



## ORIGINAL ARTICLE

# Prevalence of rubella antibodies: comparison between women with pregnancy induced by infertility treatments and those with spontaneous pregnancy

YURIA HARUNA, SHUNJI SUZUKI

Department of Obstetrics and Gynecology, Japanese Red Cross Katsushika Maternity Hospital, Tokyo, Japan

## Keywords

Rubella antibody titer • Prevalence • Infertility treatments • Japan

## Summary

*Widespread rubella epidemics have sometimes occurred in Japan. We compared the prevalence of rubella antibodies in women who had conceived after infertility treatments and in those who had conceived spontaneously. We reviewed the obstetric records of nulliparous Japanese women who had conceived after infertility treatments and whose babies had been born at the Japanese Red Cross Katsushika Maternity Hospital from 2014 to 2018. No sig-*

*nificant differences in the rates of women with rubella antibody titers < 8 or < 32 emerged between those who had been treated and those who had not (titer < 8: 4.1 vs. 3.4%,  $p = 0.58$ ; titer < 32: 17.3 vs. 15.3%,  $p = 0.45$ , respectively). It is necessary to thoroughly implement pre-conception care concerning the risk of congenital rubella infection for women undergoing infertility treatments, especially in Japanese obstetric clinics.*

## Introduction

Infections can impact the reproductive health of women and hence may influence pregnancy-related outcomes for both the mother and the child. Rubella is usually a mild infectious disease, often accompanied by rash. In pregnant women, however, rubella infection can result in miscarriage, stillbirth and a series of disabilities known as congenital rubella syndrome (CRS) [1]. In developed countries, rubella vaccination programs have reduced the incidence of rubella and CRS [2, 3]. However, widespread rubella epidemics have sometimes occurred in Japan. For example, an outbreak of rubella and CRS among adult males occurred between 2012 and 2014, and a rubella outbreak among adult males has been rekindling since 2018 [4, 5]. Indeed, in October, 2018, the US Centers for Disease Control and Prevention (CDC) issued the following Practice Enhanced Precautions: Travelers to Japan should make sure they are vaccinated against rubella with the MMR (measles, mumps, and rubella) vaccine before travel, and pregnant women who are not protected against rubella through either vaccination or previous rubella infection should not travel to Japan during this outbreak [6].

Screening and vaccination for rubella infection should be a component of pre-conception care, as there is convincing evidence that vaccination against the infection before pregnancy prevents neonatal infections [7, 8]. In Japan, more than 5% of all pregnancies are the result of the implementation of assisted reproductive technology (ART) [9]. The period of infertility treatments also offers an opportunity for pre-conception care. In Japan, infertility treatment is mainly carried out by obstetri-

cians, some of whom, however, may not be aware of the importance of CRS prevention during pre-conception care. In Japan, rubella antibody titers are measured in all pregnant women by means of the hemagglutination inhibition (HI) test during the first perinatal examination, the cost being borne by the national health service. We compared the prevalence of rubella antibodies in women who had conceived after infertility treatments and those who had conceived spontaneously.

## Methods

The study protocol was approved by the Ethics Committee of the Japanese Red Cross Katsushika Maternity Hospital. Informed consent to the retrospective analysis of data was obtained from all subjects. Our institute is one of the main perinatal centers in Tokyo, Japan, and does not carry out any infertility treatments.

In Japan, all women undergo rubella antibody measurement at public expense during early pregnancy. We reviewed the obstetric records of all nulliparous Japanese women who had conceived after infertility treatments and whose babies had been born at the Japanese Red Cross Katsushika Maternity Hospital from 2014 to 2018. Age-matched nulliparous women who had conceived spontaneously and whose first prenatal examination had been carried out on the closest date were selected as controls. In this study, we compared the prevalence of rubella antibodies in the nulliparous women who had conceived after infertility treatments with those measured in the control group. Rubella antibody titers < 32, as measured by the HI test, were considered low, in accordance with

a previous report by Ozaki et al. [10]. Data are presented as numbers (percentage: %) or averages  $\pm$  standard deviation. Statistical analyses were carried out by means of the statistical software SAS version 8.02 (SAS Institute, Cary, NC, USA).

