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MMR vaccine in the postpartum does not expose seronegative women to untoward effects

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Abstract

Background. The aim of this study was to assess whether rubella vaccination immediately after delivery could expose seronegative women to specific untoward effects.

Methods. 163 rubella-seronegative women received Measles-Mumps-Rubella (MMR) vaccine in the immediate postpartum period; they were evaluated at one month and at three months thereafter through telephone interviews. As controls, we matched 163 rubella-seropositive women, who might experience similar symptoms for any reason in the same timeframe.

Results. No relevant difference was still observed in the frequency of arthralgia and myalgia at one and three months. Instead, a statistically significant difference in the frequency of cervical lymphadenopathy and cutaneous rash at one month ($p = 0.028$ and $p = 0.005$, respectively), was observed between cases and controls. However, no statistical differences were reported at three months for the same symptoms.

Conclusions. Postpartum rubella vaccination with MMR is safe and advisable to avoid congenital rubella syndrome.

Key words

- Measles-Mumps-Rubella vaccine
- postpartum period
- congenital rubella syndrome
- vaccines

INTRODUCTION

Rubella is a febrile rash illness caused by rubella virus in susceptible children and adults. Its public health threat resides in the potentially devastating effects during pregnancy, especially in the first trimester: it can indeed result in miscarriage, fetal death, or congenital malformations, known as congenital rubella syndrome (CRS) [1].

In Italy, statutory notification of rubella cases has been activated in 1970. Notification data have shown recurrence of epidemics every 4-5 years until 1997, when the last outbreak of the nineties occurred; subsequently, the incidence of rubella remained low until the epidemic 2002-2003, and another outbreak was reported in 2008, with > 5000 notified cases [2, 3].

In 2003, Italy adhered to the WHO's European regional goal of achieving elimination of measles and rubella and prevention of congenital rubella infection by 2010 [4], and a National Plan for the elimination of measles and congenital rubella was approved (*Piano Nazionale per l'Eliminazione del Morbillo e della Rosolia Congenita, PNEMoRc*) [5]. Although progresses were made, the goal was not achieved by 2010, and the target date was deferred to 2015 [6]; consequently, the Italian National Plan (INP) was renewed until 2015 [3]. The data collected during the period 2012-2015 detected by the PASSI system (*Progressi nelle Aziende Sanitarie per la Salute in Italia*), indicate that the goal has not been reached. The percentage of women of childbearing age susceptible to rubella is currently 2%; however, fairly high percentage of women, around 37%, is not aware of their immune status [7].

It has been estimated that, in order to achieve the complete elimination of CRS, the percentage of women of childbearing age susceptible to rubella infection should be < 5% [3]. For this reason, the INP recommends rubella serology test for women with childbearing potential and subsequent vaccination of those who are found seronegative or without written record of vaccination; as well as vaccination immediately upon completion or termination of their pregnancy and before discharge from the hospital of all women found susceptible during pregnancy [5].

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Rubella-susceptible women who are not vaccinated because they are or may be pregnant should be counselled about the potential risk for CRS and the importance of being vaccinated as soon as they are no longer pregnant [8].

We are still far from achieving the goal, despite the progress made. Even if they are not notified probable or confirmed cases of congenital rubella by 2015 [9], it is necessary to strengthen the active offer of the vaccine, even in the postpartum and postabortum.

The time after delivery and before discharge from the hospital is an ideal time to administer live and attenuated vaccines. Indeed, women who plan to breastfeed may receive vaccination, as no evidence exists for any risk due to rubella vaccine while breastfeeding. It would be appropriate to create a database of women who refuse vaccination in the first instance, in order to make a motivational recall later on.

Monovalent rubella vaccine has been widely used in the past and it has also been associated to different adverse events in the general population [11-16]. The main adverse consequences described involved the musculoskeletal system (arthralgia and myalgia) and neurological system (paresthesias) [14, 17, 18]. Moreover, Tingle *et al.* have shown that postpartum administration of monovalent rubella vaccine is responsible for a significantly higher incidence of acute joint manifestations than placebo administration (30% *vs* 20%) [19]. Minor side effects may be experienced by children after MMR vaccination, including fever, malaise and cutaneous rash 5-21 days after the first vaccination (10%) and arthralgia (3%), lasting 18 days on average [20, 21] Incidence rates of arthritis and arthralgia are generally higher in women than in children (12-26% *vs* 0-3%), and the reaction tends to be more severe and longer [22, 23]. About 25% of non-immune, post-pubertal women reported joint pain after receiving rubella vaccine, and 10-30% also arthritis-like signs and symptoms [19, 24]. These reactions are generally well-tolerated and rarely interfere with daily activities [25]: anaphylaxis is indeed extremely rare [26].

