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## Original Research Article

## Association between past history of chickenpox and varicella immunity in women attending infertility clinic

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### Abstract

**Background:** If varicella is contracted during pregnancy, it has adverse implications for both fetal & maternal health. We wanted to understand the association between past history of chickenpox and varicella immunity demonstrated by specific immunoglobulin (IgG), so that patients can be made aware about the need for vaccination & can make an informed choice.

It is particularly important in resource restricted settings to determine whom to screen, where both testing for varicella immunity and the vaccines are costly.

**Aim and Objective:** This prospective cross-sectional study was conducted to find correlation between the past history of chickenpox and immunity to varicella demonstrated by specific immunoglobulin (IgG).

**Material and Methods:** Over a period of 10 months, women attending infertility clinic at an urban tertiary care centre were asked about past history of chickenpox. Their immunity to varicella was checked by varicella IgG. Demographic and clinical profile of all the patients was recorded. Sensitivity, specificity, negative & positive predictive values were calculated for a positive history and reported with 95% confidence intervals.

SPSS (Statistical Package for Social sciences) Version 25:0 was used to analyze the collected data.

**Result:** Positive History of chickenpox had PPV of 95% (95% CI 77.4–87.4), sensitivity of 52.41% (95% CI 49.9–60.6) & specificity of 87.5% (95% CI 50.9–70.2).

**Conclusion:** Although serological screening remains the gold standard, positive past history of chickenpox can be used as an important tool in preconception counseling, as it has demonstrated a high positive predictive value.

**Keywords:** Varicella immunity, History of chickenpox, Positive predictive value, Infertility, Preconceptional counselling.

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### 1. Introduction

Chickenpox is a highly communicable primary infection caused by human herpes virus 3, a DNA virus. Patient typicality gives history of a prodromal fever followed by eruption of a vesicular rash. The blisters dry up over a period of time forming crusts, ultimately turning into scabs. The virus spreads through respiratory droplets of the naso pharyngeal secretions of infected individual and via direct contact with vesicular fluid. It is highly contagious, especially in early stage of the rash eruption.

The childhood illness is quite modest and self-limited. Majority of children go through the episode without suffering

severe outcomes, conferring lifelong immunity to the disease. The virus has a potential to establish a latent infection by staying dormant in the sensory root ganglia of nerves.

Reactivation of latent infection causes herpes zoster, commonly known as shingles. Serious neurological and ocular morbidities can occur in geriatric or immunocompromised patients.<sup>1</sup> (e.g. myelitis, meningoencephalitis, cranial nerve palsies, keratitis and retinopathy). The commonest life threatening complication in this group of patients, including pregnant women, is pneumonitis which has a mortality rate of about 14%.<sup>2</sup>

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Chickenpox poses some unique challenges when acquired during pregnancy. If a pregnant woman is infected with the virus during the first & early second trimester, particularly 13-20 weeks, the fetus is at risk of a set of serious birth defects known as congenital varicella syndrome, constituting skin scarring, eye, brain, limb and gastrointestinal abnormalities. Though the risk of embryopathy is small, (about 0.4-2%),<sup>3</sup> the consequences for the affected fetus are severe, with roughly 30% fatality during the first month of life.<sup>4</sup>

Prenatal diagnosis of congenital varicella requires advanced ultrasound expertise & invasive testing in the form of cordocentesis or amniocentesis.

If the infection is acquired during a period of few days before delivery to 48 hours postpartum, the foetus is exposed to high viral load. Specific IgG antibodies develop about one week after the appearance of rash, attaining peak concentrations in a month's time. Thus the foetus remains unprotected as there isn't enough time for trans placental acquisition of maternal antibodies. The baby is born with a potentially life-threatening infection constituting pneumonia, hepatitis, thrombocytopenia, landing in secondary sepsis.

Although the mortality in neonatal varicella has reduced drastically due to advanced neonatal care, antiviral drugs & immunoglobulin, costs involved in treatment are significant.<sup>5,6</sup>

Irrespective of the timing of acquisition of maternal infection, children born to these mothers can develop herpes zoster in infancy.<sup>7</sup>

Exposure to varicella can neither be predicted nor prevented completely as infected individuals can spread the virus even before the onset of the characteristic rash.

