Tuberculosis Infection In Women

Izhar Fitrah Ahmad[1], Edward Pandu Wiriansya[2]*, Andi Puspa Ratu[3], Sharen Kasim[4]

[1]Faculty of Medicine, Universitas Muslim Indonesia, Makassar, Indonesia
[2]*Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Muslim Indonesia, YW-UMI Ibnu Sina Hospital, Makassar, Indonesia
[3]Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin, Bhayangkara Makassar Hospital, Makassar, Indonesia
[4]Universitas Tun Hussein Onn Malaysia, Malaysia
Koresponden author:
Email : edwardpandu.wiriansya@umi.ac.id.

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Abstract
The increasing number of deaths due to tuberculosis has triggered the national tuberculosis control program to continue to intensify, accelerate, extend and innovate the program.7A holistic approach must be taken in order to improve tuberculosis control and identify various risk factors associated with tuberculosis infection. The Global Tuberculosis Report 2018 reported that 90% of tuberculosis sufferers are adults and 10% are children (<15 years). Figure 1 shows tuberculosis sufferers worldwide, 64% are men and 36% are women with a ratio of 2:1. In Indonesia, data also shows that tuberculosis is more common in men than women. The high prevalence in men shows that the level of men accessing tuberculosis services is higher than women. Differences in social roles between men and women can also affect risk factors for access to health services. In women, access to tuberculosis treatment and prevention services is more difficult than in men. This is because family members do not want to pay for women's health services. Women's health in the family is considered less important than male family members. Tuberculosis problems also occur in vulnerable populations, namely pregnant women and women with tuberculosis-HIV. A fairly high mortality rate occurs in women with tuberculosis-HIV. In pregnant women, transmission of tuberculosis germs to the fetus occurs, so that the fetus can have latent tuberculosis. Understanding tuberculosis disease in women can help the target of eliminating tuberculosis by 2030. Gender equality and active participation of women in the planning, implementation, and health care processes can be an effective way to overcome the problems of difficulty in accessing tuberculosis services, stigma and discrimination, and various existing barriers.
Keywords*: Tuberculosis infection; Stigma and Discrimination.*

I. INTRODUCTION

Tuberculosis is a public health problem that causes high levels of morbidity, disability and mortality.1Global Burden Disease 2010 to 2016 reported that tuberculosis ranked third as the leading cause of death in Indonesia. WHO in the 2018 global tuberculosis report reported that Indonesia was ranked third with the highest tuberculosis burden after India and China.[2]The latest data according to the World Health Organization on the global prevalence of TB in all parts of the world reaching 10.6 million cases in 2022. Indonesia is a developing country with the second highest TB incidence rate after India.[3].

In 2017 globally, an estimated 10 million people suffered from tuberculosis, consisting of 5.8 million men, 3.2 million women and one million children.2In 2022, there will be an increase in the number of tuberculosis sufferers in women by 3.5 million and in children by 1.3 million.[3]. Tuberculosis cases in women are more common in productive age so that tuberculosis is reported to

be the biggest cause of death in women aged 20 to 59 years. In 2014, 480,000 women died from tuberculosis, including 140,000 women who died were women with tuberculosis who were HIV Positive.[4]This makes tuberculosis the biggest cause of death for mothers and children.[5] WHO in 2018 reported that tuberculosis was one of the leading causes of death in women aged 14 to 49 years with 500,000 deaths including 95,000 women suffering from tuberculosis who were HIV positive.[6]

The increasing number of deaths due to tuberculosis has triggered the national tuberculosis control program to continue to intensify, accelerate, extend and innovate the program.7A holistic approach must be taken in order to improve tuberculosis control and identify various risk factors associated with tuberculosis infection.[2]

II. EPIDEMIOLOGY

*Global Tuberculosis Report*2018 reported that overall tuberculosis sufferers were 90% adults and 10% were children (<15 years). Figure 1 shows tuberculosis sufferers worldwide, 64% are men and 36% are women with a ratio of 2:1. In Indonesia, data also shows that tuberculosis is more common in men than women. The high prevalence in men shows that the level of men accessing tuberculosis services is higher than women.[9]

The 2018 National Health Work Meeting data shows that there are 3 times more male sufferers than female sufferers and deaths due to tuberculosis in men are higher than in women.10Although globally more men are affected by tuberculosis, the death rate for women with TB/HIV co-infection is 20% higher than for men.[11]

