Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 112; No. 8; P982

The Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration

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Pertussis remains a worldwide issue; as per 2016 data from the European Centre for Disease Control, there were 48,446 cases in 30 countries, with highest rates in children under one year old; 16 of 26 deaths occurred in infants under 3 months old. Immunisation remains the most effective preventive strategy, reducing morbidity and mortality by over 90%[1], and is included in the primary vaccination schedule in most countries. In 2005 the CDC recommended booster doses of vaccine for postpartum women and those caring for young infants in an effort to protect them from disease acquisition – a strategy known as 'cocooning'[2]. This proved difficult to implement and so antenatal vaccination (third trimester) was undertaken in 2011 in the US, with a recommendation by NIAC for this in Ireland being made in 2012, (single dose of Tdap from 16 – 36 weeks). Numerous studies have proven the safety of acellular antenatal pertussis vaccine[3].

A recent paper by Healy et al. 'Association Between Third-Trimester Tdap Immunisation and Neonatal Pertussis Antibody Concentration'details a prospective observational cohort study of term neonates' pertussis antibody levels[4]. The primary outcome was the geometric mean concentration (GMC) of pertussis toxin antibodies in cord blood of dTap-exposed and unexposed neonates, and the secondary outcome was optimal gestational age for vaccine administration. This study found that GMCs of pertussis antibodies were higher in babies born to immunised mothers (47.3IU/ml vs. 12.9IU/ml (95% CI 11.7-14.3). Results remained significant when controlled for maternal age, ethnicity and gestational age at delivery. Secondary outcome measure results imply that weeks 27-31 are the best for vaccination, with GMCs highest when given at week 30 (57.3IU/ml; 95% CI 44 – 74.6) and declining thereafter. This study was observational, and single-centre, with no power calculations so results would need to be verified. In addition, no vaccines were administered in the second trimester. A study published in CID in 2016 'Maternal Immunisation Earlier in Pregnancy Maximises Antibody Transfer and Expected Infant Seropositivity Against Pertussis'[5] sought to assess noninferiority of 2nd trimester vs. 3rd trimester dTap administration. This was an observational study involving 335 women, 64% were vaccinated in the 3rd trimester, the remainder in the 2nd. The authors concluded that earlier immunisation was superior in terms of GMCs of cord blood antibodies to recombinant pertussis antigen and filamentous haemagglutinin and also expected infant seropositivity rates, which were based on calculations involving the anti-PT half-life of 36 days. A birth anti-PT concentration >30EU/ml was predicted to lead to seropositivity (defined as persistence of at least >5EU/ml of anti-PT at 3 months of age). This resulted in the Joint Committee on Vaccination and Immunisation in the UK recommending immunization be offered from gestational weeks 20-32 - previously weeks 28 – 32. This advice was endorsed by the Royal College of Obstetrics and Gynaecology, and NIAC recommends dTap from weeks 16-36.

A systemic analysis of randomized controlled trials and observational studies on the efficacy and safety of pertussis vaccination in pregnant women was performed in 2017 by Furata et al[6]. This included 12 studies and a total of 203,835 mother-infant pairs; only 2 were randomized controlled trials. The primary objective was to examine vaccine efficacy in reducing incidence of pertussis. Secondary objectives were to assess reduction of severe complications and also mothers' and infants' antibody levels. The review also looked at vaccine safety and adverse outcomes, including obstetric and/or perinatal complications. In terms of efficacy, the RCTs did not have any cases of pertussis and this had not been the primary outcome of interest, one case-control showed a lower rate of pertussis in those vaccinated during pregnancy with an adjusted OR of 0.07 (95%CI 0.03 – 0.19) but case-control studies are not ideally designed to determine disease incidence. With regard to complications, none of the studies reported these, only one showing a reduction in hospital stay in the setting of pertussis. Seven of the twelve studies involved examined antibodies in maternal and cord bloods, using ELISA. It was not possible to pool this data as the study designs and comparators were different and there was insufficient data. The safety of pertussis vaccine administration was assessed both in terms of vaccine-related adverse outcomes (more reports of injection site reactions in those receiving vaccine vs. placebo) and also obstetric or perinatal outcomes, where one study looked at death and small-for-gestational –age and three included hypertensive disorders, preterm birth and stillbirth. There was no increased risk of any of these. Overall the systemic analysis concluded that the vaccine has been demonstrated to be safe, but that further investigation is required to assess for optimal timing, types of vaccine administered and the use of the vaccine in different socio-economic settings.

The study by Healy et al. concluded that vaccination in the third trimester was associated with higher concentrations of pertussis antibody vs. no vaccination and that early in the third trimester was optimal – i.e. achieved the highest levels of antibodies, however the protective threshold for pertussis antibodies is not known. The study was observational in nature and also no women were immunized during the 2nd trimester, which had been shown to be non-inferior to 3rd trimester immunisation by Eberhardt et al. While this paper has shown an in-vitro boosting of neonatal immunity through maternal vaccination, it should be viewed alongside epidemiological data which has shown a reduction in the incidence of pertussis following introduction of antenatal vaccination at a national level[7].The costs of a prospective randomized control trial with reduction in clinical disease as a primary outcome, may be prohibitive given the low incidence of the disease in neonates. It is probably necessary now for us to rely solely on epidemiological data for our evidence base to continue with vaccination, using observational studies and case control studies based on national datasets such as PHE study [Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014;384:1521–8]. Healthcare providers who work with pregnant women should continue to recommend the vaccine in line with NIAC guidelines and look for opportunities to vaccinate at antenatal clinics in order to reduce neonatal pertussis to as low a rate as possible.

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