow-up. The VRBPAC describes it as a ‘Phase II study of the safety and immunogenicity of Gardasil when administered to approximately 2500 healthy children’. The unexplained loss of the majority of participants to 12 month follow-up and small numbers of those remaining who had reached menarche, precludes this study from competence to evaluate ongoing ovarian function. One participant

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experienced vaginal haemorrhages 26 and 42 days after 2nd and 3rd vaccinations respectively. This event was initially deemed vaccine related.

Protocol 018 [10] fully vaccinated 492 girls aged 9 to 15: mean study age 11.9. The proportion post menarche is not clear. Protocol 018 Vaccine report card (VRC) prompted for injection site reactions and also prompted for reporting of headaches, rashes, muscle/joint pain and diarrhea that occurred within 14 days of each vaccination, but not menstrual aberration. Follow-up interviews to 18 months assessed general safety and all serious adverse events [13]: hospitalization, life threatening illness, disability, death, illness requiring surgical/medical correction. Health interviews within 18 months of 1st vaccination may not have the ability to detect menstrual abnormalities in very young teens at an undetermined interval post menarche when cycle patterns are still establishing. Investigators judged which events were vaccine related, and deemed that none, including dysfunctional uterine bleeding causing anaemia, were related.

In Protocol 007, 256 older women 16 to 23 years received 3x HPV4 Gardasil™. Participants were required to use effective contraception throughout the trial.’ [14]. 57.9% used hormonal contraception and 13.2% did not complete the 3 year trial.

Phase III ‘Future 1’ [11] and ‘Future 2’ [12] studies enrolled mostly older subjects 16 to 23 years. 58% to 60% of these phase III participants used hormonal contraception, potentially masking ovarian dysfunction. All phase III subjects were ‘required to use effective contraception day 1 through month 7’. A subsequent HPV4 safety studies review [15] of 21,480 females in licensing trials states ‘new medical conditions were not considered adverse events if they occurred post month 7 or were not considered by the investigators to be vaccine/placebo- or procedure-related.’ [15]. These studies were inadequate for assessing reproductive safety. The TGA licensing body classifies an association between HPV4 and female fertility as not biologically plausible [16].

Selected placebo controls for safety trials comprised aluminium adjuvant or a combination [10] of polysorbate 80, borate, sodium chloride and yeast in young teen study 018. Each control has components implicated in ovarian pathology [3] [17].

Post-licensing Safety Studies The major post-licensing study of HPV4 safety [18] reviewed 189,629 vaccinated females including 44,000 who had received three doses. Selected outcome measures were subjects’ hospitalizations and emergency department visits following vaccination. 11 to 12 year olds who received 3 doses comprised 4.3% of the overall study population; 9 to 15 year olds comprised 12.9%. The consultation context for seeking medical management of oligomenorrhoea or amenorrhoea is not normally the emergency department and will not require hospitalization. This study had no capacity to evaluate ongoing ovarian health or to monitor ovarian safety.

The Protocol 018 group of 577 girls who completed vaccinations became the sentinel study for long term safety of HPV4 in adolescents [19]. Surveillance comprised: annual physical examination and serum collection to age 16, then twice yearly collection of a sexual history and genital clinical specimens. Serious adverse experiences deemed by the investigator to be vaccine related, pregnancy outcomes and deaths are monitored. Protocol 018 reiterates ‘the relationship between adverse experiences and vaccine was reported by the investigator according to his/her best judgment, based on exposure, time course, likely cause and probability with vaccine profile’[10, 15]. However, this vaccine’s reproductive safety profile in 2005-2007 and since has not yet been established.
The VAERS [2] notes 104 cases of new amenorrhoea post HPV4 of whom less than 9% reported a return of menses at follow-up. Only one subject out of 105 notifications had an FSH level recorded, and it was ‘elevated at 72’ (no units specified). In 62% of ongoing amenorrhoea notifications to VAERS, no further information was obtained. No anti-Mullerian hormone levels were recorded. Four teens with POF following HPV4 are recorded under ‘amenorrhoea’, ‘ovarian failure’ and ‘premature menopause’. Other published cases [3] describe onset of declining menstrual function at ages of 13, 14 and 15 after HPV4 preceding diagnoses of premature ovarian failure.

Diminished menstrual patterns do not signal as ‘Serious Adverse Events’ in surveillance and are invisible with OCP; ongoing Vaccine Safety Datalink surveillance of conditions arising post HPV4 does not include menstrual abnormalities in its focus [20]. Other surveillance methods rely on known background prevalence and controls [21].

CONCLUSION
Pre-clinical, clinical and post-licensure safety studies of HPV4 were unable to evaluate ovarian safety. This matter needs to be resolved, since a potential compromise of future ovarian function could have serious implications for population health and fecundity.

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