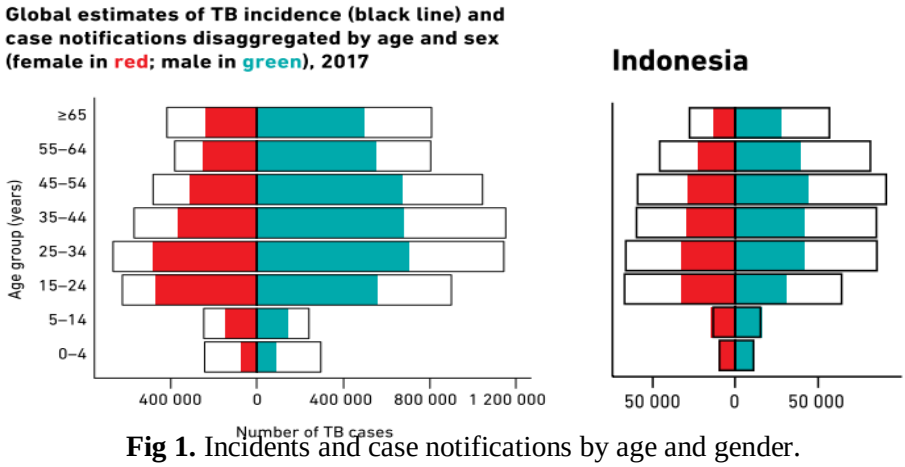

Fig 1. Incidents and case notifications by age and gender.

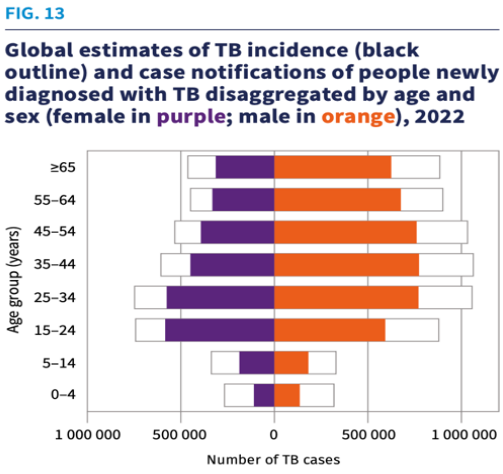

Fig 2. Incidence and case notifications by age and gender in 2022

Based on WHO data, Figure 2 shows that women aged 15 to 34 years are the age group with the highest incidence of TB and men aged 25 to 44 years have the highest incidence of TB.
Dodd et al (2015) stated that women are more likely to get tuberculosis infections through a history of close contact with tuberculosis sufferers, especially women who live in the same house or are the wives of tuberculosis sufferers.[12]Young women have a risk of suffering from tuberculosis up to 34% higher than men due to decreased immunity associated with stress during pregnancy.11
Research in Bangladesh, Malawi, South Africa shows that it is more difficult to diagnose tuberculosis in women than in men because women with pulmonary tuberculosis have a different immune response than men, so there are differences in symptoms, signs and treatment outcomes. In women, negative results from microscopic sputum tests are also more common.8This is supported by a meta-analysis study by Horton et.al (2016) which showed that women are underdiagnosed because women tend to produce less sputum and are diagnosed as BTA negative tuberculosis compared to men.[13]

Another reason for the low rate of tuberculosis detection in women is the high rate of missed cases due to limited screening of tuberculosis symptoms, especially in TB/HIV positive women and pregnant women. As many as 73% of women with positive TB cultures do not report symptoms of tuberculosis such as cough, fever, night sweats and weight loss. In pregnant women, these symptoms are disguised due to physiological changes in pregnant women.[14]
Based on research by Miele et al, it is more difficult to diagnose TB in pregnant women because there are similarities in symptoms with the physiological conditions of pregnant women such as weakness, weight changes, and shortness of breath. The incidence of TB disease is reported to be higher in the postpartum period than expected. This reflects immunological changes in pregnancy that can increase susceptibility to TB, for example suppression of the T-helper inflammatory response) and these changes can mask symptoms during pregnancy but can be found in the postpartum period.15.