## Results

No differences in socio-demographic characteristics emerged between the 2 groups ( $p > 0.07$ ), as shown in Table I. Table II shows rubella antibody titers, as measured by the HI test. There were no significant differences in the rates of women with rubella antibody titers  $< 8$  or  $< 32$  between the 2 groups: women who had conceived after infertility treatments and those who had conceived spontaneously (titer  $< 8$ : 4.1 vs. 3.4%,  $p = 0.58$ ; titer  $< 32$ : 17.3 vs. 15.3%,  $p = 0.45$ , respectively).

## Discussion

In terms of rubella antibody titers, this study did not reveal any effect of pre-conception care concerning CRS in infertility treatment facilities. During the period considered, the 411 nulliparous pregnant women who had undergone infertility treatment were referred from 38 ART facilities; however, the results of pre-pregnancy rubella antibody tests were reported only in the documents provided by two facilities (5.3%). Even though these women had attended pregnancy-related medical facilities, they did not seem to have benefited in comparison

with women who had only undergone complete first examination. It must be pointed out, however, that some of these latter women have recently begun to undergo voluntary rubella testing because of the fear of rubella infection during pregnancy. Nevertheless, it is very disappointing that obstetricians, who are familiar with the risk of CRS, had failed to perform pre-conception care regarding rubella infection. There may be various explanations for this.

In our previous study, ART was seen to be associated with a lower prevalence of Chlamydia trachomatis (CT) infection before pregnancy [11]. Indeed, women who require ART may sometimes have a history of CT infection. However, women may not be checked for a history of rubella infection because this is not associated with the causes of infertility. Moreover, the fact that the information leaflet accompanying the rubella vaccine carries a warning that 'women of childbearing age should be careful not to get pregnant for about 2 months after vaccination' [12] might also have led ART facilities to refrain from checking for a history of rubella infection. Finally, neither health education nor a past history of vaccination were considered in the study, which is a major limitation.

## Conclusions

Because doctors who treat infertility are also obstetricians, we expected women who received infertility treatment to have a higher prevalence of rubella antibodies. However, the results showed no difference in

Tab. I. Women socio-demographic features.

|                        | Women who conceived after infertility treatments (n, %) | Women who conceived spontaneously (%) |
|------------------------|---|---------------------------------------|
| Nulliparity            | 411 (100)   | 411 (100)                             |
| Maternal age (years)   | 37.0 $\pm$ 2.1  | 37.0 $\pm$ 2.1                        |
| Living in Tokyo        | 342 (83)  | 361 (88)                              |
| Economic difficulties* | 0 (0)   | 4 (1)                                 |
| Total                  | 411   | 411                                   |

\* Economic difficulties are defined according to the Japanese hospitalization assistance policy system [13].

Tab. II. Rubella antibody titers in nulliparous women who conceived after infertility treatments (n = 411) and those who conceived spontaneously (n = 411).

| Rubella antibody titer* (%) | Women who conceived after infertility treatments (%) | Women who conceived spontaneously (%) |
|-----------------------------|--|---------------------------------------|
| $< 8$                       | 17 (4.1)   | 14 (3.4)                              |
| 8                           | 18 (4.4)   | 15 (3.6)                              |
| 16                          | 36 (8.8)   | 34 (8.3)                              |
| ( $< 32$ )                  | 71 (17.3)  | 63 (15.3)                             |
| 32                          | 106 (26.8)   | 91 (22.1)                             |
| 64                          | 114 (27.7)   | 126 (30.7)                            |
| 128                         | 69 (16.8)  | 81 (19.7)                             |
| 256                         | 36 (8.8)   | 29 (7.1)                              |
| $> 256$                     | 15 (3.6)   | 21 (5.1)                              |
| Total                       | 411  | 411                                   |

\* Rubella antibody titer measured by hemagglutination inhibition test.

rubella antibody titers between the two groups. Given that rubella epidemics have frequently occurred in Japan, it is necessary to thoroughly implement pre-conception care concerning the risk CRS for women undergoing infertility treatments, especially in Japanese obstetric clinics. We believe that this is the duty of the obstetrician, who is most familiar with the risk of CRS.

