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Relationship between Chlamydia Trachomatis Infection with Patency Tubal and Non-Patency Tubal Occurrence in Infertile Women

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Abstract

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AIM: To determine the relationship between *Chlamydia Trachomatis* infections with patency tubal and non-patency tubal occurrence in infertile women.

METHODS: This research was an observational analytic research with a cross-sectional study. This research was conducted at Haji Adam Malik General Hospital Medan, Pramita Laboratory Medan and Medical Faculty of Medicine Universitas Sumatera Utara. Laboratory on October 2017 until the number of samples was fulfilled. The samples were women who were referred to Pramita Laboratory Medan for hysterosalpingography procedure in accordance which corresponded to the inclusion criteria by using consecutive sampling technique.

RESULTS: From this research, it was found that the most infertile women were aged 31-35 years, with the most infertility type was primary infertility (83.8%) with the longest infertility duration was ≥ 3 years (44%). From all samples who were infertile, 26% among them were positive to chlamydia infection. Eight from twelve people who were infected by *Chlamydia Trachomatis* experienced non-patency tubal (66.7%) with p-value = 0.001 which showed that there was a relationship between *Chlamydia Trachomatis* infection with patency tubal and non-patency tubal occurrence in infertile women.

CONCLUSION: The proportion of *Chlamydia Trachomatis* infection in tubal abnormality in this study was 66.7%, whereas *Chlamydia Trachomatis* infection in the normal tube was 13.2%. It was obtained that there was a significant relationship between Chlamydia Trachomatis infection with tubal abnormality (non-patency tubal) with p-value < 0.005 (p = 0.001).

Introduction

Infertility is the absence of pregnancy after marriage for 12 months or more, even though the couple has had sexual intercourse regularly without any contraceptive use [1]. About 10-15% of couples worldwide experience infertility problems. The number of infertile couples in the world as well as in Indonesia is increasing, where there is an increase in the number of infertile couples of around 2% every 5 years [1]. In the United States, there are around 80 million reproductive age couples recorded [2].

According to the World Health Organization (WHO), the prevalence of women with infertility in Indonesia in 2004 at the age of 20-24 years was

21.3% and at the age of 25-29 years 16.8% [3]. Mashuri in 2006 against 93 infertile couples at dr. Pirngadi hospital Medan, found infertility originating from the wife's side as much as 49.46%, from the husband's side as much as 43.01% and 7.34% of both [4].

From the couple has had sexual intercourse regularly without using contraception, around 10-15% of couples worldwide experience infertility. Factors that cause infertility in women are divided into ovulation dysfunction factors (40%), pathological factors in the tube and peritoneal (40%), the presence of uterine problems (10%), and unexplained causes (10%). Genital infection by *Chlamydia trachomatis* is the main cause of tubal factor infertility [5], [6].

A case-control study conducted in Iran using

the Polymerase Chain Reaction (PCR) method showed that *Chlamydia trachomatis* was detected in 32% in infertile women and 8.7% infertile women [5]. Likewise in Nigeria, the prevalence of IgG *Chlamydia trachomatis* was 74% in infertile women [6]. In a study conducted in Egypt by Ahmed et al., IgG positive *Chlamydia trachomatis* was found in 30 of 78 infertile patients with tubal occlusion [7]. The study by Sharma et al., in Africa showed that tubal damage caused by *Chlamydia trachomatis* infection contributed more of 70 percent of infertility cases [8]. Various studies also found that the incidence of infertility due to tubal occlusion after infection with *Chlamydia trachomatis* ranged from 10-20% [9], [10], [11], [12]. From several studies it was also concluded that exposure to chronic infections from *Chlamydia trachomatis* is major predisposing factors resulting in chronic inflammation and causing damage to the tube resulting in infertility [13], [14].

Chlamydia trachomatis is an obligate intracellular microorganism that has the same cell wall as gram-negative bacteria and mainly infects the urethra, cervix, and tubal tract [15]. WHO reported the incidence of *Chlamydia trachomatis* infection is around 131 million worldwide with varying prevalence rates. in each country [16]. According to the 2014 Centers for Disease Control and Prevention (CDC), *Chlamydia trachomatis* infection is a sexually transmitted disease with the highest incidence in the United States of 1.4 million [17]. *Chlamydia trachomatis* is also the most common cause of sexually transmitted infections often reported in Europe, with a prevalence of 1.7-17% in European women and 4.1% in women in Spain [18], [19]. *Chlamydia trachomatis* infection as much as 80% in women is asymptomatic so screening is needed so infection control can be achieved [20], [21].