III. TUBERCULOSIS BURDEN IN WOMEN

Access to Tuberculosis Services

Differences in social roles between men and women can also affect risk factors for access to health services. In women, access to obtain tuberculosis treatment and prevention services is more difficult than in men. This is because family members are unwilling to pay for women's health services. Women's health in the family is considered less important than male family members. Other findings show that women have not received optimal services due to stigma, low access and women's control in managing health resources which is still lacking, causing the discovery of cases of women to be higher than men, but in the process of diagnosis and treatment there are actually more men than women.[16]Women in prison generally have less access to tuberculosis treatment than men.[10]

Another cause that can affect is the lack of privacy in health clinics or health centers used for tuberculosis treatment, which becomes a problem for women with shame and anxiety. This is an obstacle for female tuberculosis sufferers to seek treatment.[17]

Research in Nepal suggests that women delay seeking medical attention because they prefer traditional medicine due to lower costs.[8]In Indonesia, tuberculosis services are provided by the government and are given free of charge. The Indonesian government guarantees that tuberculosis patients, both men and women, are not separated from their families, communities and jobs.[1]

Stigma and Discrimination

Women are reported to experience stigma and discrimination in their families and social environments. Research shows that the consequences of women suffering from tuberculosis are divorce.[16]18Women with tuberculosis infection experience difficulties in marriage compared to men.[17],[19]Unmarried women will have more difficulty finding a husband when they are found to have tuberculosis.[8]

Rejection, neglect and isolation are the consequences for some women who are diagnosed with tuberculosis. They are isolated from their families and communities after being diagnosed with tuberculosis.8

Tuberculosis in Female Prisoners

Globally, tuberculosis infection in prisoners is very high and the rate of tuberculosis infection in female prisoners is higher than in male prisoners. Research data based on gender shows that female prisoners' access to tuberculosis services is very limited. Thiscaused by several things such as lack of awareness by prisoners of the importance of health services such as not taking medication on the medication schedule, limited medical personnel, inadequate treatment room facilities, and lack of facilities and infrastructure, lack of drug budget. There are many infectious diseases in prisons, such as tuberculosis and skin diseases. This is because the prisons are too full and the air ventilation is inadequate. There are still prisoners who are not registered as BPJS participants and the referral process to the hospital cannot be done quickly because prisoners must notify the institution in charge[20].

A UN report on female prisoners in Pakistan indicates that tuberculosis services are not always available to women, even when they are provided to male prisoners.[8]

Socioeconomics

Tuberculosis is a disease associated with poverty and vulnerable groups. Most deaths from tuberculosis occur in developing countries, where gender disparities persist. Malnutrition can exacerbate the risk of tuberculosis. Other risk factors such as increasing rates of tobacco/cigarette use and diabetes mellitus among women have resulted in an increased burden of tuberculosis.[4]

Tuberculosis mainly attacks women who are economically active and productive. The impact of this disease is felt by children and their families, especially in terms of households.4Mothers who suffer from tuberculosis are at risk of losing their livelihood outside the home and reducing routine household activities such as washing, cooking, cleaning and serving food.[21]

Maternal tuberculosis can also affect child care. Mothers with tuberculosis have difficulty feeding their children, taking care of their children's daily needs and their children's educational needs.[21]

1. METHOD

a) Tuberculosis-HIV

The biggest risk factor for tuberculosis in women is HIV co-infection. Globally, about half of HIV-infected patients are women. In Sub-Saharan Africa, 60% of TB-HIV patients are women and >70% of women in South Africa with an age range of 20-30 years.[22]

In Haryani L's research, it was shown that 43 out of 60 (71.7%) HIV patients suffered from TB.[23]. HIV Tuberculosis in HIV-infected mothers is associated with a two-fold increase in the risk of vertical transmission of HIV to the fetus. Tuberculosis-HIV in pregnant women is a risk factor for maternal and child mortality with a rate of almost 300%.[4]

b) Biological factors

Biologically, men are different from women, so there are differences in symptoms, signs, and treatment results.8Men have only one X chromosome, while women have a diploid X chromosome. The X chromosome code is highly associated with genes encoding various immune system functions, supporting the hypothesis that genes encoded by the X chromosome may contribute to sex-related susceptibility to tuberculosis.[24]

There are 1500 genes on the X chromosome, most of which play a role in the innate and adaptive immune systems. To balance gene expression in males, one of the female X chromosomes must be inactivated. This inactivation occurs randomly in each cell. Random inactivation provides mosaic function to X-linked genes so that females are more resistant to deletion mutations and are better immune than males.[24]