The aim of this study was to investigate the incidence of arthralgia and arthritis in women vaccinated in the immediate post-partum period as compared to already immune women, who may experience similar symptoms for any other reason, because the joint pain in one of the most frequently reported side effects in literature [11-16].

MATERIALS AND METHODS

This was a case-control study of women who gave birth at Castelli Hospital in Verbania and at SS. Pietro e Paolo Hospital in Borgosesia, (Piedmont region, Italy), between January 2011 and December 2014. Serology test for rubella was performed in all women during the first trimester of pregnancy. A commercial enzyme-linked immunosorbent assay (ELISA) kit (Enzygnost Anti-Rubella-Virus/IgG, Dade Behring, Marburg, Germany) was used. Rubella-susceptible women received a single dose of MMR vaccine (MMR VAXPRO, Sanofi Pasteur MSD) during the 24-48 hours following delivery.

Case-control matching was based on rubella seropositive women (as controls) who gave birth immediately after each enrolled case according to the same delivery procedure: vaginal delivery vs caesarean section.

Exclusion criteria were age < 18 years, contraindication to immunization, current immunosuppressive therapy or serious illnesses, and any immunodeficiency.

Before MMR vaccine administration, patients received counselling about the potential risks and benefits of the intervention, and signed informed consent to vaccination and follow-up evaluation. Institutional review board consent was waived, as treatment was considered routine clinical practice at our institution and in agreement with national recommendations.

Age, parity, current or former medications, underlying diseases, results of diagnostic tests, history of allergic reactions, and previous post-vaccine complications were collected for each woman participating in the study.

Short-term complications were defined as events that occurred within the first 28 days from vaccine administration. Long-term complications were defined as events that occurred from 28 days after vaccination until the end of the follow-up.

After discharge, patients were evaluated at one month and three months after vaccination. Follow-up consisted of a telephone interview aimed at determining the state of subjective well-being or the experience, if any, of musculoskeletal complications.

Statistical analysis was performed with 2 x 2 table using OpenEpi® software.

RESULTS

One hundred-seventy-one seronegative women were asked to participate (142 in Verbania and 29 in Borgosesia). Of these, 163 were enrolled in the study. Three refused to be enrolled but nonetheless accepted to get vaccinated (1 in Verbania and 2 in Borgosesia), 5 women refused both, stating as a reason to refuse the case Wakefield [27] despite the scientific community uncovered the intellectual fraud [28, 29], in total they were enrolled for the study 163 cases and 163 controls, matched by mode of delivery: 72% spontaneous delivery, 18% caesarean section. At one-month follow up, 162 women in the case group and 161 women in the control group agreed upon answering our telephone interview; at three month follow-up, 154 women in the case group and 159 women in the control group answered, total loss of subjects during the follow-up was 13 (9 cases and 4 controls). Failure to answer the telephone interview brought to exclusion from the study. Nearly 15% (24/163) of the cases the sample was not at first pregnancy and a substantial proportion was of North African origin (37/163); furthermore, at one month follow-up 83% of women who received vaccination exclusively breastfed their infants, compared with 89% of women who did not. At three months, percentages dropped to 78% and 82%, respectively; socio-demographic characteristics of subjects are summarized in *Table 1*. At one month follow-up, arthralgia occurred in 17 cases (10.4%) and 14 controls (8.6%) (p = 0.29; OR 1.23 [95% CI 12.58 - 2.63]) *(Table 2)*. No difference was reported between the two groups in the frequency of acute myalgia (p = 0.19), acute paresthesia (p = 0.15) or pharyngitis (p = 0.32). However, the difference in the