Chlamydia trachomatis infection can generally be diagnosed using culture examination, antigen detection test, antibody test, and Nucleic Acid Amplification Technique test (TAAN), such as PCR and Ligase Chain Reaction (LCR) [21]. TAAN has sensitivity 80-90% with specificity > 98% and can be used to check large quantities of samples [22]. PCR is one of the TAAN techniques by amplifying millions of DNA segments in just a few hours. This method is very promising for the initial detection of *Chlamydia trachomatis* infection with a sensitivity of 95% and specificity of 99.3% [23].

To date, there is no accurate data regarding the overall prevalence of *Chlamydia trachomatis* infection in Indonesia. Research on the prevalence of *Chlamydia trachomatis* infection in patients who experience differences caused by tubal patency with tubal non-patency in Indonesia is also not yet available. This is because *Chlamydia trachomatis* examination is not routinely done in infertility management in various education centers even though this has been recommended in the national consensus on handling infertility. At Haji Adam Malik

Hospital itself, which is a national referral hospital, it has not yet made the examination and prophylactic therapy of *Chlamydia trachomatis* as a routine examination and therapy in temporary infertility management. most are caused by *Chlamydia trachomatis* infection.

So based on the above explanation, the author feels it is important to know the relationship between *Chlamydia trachomatis* infection and the incidence of tubal patency and non-patrol tubal infections in infertile women.

Material and Methods

This study aims to determine the relationship between *Chlamydia trachomatis* infection and the incidence of tubal patency and non-tubal patency in infertile women, an observational analytic study with a cross-sectional study approach. This research was conducted at Haji Adam Malik General Hospital Medan, starting in October 2017 until the sample was fulfilled then the sample was taken to the FK USU Laboratory for examination. The study population was all infertile women who were referred from SpOG private practice in the Medan region to Pramitha Laboratory who agreed to take hysterosalpingography (HSG).

The method of selecting samples in this study was done by consecutive sampling, where all infertile patients who met the inclusion and exclusion criteria and agreed to be examined after informed consent was included in the study until the required number of subjects was fulfilled.

The sample size is calculated statistically based on the formula:

Exp:

$$n = \frac{Z^2 p q}{d^2} = \frac{Z^2 p (1-p)}{d^2} \quad \text{(Snedecor GW \& Cochran WG, 1967)} \\ \text{(Lemeshowb dkk, 1997)}$$

n = Minimum number of samples needed

Z = If $\alpha = 0.05$ then Z score = 1.96

p = Proportion of *Chlamydia trachomatis* infection in tubal occlusion

$q = 1 - p = 0.15$

α = Degree of trust = 5%

d = Precision = 10%

$$n = \frac{(1.96)^2 \times 0.85 \times 0.15}{(0.1)^2}$$

$$n = \frac{(1.96)^2 \times 0.85 \times 0.15}{(0.1)^2} = 48.98 \approx 50$$

Based on the above formula, the minimum number of samples obtained in this study were 50 subjects.

Inclusion Criteria: 1. Women aged 21-40 years; 2. Infertile women who are willing to do HSG examinations; 3. Infertile women who have never had abdominal and pelvic surgery, and have no myoma; 4. Willing to take part in the study and sign the consent form to take part in the study; and 5. Infertility occurs not due to male infertility.

Exclusion Criteria: Error results (illegible DNA on PCR).