Inactivation of 15% of X chromosome-related genes results in increased expression of several gene products. In fact, the X chromosome has many micro-RNAs (miRNAs) totaling 112 compared to only two miRNAs on the Y chromosome. Most of the expressed miRNAs are immunomodulatory.[22]
In relation to immunity, the X chromosome contains several genes involved in the immune response, such as genes encoding Toll-Like Receptors (TLR-7 and TLR-8), cytokine receptors, transcription factors and proteins that participate in the activation of T cells and B cells.[24]

c) Immunity

The influence of sex hormones (estrogen and progesterone) plays an important role in the immune response. Sex hormones have diverse effects on the immune system, including B cells, T cells, neutrophils, dendritic cells, macrophages, Natural Killer (NK) cells, estrogen receptor expression (ER-alpha and ER-beta). Sex and sex hormones can help to understand the immune response required to keep tuberculosis under control.[22],[25],[26]
Most immune cells express specific receptors for sex hormones and are responsible for changes in hormone levels. They are the main cell types responsible for immune control of M. tuberculosis.25
Women have a higher innate and adaptive immune response than men. This results in increased rates of killing pathogens, but this high response can also increase the likelihood of inflammation and autoimmune disease.[27]

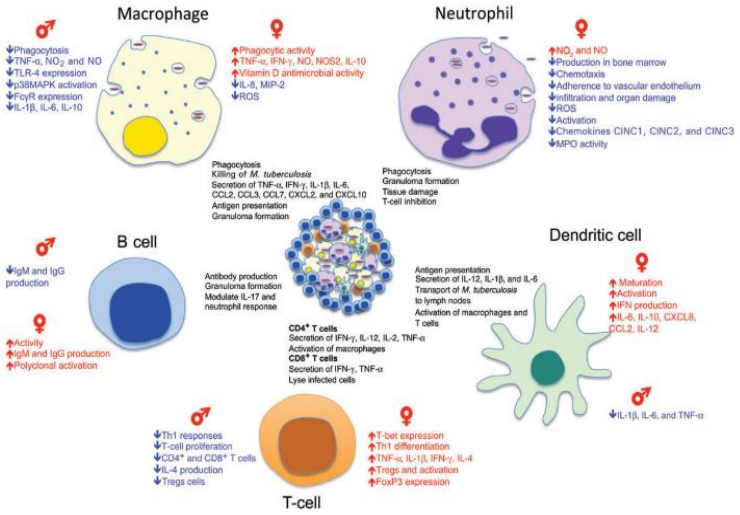

Fig 3. Sex hormones modulate the immune response to mycobacterium tuberculosis.

Figure 2 shows the role of each cell type and how this function can be modulated by sex hormones.22The sex hormones in Figure 2 are shown with male and female symbols referring to estrogen and progesterone (in women) or testosterone (in men).
Estrogen is an activator of the immune response by increasing pro-inflammatory cytokines (TNFα), while testosterone acts as an immune suppressor. It increases anti-inflammatory cytokines (IL-10) and chemokines (such as monocyte chemoattractant protein 1 and macrophage inhibitory protein 1α).[28]This explains why men are more susceptible to infectious diseases than women.
Estrogen is believed to enhance Th1 responses while testosterone downregulates Th1 responses. For example, low levels of 17B-estradiol enhance Th1 differentiation and production of cytokines such as TNF-α, while high levels enhance Th2 polarization which impacts cytokine production. CD4 T cell regulation is also known to fluctuate with changes in hormone levels during the menstrual cycle. Estrogen also stimulates INF-γ and IL-12 and inhibits IL-γ production [10].[22]
Here are some immune cells that are important in tuberculosis infection:
1) T Helper 1 (Th1)

Th1 immune response is characterized by the production of interferon γ (IFN-γ) and tumor necrosis factor α (TNF-α) which are important for controlling tuberculosis. CD4+ regulatory T cells (Tregs) are also known to fluctuate significantly according to changes in hormone levels during the menstrual cycle. Regulatory T cell responses play an important role in limiting tissue damage during the tuberculosis infection process.[22]

2) Macrophage Response

Macrophages are the control center for tuberculosis by killing the mycobacterium tuberculosis bacillus.22Estradiol is known to increase macrophage activation. Phenotype of immune cells in the peritoneal cavity of mice showed increased TLR expression and increased phagocytosis so that bacterial killing activity was higher in women than in men. In addition, estradiol also increased the transfer of IgA to the respiratory tract mucosa. Yang et.al studied that the main bacterial killer in women was carried out by alveolar macrophages, so that inflammation in the lungs was reduced more quickly.27,29

Macrophages and epithelioid cells form elongated and dense tubercles. Some of these cells merge to form giant cells. Tubercles appear as granular nodules (granulomas), this is a host mechanism to inhibit bacillus multiplication and limit the inflammatory process. [30]

