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Rubella seronegativity in antenatal screening – Is it influenced by the introduction of universal childhood rubella immunization?

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ABSTRACT

Objective: This study examined the impact of rubella immunization, implemented in Hong Kong in phases since 1978, on antenatal rubella serological status in Chinese women.
Methods: In a retrospective cohort study, the incidence of antenatal rubella seronegative status in our parturients managed from 1998 to 2013 was analyzed by their year-of-birth as follows: <1965 (no childhood immunization), 1965–1982 (single dose at Primary 6), and ≥1983 (two doses at age 12 months and 12 years), adjusting for other factors including age, parity, body mass index, place-of-birth status and hepatitis B surface antigen (HBsAg) status.
Findings: Rubella seronegativity decreased from 12.9%, 10.5%, to 9.8% respectively, and correlated inversely ($P < 0.001$) with year-of-birth cohorts. Despite similar demographic profiles, this correlation was found only in Hong-Kong-born women (from 12.6%, 7.5% to 6.5% respectively), who also had significant lower incidences of rubella seronegativity (OR 0.73, 0.31 and 0.29 respectively) and HBsAg seropositivity (OR 1.09, 0.63 and 0.48 respectively) than China-born women. On regression analysis, rubella seronegativity was actually significantly increased following the implementation of immunization (aOR 1.20) while it was the reverse for non-residents (aOR 0.61).
Conclusion: Although rubella seronegativity decreased with immunization, the effect was less than expected when adjusted for other risk factors.

1. Introduction

The mumps-measles-rubella (MMR) vaccine is highly effective [1], yet rubella susceptibility rate in women aged 15–39 years remained between 1.4% and 13.4% in European countries with implementation of rubella immunization [2]. Furthermore, recent findings indicated declining rubella immunity and incidence of antibody levels of ≥10 IU/ml among women born after, compared with women born before, the introduction of routine universal rubella immunization in Sweden [3], the UK [4–6], Israel [7,8], Poland [9] and Taiwan [10]. A rubella-specific antibody titer of <10 IU/ml usually equates susceptibility, predisposing to fetal congenital rubella syndrome (CRS) if infection occurs in pregnancy. Rubella susceptibility is influenced by age, immunization compliance, gravidity and parity, and country of origin/birth [11–18], the last factor probably being the most important as Asians and Chinese have either accounted for the majority of rubella seronegative women, or an overall lower rate of seropositivity or antibody titer, compared with Caucasians in multiethnic communities [11,13,14,18,19]. Country of origin/birth could also impact through epidemiological factors, such as chronic hepatitis B virus (HBV) infection, which was associated with increased antenatal rubella seronegative status in Hong Kong [20]. As chronic HBV infection in our locality is mostly attributed to vertical transmission [21,22], thus antedating rubella vaccination, the progressive functional decline of virus-specific CD8 responses with weakened virus-specific T-cell responses and eventual virus-specific T-cell depletion and induced immune tolerance [23,24] could account for the lower rubella seropositivity and antibody titer found in Asians and Chinese women.

In Hong Kong, mandatory rubella immunization for Primary 6 schoolgirls commenced in 1978, and was then extended to postpartum mothers and susceptible women of child-bearing age [25]. From 1990, the MMR vaccine is administered to all children at one year of age [25,26]. As well, the Maternal and Child Health Centers (MCHC) under the Department of Health (DH) provide free vaccinations to local residents and their offspring, and coverage for Primary 6 schoolgirls was over 98% [25]. Our parturients born in Hong Kong between 1965 and 1982 would have received at least one dose of

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childhood rubella vaccination. Since 1996, a second dose is administered to all 12-years old children, with 99% coverage of all Primary 6 students [26,27], so that all children born Hong Kong in/after 1982 would be covered by the two-dose protocol. Compliance is maintained by an immunization record provided to parents, which is checked at schools for any necessary remedial action [25,27]. In Hong Kong, reported rubella cases remained between 19 and 53 from 2001 to 2008, while no cases of CRS was listed in 2000–2007 and only one case in 2008 [28,29]. Despite the impressive statistics, 8.1% of our Hong-Kong-born parturients were seronegative [30]. In light of declining rubella immunity despite universal rubella immunization reported elsewhere [3–10], and the sizable influx of non-Hong-Kong-born parturients (mostly from mainland China) in the past decade, this study was performed to examine the impact of rubella immunization, using maternal year-of-birth as proxy for exposure to the different childhood immunization protocols, on antenatal rubella serology in Hong-Kong-born parturients, comparing with non-Hong-Kong-born parturients who were not covered by the same immunization protocols.

2. Material and methods

In Hong Kong, antenatal screening tests are performed by the accredited central laboratory under DH if antenatal booking occurs at the MCHC, and accredited hospital pathology laboratories if booking occurs at hospitals. In the routine screening for rubella IgG antibody by EIA (Axsym, Abbott), women with titer <10 IU/ml are labeled as non-immune and will be referred for postpartum rubella vaccination at the MCHC, where their babies will also receive their follow-on vaccinations. Routine antenatal screening for hepatitis B surface antigen (HBsAg) is done because of the high local prevalence [31]. Results of the antenatal screening and clinical information are captured in a computerized database set up by the local Hospital Authority for the generation of statistics. Data entry is made by trained midwives and obstetricians in the clinics and wards, and is double-checked after delivery.