Work Arrangement

Subjects were explained about the purpose of the study, the examination procedure, and the benefits of the research obtained from this study. If the subject is willing to take part in this study, the subject of the statement letter agrees to participate in the study. Patients who meet the inclusion and exclusion criteria are interviewed about identity which includes: name, age, gender, type, and duration of infertility. How it works to take endocervical smears: 1. The subject is given an explanation in advance about the examination to be carried out so that the patient does not feel afraid; 2. Using personal protective equipment, in the form of laboratory suits, gloves, masks, and glasses; 3. The patient was previously asked to urinate and remove underwear, then the patient was positioned lithotomy; 4. If there are too many secretions in the vulva, clean them first with a NaCl solution; 5. Then the left hand opens the labia may then input the bottom Sims and Sims up inside the vagina; 6. With the help of floodlights. Look for the cervical portion; 7. Observe whether there are mucopurulent endocervical secretions, erythema, erosion, and edema; 8. The cervix: cleanses the endocervix area with sterile gauze, then smears with a sterile swab; and 9. The sample was put into a microcentrifugation tube which was filled with TE buffer liquid and then taken to the integrated laboratory of the Faculty of Medicine, University of North Sumatra.

Statistical Analysis

After all the data was collected, a descriptive analysis was conducted to determine the characteristics of the research subjects. Then bivariate analysis was performed to determine the relationship between Chlamydia trachomatis infection and the incidence of tubal patency and non-patency of the tube in women. To see the strength between the two variables, researchers used the Chi-square test in table 2 x 2 with a value of $p < 0.05$.

Results

Table 1 describes the characteristics of the study participants. In this study, it was found that the age most experienced Chlamydia Trachomatis infection was the age range in of 31-35 years, and the least was found in the age range of 21-25 years (Table 1).

Table 1: Characteristics of Infertile Patients by Age, Type of Infertility and Duration of Infertility

| Characteristic | Chlamydia trachomatis infection (PCR) | | | | | |
|----------------|---------------------------------------|--------|----------|--------|-------|--------|
| | Positive | | Negative | | Total | |
| | n | % | n | % | n | % |
| Age | | | | | | |
| 21-25 | 1 | 7.7% | 0 | .0% | 1 | 2.0% |
| 26-30 | 2 | 15.4% | 13 | 35.1% | 15 | 30.0% |
| 31-35 | 3 | 23.1% | 20 | 54.1% | 23 | 46.0% |
| 36-40 | 7 | 43.9% | 4 | 10.8% | 11 | 22.0% |
| Total | 13 | 100.0% | 37 | 100.0% | 50 | 100.0% |
| Infertility | | | | | | |
| Primary | 10 | 76.9% | 31 | 83.8% | 41 | 82.0% |
| Secondary | 3 | 23.1% | 6 | 16.2% | 9 | 18.0% |
| Total | 13 | 100.0% | 37 | 100.0% | 50 | 100.0% |
| Duration | | | | | | |
| 1-2 | 1 | 7.7% | 6 | 16.2% | 7 | 14.0% |
| 2-3 | 7 | 53.8% | 14 | 37.8% | 21 | 42.0% |
| ≥ 3 | 5 | 38.5% | 17 | 45.9% | 22 | 44.0% |
| Total | 13 | 100.0% | 37 | 100.0% | 50 | 100.0% |

Table 1 also illustrates the characteristics of the type of infertility. From 50 research subjects, there were 41 subjects with primary infertility and 9 subjects who experienced secondary infertility. Of the 41 subjects who experienced primary infertility, 10 people were infected with Chlamydia trachomatis 76.9% and 31 subjects who were not infected with Chlamydia Trachomatis. Of the 9 subjects who experienced secondary infertility, 3 of them were infected with Chlamydia Trachomatis, and 6 were not infected with Chlamydia Trachomatis.

Table 1 also illustrates the duration of infertility. From the table, it was found that the highest duration of infertility was > 3 years of parity, which was as many as 22 people (44%) and the least was with a duration of 1-2 years, as many as 7 people (14%). Of the 22 people who had > 3 years of infertility, 5 of them were infected with Chlamydia trachomatis, and 17 of them were not infected with Chlamydia trachomatis. Of the 7 people who had 1-2 years of infertility, 1 of them was infected with Chlamydia trachomatis, and 6 of them were not infected with Chlamydia trachomatis.

In Table 2 are shown the results obtained from 50 samples studied, and we can see that 13 people (26%) were infected by Chlamydia trachomatis, and 37 people (74%) were not infected.