Currently, two effective and safe live attenuated virus vaccines are available, both containing the Japanese varicella virus strain Oka. In India, vaccination against varicella is not a part of National Immunization Program at present.

As recommended by Indian Academy of Paediatrics,<sup>8</sup> it is a voluntary, informed choice of the parents.

The simplest strategy to avert varicella infection in pregnancy would be to know the status of immunity of the woman before conception and give the vaccine if found susceptible. ASRM in its guidelines for pre-conceptual counselling advises the same.<sup>9</sup>

In women with infertility, it is equally important, if not more, as infertility treatments are quite resource intensive. It is only prudent to check for the known preventable risk factors & address them before planning the premium pregnancy.

Testing for varicella immunity and varicella vaccines both add to the costs of pre pregnancy optimization. It can be advantageous to know the association between positive history of chickenpox in the past with varicella immunity in women planning to conceive.

It is intended to provide cost effective care & assist in patient counselling.

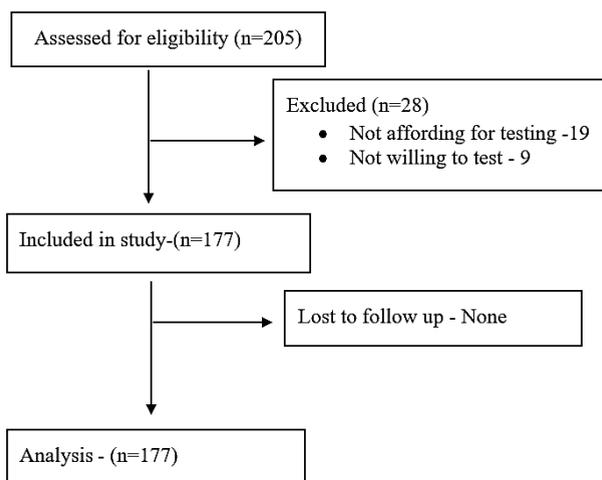
## 2. Material and Methods

This prospective cross-sectional study was conducted at the Department of Reproductive Medicine & Surgery, Bharati Hospital at Bharati Vidyapeeth University Medical College, Pune. Institutional ethics committee approval was obtained. (BVDUMC/IEC/16).

STROBE guidelines for prospective cross-sectional study were followed.

Considering the seroprevalence in India about 81%,<sup>10</sup> sample size was estimated to be 140 with a confidence interval of 95% (5% level of significance & 80% power).

Patients were recruited as demonstrated in **Figure 1**.



**Figure 1:** Patient recruitment flowchart

Women attending infertility clinic at the department of reproductive medicine were asked about history of chickenpox in childhood. A description of an episode of generalized vesicular rash with fever was considered as positive.

Women were asked specifically about the signs & symptoms of chickenpox in past & the characteristic vesicular rash. To address the recall bias, they were encouraged to confirm the same with their parents.

They were asked if they knew about possibility of contracting varicella during pregnancy and the associated risks to mother and fetus. The responses were recorded. Patients who had no knowledge were counselled about the same.

These women were offered test for Varicella IgG.

If a woman was not willing to check the immunity to varicella irrespective of positive or negative history for any reason, consent was obtained and she was excluded from the study.

If found seronegative, they were given 2 doses of varicella vaccine at interval of 1 month and offered contraception till 4 weeks after second dose of vaccine, before starting treatment of infertility.

Positive predictive value, sensitivity & specificity of positive history as compared to varicella IgG seropositivity were calculated.

The presence of anti-varicella IgG in serum samples was determined by anti-VZV IgG ELISA (enzyme linked immunosorbent assay). Value of ratio  $\geq 1.10$  was taken as positive and  $< 0.80$  as negative, according to the manufacturer's directives. This being a qualitative test, the numeric value does not indicate the amount of antibody present. Values above cut off for the assay signify detection of specific antibodies, suggesting prior exposure or vaccination. Individuals testing positive are considered immune to varicella-zoster. Equivocal results (between 0.80-1.10) were considered negative for purpose of statistical analysis & patient management. Negative results amount to absence of IgG antibodies suggesting no past exposure to the varicella virus, or lack of specific immune response, if vaccinated.