Our hospital is a regional referral center catering for 1.7 million people. For this retrospective cohort study approved by the Institutional Review Board (CRE-2009.271), demographic and anthropometric data of the pregnant women with results on rubella and HBsAg screening and managed from January 1998 to December 2013 were extracted from our hospital database, which was validated previously [30]. We labeled women with rubella-specific IgG level <10 IU/mL as having rubella seronegative status since it was impossible to establish whether their low antibody titer was due to primary or secondary vaccine failure, or whether they were naïve to the natural infection or vaccination. Maternal characteristics that included age, parity status, height, weight, calculated body mass index (BMI in kg/m^2, calculated using weight and height measured at antenatal booking), and HBsAg status, were analyzed according to year-of-birth as follows: <1965 (no childhood immunization); 1965–1982 (single dose at primary 6); and ≥1983 (two doses at 12 months and 12 years). The Hong-Kong-born parturients were compared with non-Hong-Kong-born parturients, mostly ethnic Chinese from mainland China who were not protected by universal childhood rubella immunization [30].

Included in the analysis of factors that could influence immune response were maternal age [32–37] with advanced age defined as ≥35 years; BMI [36,37] with high BMI defined as >25 kg/m^2; height, which reflected nutritional and health status during childhood and adolescence, with short stature defined as <151 cm; parity status [38,39]; and multiple pregnancy due to the fetal cells crossing into the maternal circulation [40], which could be increased in multiple pregnancy thus enhancing further maternal-fetal tolerance through mechanisms such as the HLA-G system [41,42] with further maternal immunosuppression. We examined in addition chronic HBV infection, which induces immune tolerance [23,24], was associated with rubella susceptibility [20], as well as human papilloma virus-induced cervical carcinoma [43].

For statistical analysis, Oneway ANOVA method was used for continuous variables with post hoc analysis by Duncan's multiple range test, and chi square test and Spearman's correlation for categorical variables. This study included all cases in the database who had received our care, with data on the required information for analysis, irrespective of the pregnancy outcome (miscarriage, termination, or delivery) or the eventual place of delivery (in our hospital or other hospitals). The cases for this study were extracted with the relevant information from the master database to create a research database (for anonymity) for analysis. Comparison between residents and non-residents was performed using chi square test and calculation of odds ratio (OR) with 95% confidence intervals (CI), and the trend with year-of-birth was tested with Spearman's correlation. Multiple logistic regression analysis was finally performed to determine the independent effect of childhood immunization, using year-of-birth as proxy, and incorporating the significant factors in the univariate analysis, to calculate the adjusted odds ratio (aOR) with 95% CI, for the entire group and then by resident status. The models also tested the impact of maternal HBsAg carriage on rubella seronegative status. Statistical analysis was performed using a commercially available statistical package (IBM SPSS Statistics version 20).

3. Results

The analysis included 106,864 eligible cases, their distribution by year-of-birth was 6.6%, 79.7% and 13.7% respectively for the <1965, 1965–1982, and ≥1983 birth cohorts (Table 1). There were significant differences in the mean maternal age, height, and booking weight and BMI, together with significant differences among and inverse correlation with the birth cohorts for the incidences of advanced maternal age (≥35 years), short maternal stature, high booking BMI, multiple pregnancy, and residents. Overall, the incidences of rubella seronegative and HBsAg seropositive status were similarly different and inversely correlated with year-of-birth cohorts, while there was significant progressive increase in the incidence of nulliparity status.

There were 80,965 residents and 25,899 non-residents, and the distributions among the birth cohorts are shown in Table 2. Significant differences among, and inverse correlation with, year-of-birth cohorts were found with nulliparity status, advanced maternal age, short stature, and high booking BMI, in both groups, except for multiple pregnancy which was inversely correlated with year-of-birth cohorts only for residents. This could have been related to the popular trend that mainland Chinese women who conceived by IVF treatment preferred to deliver in Hong Kong.

Residents showed a significant difference and progressive decrease with year-of-birth, while non-residents demonstrated only significant differences among, but no correlation with, year-of-birth, for both HBsAg seropositivity and rubella seronegativity (Table 3). Within the same birth cohorts, residents have significantly reduced HBsAg seropositivity for the 1965–1982 and ≥1983 cohorts, and reduced rubella seronegativity for all three-birth cohorts.

Multiple logistic regression analysis was performed to confirm the independent association between birth cohorts with rubella seronegativity (Table 4). Model 1 included all the factors shown previously in the univariate analysis and both residents and non-residents. Advanced maternal age, high booking BMI, short stature, and HBsAg seropositivity were all independently associated with increased seronegativity, while nulliparity status had the

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