Table 2: Frequency of Chlamydia trachomatis infection with PCR Method

| Total | PCR | | Total |
|-------|---------------------------|---------------------------|-----------|
| | Chlamydia trachomatis (+) | Chlamydia trachomatis (-) | |
| Total | 13 (26%) | 37 (74%) | 50 (100%) |

In Table 3 we can see the prevalence of Chlamydia trachomatis infection in infertile women. As many as 8 people (66.7%) from 12 people with Non-Patent Tuba and as many as 5 people (13.2%) from 38 people with Tuba Patency have positive infection established with PCR. This is consistent with research by Sharma et al., in Africa showing that tubal damage caused by Chlamydia trachomatis infection accounts for more than 70% of cases of infertility.

Table 3: Prevalence of Chlamydia trachomatis infection with Tuba Patent and Non-Patent Tuba Events in Infertile Women

| Chlamydia infection | Tubal Patency | | | |
|---------------------|---------------|-------|--------|-------|
| | Non-paten | | Patent | |
| | n | % | n | % |
| Positive | 8 | 66.7% | 5 | 13.2% |
| Negative | 4 | 33.3% | 33 | 86.8% |
| Total | 12 | 100% | 38 | 100% |

Relationship Between Chlamydia trachomatis infection and the incidence of tubal patency and non-patent of the tuba in infertile women

Chlamydia trachomatis infection is one of the causes of infertility experienced by mothers due to tubal patency.

Table 4 describes the proportion of Chlamydia trachomatis infection in tubal abnormalities. In this study, tubal abnormalities in the form of Non-Patent Tubes were found in 8 of 13 people infected with Chlamydia trachomatis (61.5%), higher than the proportion of Chlamydia trachomatis infection in normal tubal, i.e., 5 from 13 people (38.5%).

Table 4: Relationship Between Chlamydia Trachomatis Infection with Patency Tubal and Non-Patency Tubal

| Tubal Patency | Chlamydia Infection | | | | | | P Value |
|---------------|---------------------|--------|----------|--------|-------|--------|---------|
| | Positive | | Negative | | Total | | |
| | N | % | N | % | N | % | |
| Non patency | 8 | 61.5% | 4 | 10.8% | 12 | 24.0% | 0.001 |
| Patency | 5 | 38.5% | 33 | 89.2% | 38 | 76.0% | |
| Total | 13 | 100.0% | 37 | 100.0% | 50 | 100.0% | |

Discussion

Our results are not in accordance with several studies conducted by Ioannis which illustrate that the most Chlamydia trachomatis infections in the age range under 25 years in the USA. Due to this age, it is often associated with sexual experience, changing sexual partners and the number of new sexual partners. This may be different from the Indonesian state that does not adhere to free sex, so that hygiene and education factors are factors that influence the incidence of Chlamydia Trachomatis infection in the age range of 31-35 years, besides, it is said that the age at first sexual intercourse was also higher in the USA compared to developing countries [13]. The

study conducted by Sayed on 150 infertile women in Iran, also illustrates that the most age for infection with Chlamydia Trachomatis is the age range of 25-29, which is as many as 80 people [8].

This result is consistent with a study conducted by Haifa in Saudi Arabia, of 456 who experienced infertility, 368 were primary infertility, and 89 were secondary infertility, according to a study conducted by Samiha, et al., conducted on 215 infertile women, of which 172 among them are primary infertility (80%), and 43 other women are secondary infertility (20%). This occurs because patients with primary infertility have greater concern than secondary infertility patients who already have children so that awareness of self-examination and seeking medical assistance in dealing with infertility problems is better than patients with secondary infertility. Women suffer from primary infertility because of several risk factors, such as menarche above 16 years, irregularities of the menstrual cycle, age at marriage, and infection.

This is in accordance with a study by Wafirotus in Indonesia in 42 infertile women who found that the duration of infertility was at most between 3 years and > 5 years, at 35.7%. Whereas in a study conducted by Gendarme et al., In Mongolia, of 430 infertile couples, the longest infertile duration was 4-8 years as many as 153 people (35.6%) and 2-4 years as many as 152 people (35.4%). The thing that causes the duration of infertility is because the average couple will seek treatment for infertile problems over 2 years [30].

Our results are consistent with a study conducted by Sayed et al., of the 150 samples of infertile women studied, where 48 (32%) subjects were infected with Chlamydia trachomatis established through PCR [8].