### 2.1. Statistical analysis

SPSS version 25.0 (Chicago, Illinois, USA) was used for data analysis.

Seroprevalnce was calculated as the number of samples tested positive for varicella IgG divided by the total number of examined serum samples.

The presence of varicella IgG was considered as gold standard for immunity to chickenpox.

We calculated Sensitivity, specificity, negative & positive predictive values for a positive history of infection, reported with 95% confidence intervals.

### 3. Result

As depicted in (Table 1), majority 59.32% women belonged to age group of 21-30 years. Mean age of the cohort was 29.1 years.

Mean age at marriage was 23.95 years, while mean duration of marriage was 5.08.

76.83% women had primary infertility, while 23.16% had conceived before.

**Table 1:** Socio-demographic characteristics

| Age             | Age group               | Number | %     |
|-----------------|-------------------------|--------|-------|
|                 | Age<20                  | 2      | 1.13  |
|                 | Age 21-30               | 105    | 59.32 |
|                 | Age 31-40               | 68     | 38.42 |
|                 | Age41 -50               | 2      | 1.13  |
| Total           | 177                     | 100    |       |
| Education       | Education               | Number | %     |
|                 | Primary                 | 6      | 3.39  |
|                 | Secondary               | 55     | 31.07 |
|                 | Graduation              | 83     | 46.89 |
|                 | Post-graduation         | 33     | 18.64 |
| Total           | 177                     | 100    |       |
| Age at marriage | Age at marriage (Years) | Number | %     |
|                 | <20                     | 46     | 25.99 |
|                 | 21-30                   | 116    | 68.53 |
|                 | 31-40                   | 14     | 7.91  |
|                 | 41-45                   | 1      | 0.56  |
| Total           | 177                     | 100    |       |

**Table 2:** History of chickenpox

| History of past varicella infection | Number | %     |
|-------------------------------------|--------|-------|
| Yes                                 | 80     | 45.19 |
| No                                  | 73     | 41.24 |
| Unsure                              | 24     | 13.56 |
| Total                               | 177    | 100   |

45.19% women gave a positive history of chickenpox, 41.24% were certain that they never had chickenpox in the past. For purpose of statistical analysis, those who were not sure about the history (13.56%) were considered as never having disease in the past.

**Table 3:** Varicella serostatus

| Varicella IgG | Number | %     |
|---------------|--------|-------|
| Negative      | 32     | 18.07 |
| Positive      | 145    | 81.92 |
| Total         | 177    | 100   |

**Table 4:** Varicella serostatus by age

| Varicella IgG | <20 years | 21-30 years | 31-40 years | >40 years |
|---------------|-----------|-------------|-------------|-----------|
| Negative      | 2         | 20          | 10          | 0         |
| Positive      | 0         | 85          | 58          | 2         |
| Total         | 2         | 105         | 68          | 2         |

Overall Seroprevalance of varicella in the study population was 81.92%. (Table 3), 0% in <20 years, 80.95% in age group 21-30 years, 85.29% in age group 31-40 years & 100% in 41-50. (Table 4)

Highest proportions of susceptible women were found under the age of 30 years (20.56%). (Table 4)

**Table 5:** Contingency table -history of varicella versus true seroconversion

| History             |     | IgG Positive | IgG Negative | Total |
|---------------------|-----|--------------|--------------|-------|
| Positive chickenpox | H/O | 76           | 04           | 80    |
| Negative Chickenpox | H/O | 69           | 28           | 97    |
| Total               |     | 145          | 32           | 177   |

Out of 80 women with positive history of chickenpox, only 4 (5%) were found VZV IgG negative, while 62.85% women who said they never had chickenpox in past, turned out VZV IgG positive. (Table 5).

Positive history of chickenpox had PPV of 95% (95% CI 77.4–87.4), sensitivity of 52.41% (95% CI 49.9–60.6) & specificity of 87.5% (95% CI 50.9–70.2). (Table 5)

Only 4.8.% women communicated that they had heard of vaccines for varicella. Mere 12.2% knew about fetal &/or maternal risks of varicella infection during pregnancy

#### 4. Discussion

Though data about the seroprevalance of varicella in India is quite scarce, available data indicates the proportion of susceptible adults to be as high as 14% to 30%.<sup>11-15</sup>

Women of reproductive age group form an important subset, as infection contracted during pregnancy can not only lead to serious complications in the mother & fetus, but can have long lasting adverse effects on the health of the neonate.