Table 1
Demographic characteristics of the study population

	Vaccination N = 163 (%)	No vaccination N = 163 (%)
Age (years)		
18 - 23	21 (12.8)	31 (19)
24 - 29	49 (30)	38 (23.3)
30 - 35	89 (54.6)	92 (56.4)
36 - 41	4 (2.4)	2 (1.2)
Ethnic origin		
Italy	107 (65.6)	111 (68)
Est Europe	9 (5.5)	3 (1.8)
North Africa	37 (22.6)	41 (25.1)
Oriental	7 (4.2)	6 (3.6)
Other	3 (1.8)	2 (1.2)
Obstetric history		
Nulliparous	139 (85.2)	143 (87.7)
Primiparous	17 (10.4)	9 (5.5)
Multiparous	7 (4.2)	11 (6.7)
Breastfeeding at 1 month		
Exclusive	83%	89%
Mixed	4%	1%
Artificial	13%	10%
Breastfeeding at 3 months		
Exclusive	78%	82%
Mixed	5%	9%
Artificial	17%	9%

frequency of cervical lymphadenopathy and cutaneous rash between the two groups was statistically significant (p = 0.028 and p = 0.005, respectively). A three-month follow-up, the difference in the frequency of cervical lymphadenopathy and cutaneous rash was no longer observed (p = 0.19 and p = 0.27, respectively); arthralgia was present in 11 cases (7.1%) and 8 controls (5%) (p = 0.21; OR 1.45 [CI 0.56 - 3.87]. No difference was reported in the frequency of myalgia (p = 0.15), paresthesia (p = 0.15), and pharyngitis (p = 0.34). Overall, the frequency of chronic adverse reactions is summarized in *Table 3*.

DISCUSSION

Several national and international health authorities promoted awareness campaigns aimed at reducing the incidence of rubella. In Italy, the National Plan for the Elimination of Measles and Congenital Rubella *PNEMoRc* has set goals of reaching a vaccination coverage rate for MMR vaccine ≥ 95%, and of reducing the percentage of rubella-susceptible women of childbearing age to less than 5% [3]. However, the changing scenario of resident population in our country may hamper achieving these targets in the future. Indeed, the increasing number of immigrants and refugees hosted or rescued entails that a large part of this new population coming from low-income countries could likely have skipped national vaccine campaigns (if any), thus enabling recirculation of rubella virus among susceptible subjects [30-32].

Immediate postpartum (and postabortum) could be therefore an additional opportunity to intercept susceptible women and then to lessen the likelihood of new outbreaks; however, robust data about safety and effectiveness of rubella vaccine at this time point are still lacking [33].

The side effects of vaccination may be a cause of rejection, especially in mothers who are breast feeding. Interestingly, we found no difference between cases and controls with respect to the onset of arthralgia and myalgia after vaccination. We also found a statistically significant difference in the frequency of cervical lymphadenopathy and skin rash at one month, but not at three months. Moreover, the rash indicated by respondents (cases) was only limited to the inoculation area, while in the controls it was on the face.

Moreover, at three month follow-up, incidence of arthralgia and myalgia was not statistically significant between the two groups either.

Another advantage could be that rubella vaccination has not been shown to interfere with breastfeeding *(Table 1)*.

Our study has some limitations: the first is the sample size that cannot be considered an expression of the general population. Furthermore, the analyzed sample was not referred to clinical evaluation, but only to telephone interview to assess our hypothesis. The second is that the

Table 2
Follow-up results, 1 month

Symptoms	Vaccination N = 162	No vaccination N = 161	Odds ratio (95% CI)	x^2
Rash	11 (6.7)	2 (1.2)	5.76 (1.40-38.84)	p = 0.0055
Pharyngitis	10 (6.1)	12 (7.4)	0.81 (0.33-1.97)	p = 0.32
Arthralgia	17 (10.4)	14 (8.6)	1.23 (0.58-2.63)	p = 0.29
Cervical lymphadenopathy	6 (3.7)	1 (0.6)	6.126 (0.89-143.3)	p = 0.02
Myalgia	11 (6.7)	7 (4.3)	1.6 (0.60-4.49)	p = 0.16
Paraesthesias	3 (1.8)	1 (0.6)	3.00 (0.31-79.94)	p = 0.15
Temperature	0	0	\	\