Similar results were also found in the Sami et al. From 100 samples of infertile women in the study group, 36 subjects (36%) were infected by Chlamydia trachomatis. The cause of infertility in Chlamydia trachomatis sufferers was due to non-patent tuba.

This is in line with the study by Sami et al., who examined the relationship between infertility and Chlamydia trachomatis infection in 200 women in Al-Sadar hospital, illustrating that 60 people had tubal disorders and 25 (41.6%) people with Chlamydia trachomatis infection with a value of $p < 0.005$, illustrates the close relationship between Chlamydia trachomatis infection with tubal disorders that cause infertility in women. The disorder is due to obstruction or occlusion of the tube due to untreated Chlamydia trachomatis infection. Another study conducted by Swapnil Singh on 200 infertile women, found 10 people suffering from Chlamydia trachomatis, and among those 10 people, all had tubal abnormalities, especially tubal occlusion. The most frequent occlusion site is in the fimbrial region as much as 34%, followed by the Cornual section 32%,

hydrosalpinx 20.6%, ampullary section 8.6% and the isthmus section 3.4%.

Another study conducted by Wafirotus et al., In 42 infertile women infected with Chlamydia Trachomatis, 76.1% had infertility due to tubal disorders, both those caused by perituba attachment, fimbriae phimosis, tubal occlusion, and hydrocephalic.

The study conducted by Gendarme et al., in Mongolia, performed in 280 women who experienced infertility, 55.6% were caused by infection, and 36% were due to tubal abnormalities, namely bilateral tubal occlusion and pelvic adhesion [30]. Another study conducted in Saudi Arabia by Alffaraj et al in 100 infertile women, found that 8% were infected by Chlamydia trachomatis, and 53.3% were due to tubal problems, this is because Chlamydia trachomatis that infects pelvic can spread to the uterus even to the fallopian tubes and cause local inflammation.

Also the study conducted by Ahmed et al., showed that of 80 infertile women, 30 women (37.5%) were infected with Chlamydia trachomatis, and 23 of them had tubal occlusion (76.6%), $p < 0.005$. Where 18 people experienced occlusion in the distal part, and 5 people experienced occlusion in the proximal part.

All tubal disorders caused by Chlamydia trachomatis infection causing infertility, have a complex mechanism. The mechanism by which Chlamydia trachomatis induces inflammation and tissue damage has not been fully understood. However, it is known that Chlamydia trachomatis target cells are squamocolumnar epithelial cells of the endocervix and upper genital tract in women. Apart from this place, the initial response to infection appears to be primarily a polymorphonuclear leukocyte response. Infected epithelial cells in vitro produce interleukin-8 (IL-8) and other proinflammatory cytokines, which stimulate the initial neutrophil response. Lipopolysaccharide may be the dominant Chlamydia trachomatis antigen capable of inducing proinflammatory cytokines.

Studies have explained the mechanism by which infected epithelial cells produce cytokines that direct the initial innate response and are obtained in Chlamydia trachomatis infection. Early neutrophil infiltration is followed by tissue infiltration with lymphocytes, macrophages, plasma cells, and eosinophils. In genital infections, plasma cells are generally present in large numbers. In genital diseases with biovar trachoma, lymphoid follicles (aggregate lymphocytes and macrophages in the submucosa) form when acute inflammation begins to subside. Thinning or loss of epithelium occurs around the follicle and can become necrotic when this disease occurs. When the infection begins to heal, fibrosis and scar tissue are formed.

The results of this study indicate that there is a significant relationship with a value of $p = 0.001$

where the value is smaller than 0.05, between Chlamydia trachomatis infection and the incidence of Non-Patent Tuba.

In conclusion, a significant relationship was obtained between Chlamydia Trachomatis infection and tubal abnormalities (non-patent tubal) with a value of $p = 0.001$ ($p < 0.05$), with the most research subjects being the age group 31-35 years and the primary infertility type being 41 subjects (82%). the highest duration of infertility is ≥ 3 years (44%). The frequency of Chlamydia trachomatis infection with the PCR method found that 13 subjects (26%) of the 50 subjects studied. The prevalence of Chlamydia trachomatis infection in tubal abnormalities in this study was 66.6%, while Chlamydia trachomatis infection in the normal tube was 13.2%.

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