### Availability of data and materials

The datasets are not open to the public.

### Ethics approval and consent to participate

This study was carried out in accordance with the Declaration of Helsinki. Informed consent for data analysis was obtained from all subjects. The protocol was approved by the ethics committee of the Japanese Red Cross Katsushika Maternity Hospital.

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### Conflict of interest statement

The authors declare no conflict of interest.

### Authors' contributions

YH: collected the data and wrote and reviewed the manuscript. SS: designed the report, analyzed the data,

wrote and reviewed the manuscript, and approved the final draft.

### References

- [1] Reef SE, Plotkin SA. Rubella vaccine. Vaccines 6<sup>th</sup> ed. Philadelphia: Elsevier 2013, pp. 688-717.
- [2] Mason WH. Rubella. Nelson textbook of pediatrics 19<sup>th</sup> ed. Philadelphia: Elsevier 2011, pp.1075-178.
- [3] Ueda K. Epidemiology of rubella and congenital rubella syndrome in Japan before 1989. Vaccine 2016;34:1971-4. <https://doi.org/10.1016/j.vaccine.2015.10.010>
- [4] The National Institute of Infectious Disease. Emergency information on rubella outbreak. 2019. <https://www.niid.go.jp/niid/images/epi/rubella/2019/rubella190109.pdf> (accessed on 01/16/2019).
- [5] Center for Disease Control and Prevention. Traveler's health: rubella in Japan. <https://wwwnc.cdc.gov/travel/notices/alert/rubella-japan> (accessed on 01/16/2019).
- [6] Berghella V, Buchanan E, Pereira L, Baxter JK. Preconception care. Obstet Gynecol Surv 2010;65:119-31. <https://doi.org/10.1097/OGX.0b013e3181d0c358>
- [7] Ergenoğlu AM, Yeniel AO, Yildirim N, Kazandi M, Akercan F, Sağol S. Rubella vaccination during the preconception period or in pregnancy and perinatal and fetal outcomes. Turk J Pediatr 2012;54:230-3.
- [8] Japan Association of Obstetricians and Gynecologists. Assisted reproductive technology (in Japanese). <http://www.jaog.or.jp> (accessed on 01/16/2019).
- [9] Ozaki T, Nishimura N, Gotoh K, Ohe K, Funabashi K, Maeda K, Okuno Y. Phases 3 and 4 immunization immunogenicity with combined measles-rubella vaccine (in Japanese). Kansenshogaku Zasshi 2011;85:250-5.
- [10] Kato M, Suzuki S. History of assisted reproductive technology and Chlamydia trachomatis infection in pregnancy. J Clin Med Res 2016;8:244-5. <https://doi.org/10.14740/jocmr2444w>
- [11] Mitsubishi Tanabe Pharma. Freeze-dried live attenuated rubella vaccine (in Japanese). [http://www.info.pmda.go.jp/downfiles/ph/PDF/630144\\_631340BD1037\\_1\\_26.pdf](http://www.info.pmda.go.jp/downfiles/ph/PDF/630144_631340BD1037_1_26.pdf) (accessed on 01/16/2019).
- [12] Hiraizumi Y, Shunji Suzuki. The hospitalization assistance policy system in Japan. J Nippon Med Sch 2011;78:267-9.

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**Correspondence:** Shunji Suzuki, Department of Obstetrics and Gynecology, Japanese Red Cross Katsushika Maternity Hospital, 5-11-12 Tateishi, Katsushika-ku, Tokyo 124-0012, Japan - Tel. +81 336935211 - Fax +81 336948725 - E-mail: czg83542@mopera.ne.jp

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