Table 3
Follow-up results, 3 months

Symptoms	Vaccination N = 154	No vaccination N = 159	Odds ratio (95% CI)	x^2
Rash	2 (1.2)	1 (0.6)	2.07 (0.15-61.69)	p = 0.27
Pharyngitis	9 (5.8)	11 (6.9)	0.83 (0.32-2.10)	p = 0.34
Arthralgia	11 (7.1)	8 (5)	1.45 (0.56-3.87)	p = 0.21
Cervical lymphadenopathy	4 (2.5)	2 (1.2)	2.08 (0.36-16.51)	p = 0.19
Myalgia	3 (1.9)	1 (0.6)	3.12 (0.32-83.13)	p = 0.15
Paresthesia	1 (0.6)	0	NT	p = 0.15
Temperature	0	0	\	\

comparison has been performed with women in whom symptoms might occur for any other reason: this means that also our cases could have experienced such symptoms for different reasons. However, our analysis seems to confirm that a higher incidence of untoward effects directly linked to vaccination should not be expected.

In our opinion, this experience shows that the vaccination proposal has a high acceptance rate and can be safe in the immediate postpartum, and that seronegative women should be vaccinated after delivery with one dose of MMR before leaving the hospital [10]. One advantage of our approach is that now offering postpartum vaccination is a shared culture among health operators, physicians of territorial health service, and public and private obstetricians working in this area. All seronegative women admitted to our hospitals during pregnancy have already been informed that vaccination will be offered during postpartum and then most of them have already decided to accept it. Women who have rejected it have done to preconceived ideas about vaccinations in general. Likewise, the increase of information and education gained during pregnancy may allow women to avoid the risk of CRS in a future pregnancy.

Conflict of interest statement

There are no potential conflict of interest or any financial or personal relationships with other people of organization that could inappropriately bias conduct and findings of this study.

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REFERENCES

1. WHO. Rubella and congenital rubella syndrome control and elimination – global progress 2012. *WHO Weekly Epidemiological Record* 2013;88:521-32.
2. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. *Rosolia – Aspetti epidemiologici*. Available from: www.epicentro.iss.it/problemi/rosolia/epid.asp.
3. Ministero della Salute. *Piano nazionale per l'eliminazione del morbillo e della rosolia congenita 2010-2015*. Available from: www.salute.gov.it/imgs/c_17_pubblicazioni_1519_allegato.pdf.
4. World Health Organisation Europe. *Strategic plan for measles and congenital rubella infection in the European Region of WHO*. WHO; 2003. Available from: www.euro.who.int/__data/assets/pdf_file/0020/79022/E81567.pdf.
5. Ministero della Salute. *Piano nazionale per l'eliminazione del morbillo e della rosolia congenita 2003-2007*. Available from: www.salute.gov.it/imgs/C_17_pubblicazioni_730_allegato.pdf.
6. World Health Organisation Europe. *Strengthening national immunisation systems through measles and rubella elimination and prevention of congenital rubella infection in WHO's European Region*. WHO; 2005. Available from: www.euro.who.int/__data/assets/pdf_file/0003/88086/RC55_eres07.pdf.
7. Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. *La sorveglianza Passi. Vaccinazione antirosolia*. Available from: www.epicentro.iss.it/passi/dati/VaccinazioneAntirosolia.asp.
8. Centers for Disease Control and Prevention. Measles, Mumps, and Rubella – Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1998;47:32-3.
9. Giambi C, Del Manso M, Bella A, Filia A, Rota MC, Nacca G, Declich S. *Rosolia congenita e in gravidanza News*. Settembre 2016.
10. Pickering LK, Baker CJ, Kimberlin DW, Long SS (Eds). *Red Book:* 2012 *Report of the Committee on Infectious Diseases. 29th Edition*. Elk Grove Village, IL: American Academy of Pediatrics; 2012. Available from: http://ebooks.aapublications.org/content/red-book-29th-edition-2012.
11. Cooper LZ, Ziring PR, Weiss HJ, Matters MA, Krugman S. Transient arthritis after rubella vaccination. *Am J Dis Child* 1969;118:218-25.
12. Lerman SJ, Nankervis GA, Heggie AD, Gold E. Immunologic response, virus excretion, and joint reactions with rubella vaccine: a study of adolescent girls and young women given live attenuated virus vaccine (HPV-77:DE-5). *Ann Intern Med* 1971;74:67-73.
13. Thompson GR, Ferreyra A, Brackett RG. Acute arthritis complicating rubella vaccination. *Arthritis Rheum* 1971;14:19-26.
14. Thompson GR, Weiss JJ, Shillis JL, Brackett RG. Intermittent arthritis following rubella vaccination. A three-