As observed in previous studies, varicella seroprevalance rate of >90% were achieved by the age of 30 years in Indian population, while similar rate of seroprevalance was observed by the age of 15 years in UK.<sup>16</sup> 80% seroprevalance was reached by the age of 7 years in Spain,<sup>17</sup> & 83% by the age of 9 years in Japan.<sup>18</sup>

The median age at first marriage for Indian women was 19.2 years in 2019-21.<sup>19</sup> By the time they reach their thirties,

significant number of girls and young women have been through one or more pregnancies or are trying to conceive.

Varicella vaccine is still not a part of our national immunization schedule, as policy opinion on the topic remains divided.

Our study reported overall seroprevalance of 81.92% in the study population (0 in <20 years, 80.95% in age group 21-30 years, 85.29% in age group 31-40 years, & 100% in 41-50), which is in agreement to study done by Lokeshwar et al. They found that although varicella seroprevalance in Indian population increases with age, a striking proportion of young adults remain susceptible to varicella infection.

Our data, collected from women attending infertility clinic showed history of chickenpox in the past had PPV of 95% (95% CI 77.4–87.4), sensitivity of 52.41% (95% CI 49.9–60.6) & specificity of 87.5% (95% CI 50.9–70.2).

Conversely, negative history was not predictive of lack of immunity to chickenpox as shown by low predictive value of 28%.

A study done in Singapore amongst military recruits found the positive predictive value, sensitivity & specificity of self-reported positive history for varicella to be 94.3%, 87.2% & 83.2%, respectively.<sup>20</sup>

A study in pregnant women from urban & rural areas from south India showed recollected history of varicella had a positive predictive value of 82.4%.<sup>21</sup>

A similar study from Sri Lanka reported a positive predictive value of 89.5% and negative predictive value of 53.1% though they had included positive past history as well as history of vaccination.<sup>22</sup>

Multiple studies done in the temperate regions of the world reported PPV of more than 95% among pregnant women, although it is worth to acknowledge that the epidemiology of the primary varicella infection is different in temperate & tropical countries.

In temperate countries, chicken pox is a childhood disease, while in tropics it occurs more commonly in adolescents and young adults.<sup>23-25</sup>

Vaccination policy also differs worldwide. Only few countries around the globe have included varicella vaccine in their schedule as a part of universal vaccination program.

Many studies have drawn a conclusion that history of chickenpox in past can be used safely to exclude patients from serological testing.<sup>26-28</sup>

On the contrary, other researchers have inferred that history alone cannot be relied upon completely as a sole indicator of immunity for chickenpox.<sup>29,30</sup> They suggested

serologic testing to recognize susceptible patients, who would benefit from the vaccine.

## 5. Strength

Evident limitation of the previous studies done in pregnant women is that even if found susceptible, they can't be administered varicella vaccine, as it is a live attenuated vaccine. Our study focuses on knowing the seroprevalence in women planning to conceive, providing a window of opportunity for prevention.

We collected the data from prospectively recruited women attending the infertility clinic, seeking treatment to conceive. These women are the ones, who for obvious reasons will have a planned pregnancy.

As majority of pregnancies in India are unplanned, women are oblivious to the concept of preconceptional optimization.

## 6. Limitations

We could not collect data regarding prior immunization owing to difficulties in ascertaining vaccination due to lack of documentation and recall bias.

## 7. Conclusion

Consultation for infertility treatments can be & should be used as an opportunity to screen for preventable risks factors and offer appropriate measures, same is the case with couples coming for preconceptional counselling.

Our study concludes that although serological screening remains the gold standard, past history of chickenpox has demonstrated high positive predictive value & can be used as an important counselling tool in resource restricted setting. The patient should be informed regarding positive predictive value of history so that she can make informed choice.

## 8. Source of Funding

Nil.

## 9. Conflict of Interest

None.

## 10. Ethical Committee Approval

Institutional ethics committee approval (BVDUMC/IEC/16).

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