year follow-up. *Am J Dis* Child 1973;125:526-30.
15. Tingle AJ, Yang T, Allen M, Kettles GD, Larke RP, Schulzer M. Prospective immunological assessment of arthritis induced by rubella vaccine. *Infect Immun* 1983;40:22-8.
16. Geier DA, Geier MR. Rubella vaccine and arthritic adverse reactions: an analysis of the Vaccine Adverse Events Reporting System (VAERS) database from 1991 through 1998. *Clin Exp Rheumatol* 2001;19:724-6.
17. Tingle AJ, Ford DK, Price GE, Kettlys DW. Prolonged arthritis in identical twins after rubella immunization. *Ann Intern Med* 1979;90:203-4.
18. Tingle AJ, Kettyls GD, Ford DK. Studies on vaccine-induced rubella arthritis. Serologic findings before and after immunization. *Arthritis Rheum* 1979;22:400-2.
19. Tingle AJ, Mitchel LA, Grace M, Middleton P, Mathias R, MacWilliam L, *et al*. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 1997;349:1277-81.
20. Harnden A, Shakespeare J. 10-minute consultation: MMR immunisation. *BMJ* 2001;323:32.
21. Thompson GR, Ferreyra A, Brackett RG. Acute arthritis complicating rubella vaccination. *Arthritis Rheum* 1971;14:19-26.
22. Gershon AA, Frey HM, Borkowsky W, Steinberg S. Live attenuated rubella virus vaccine: comparison of responses to HPV-77–DE5 and RA 27/3 strains. *Am J Med Sci* 1980;279:95-7.
23. Weibel RE, Villarejos VM, Klein EB, Buynak EB, McLean AA, Hillman MR. Clinical and laboratory studies of live attenuated RA 27/3 and HPV-77-DE rubella virus vaccines. *Proc Soc Exp Biol Med* 1980;165:44-9.
24. Polk BF, Modlin JF, White JA, DeGirolami PC. A controlled comparison of joint reactions among women receiving one of two rubella vaccines. *Am J Epidemiol* 1982;115:19-25.
25. *M-M-R® Ii (Measles, Mumps, And Rubella Virus Vaccine Live).* Available from: www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123789.pdf.
26. Carapetis JR, Curtis N, Royle J. MMR immunisation. True anaphylaxis to MMR vaccine is extremely rare. *BMJ* 2001;323(7317):869.
27. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, *et al*. Ileal lymphoid-nodular hyperplasia, non specific colitis and pervasive developmental disorder in children. *Lancet* 1998;351(9103):637-41.
28. Editors of the Lancet. Retraction: Ileal lymphoid-nodular hyperplasia, non specific colitis and pervasive developmental disorder in children. *Lancet* 2010;375:445.
29. Goodle F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. *BMJ* 2011;342:64-6.
30. Daynes L. The health impacts of the refugee crisis: a medical charity perspective. *Clin Med (Lond)* 2016;16(5):437-40.
31. Jablonka A, Happle C, Grote U, Schleenvoigt BT, Hampel A, Dopfer C, *et al*. Measles, mumps, rubella, and varicella seroprevalence in refugees in Germany in 2015. *Infection* 2016;44:781-7. DOI: 10.1007/s15010-016-0926-7
32. Brockmann SO, Wjst S, Zelmer U, Carollo S, Schmid M, Roller G, *et al*. [Public Health initiative for improved vaccination for asylum seekers]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2016;59(5):592-8. DOI: 10.1007/s00103-016-2335-6
33. Demicheli V, Rivetti A, Debalini MG, Di Pietrantonj C. Vaccines for measles, mumps and rubella in children. *Cochrane Database of Systematic Reviews* 2012;2:CD004407. DOI: 10.1002/14651858.CD004407.pub3