3) Cytokines

In tuberculosis, cytokines and chemokines play an important role in the results of anti-tuberculosis therapy. Cytokines and chemokines are secreted by specific cells in the immune system. Research conducted by Chavez et.al showed that women had high levels of CXC Chemokine Liga 9 (CXCL9) before anti-tuberculosis drug treatment. After one month of treatment, CXCL9 levels decreased rapidly indicating the success of anti-tuberculosis drug therapy.25Other studies have shown that women are at high risk of drug-induced hepatotoxicity during tuberculosis treatment due to cytokine dysregulation. Hepatotoxicity during tuberculosis treatment can cause a decrease in the immune response to mycobacterium tuberculosis infection and result in worsening of the disease with cytokine dysregulation and other immune markers.[31]

4) Neutrophils

Neutrophils are considered to be the dominant cell type infected in pulmonary tuberculosis. Microassay profiles of patients with tuberculosis show the presence of neutrophils produced by interferon (IFN) type 1. Neutrophils help reduce the number of mycobacterium tuberculosis germs through phagocytosis by macrophages and kill mycobacterium tuberculosis through the NADPH oxidase (Nicotinamide Adenine dinucleotide phosphate oxidase) mechanism.

A study of 142 Swedish women who underwent oophorectomy for salpingitis found that 7% died from tuberculosis. In addition, lung disease caused by M. Avium is most often found in postmenopausal women.27It has been reported that older women with decreasing estrogen levels (post-menopause) are at increased risk of chronic pulmonary infections caused by mycobacterium other than tuberculosis (MOTT) infection.[28]

2. Tuberculosis in women with special circumstances

a) Genital Tuberculosis

Genital tuberculosis is a rare form of extrapulmonary tuberculosis. Genital tuberculosis occurs in communities with a high prevalence of pulmonary tuberculosis. The tubercle bacillus reaches the genital tract through hematogenous spread from outside the genitals. The fallopian tubes, endometrium and ovaries are the organs most commonly affected by tuberculosis infection.[32]

Genital tuberculosis often occurs in patients who present with complaints of infertility, chronic pelvic pain, and irregular menstruation.33Genital tuberculosis can occur together with other diseases such as endometriosis. The female genital organs involved in genital tuberculosis are the fallopian tubes (90-100%), uterus (50-80%), ovaries (20-30%), cervix (5-15%), and vagina and vulva (1-2%).34Female genital tuberculosis is a disease with late onset, accompanied by abnormal genital bleeding,

dyspareunia. These patients present with clinical and radiological symptoms such as ascites or abdominal distension with symptoms suggestive of malignant tumors especially in older patients.[35] Clinical presentation cannot be used as a basis for the diagnosis of genital tuberculosis. Multiple imaging techniques are not specific for confirmation of tuberculosis. Histopathological evidence with biopsy in the premenstrual phase can provide good diagnostic results for examination of Acid-Fast Bacteria (AFB), culture, GeneXpert, PCR and other tests.34Misdiagnosis also often occurs in patients with ovarian tubal tuberculosis with ascites and increased serum CA-125. These patients are often diagnosed as ovarian carcinoma, resulting in unnecessary surgical therapy.[33]

b) Tuberculosis in Pregnancy

Tuberculosis mostly occurs at the age of 20-35 years, and at this age is the reproductive age for women. An estimated 216,500 pregnant women suffer from tuberculosis each year. A cohort study of 192,801 pregnant women in the UK showed that the incidence of tuberculosis in pregnancy or 6 months post-partum was higher (15.4 per 100,000) compared to non-pregnant women. In the lower middle-income country group, tuberculosis is a major cause of maternal death, especially with HIV co-infection.36In Indonesia, there is no data that specifically calculates the prevalence of tuberculosis in pregnant women.

During pregnancy, transmission of tuberculosis germs to the fetus can occur. Transmission usually occurs lymphatic, hematogenous or directly. The fetus can be infected through blood originating from placental infection through the umbilical vein or aspiration of amniotic fluid.[37]
The maternal immune system during pregnancy undergoes several important changes to maintain immune tolerance between the mother and fetus. These changes are mainly triggered by the hormones estrogen and progesterone. It is assumed that the cellular immune system is suppressed while the humoral immune system components are enlarged. This has an impact on increasing the risk of reactivation of latent tuberculosis infection in pregnant women. This effect increases during pregnancy as illustrated in Figure 4.[38]

Symptoms of tuberculosis can occur in normal pregnancy such as fever, fatigue, night sweats, and cough. Sputum examination and chest X-ray are important in diagnosing tuberculosis in pregnant women. WHO recommends the standard for sputum examination with Xpert MTB/RIF as the first-line diagnostic. Chest X-ray examination is performed with a low radiation dose with an apron covering the abdomen.[36]

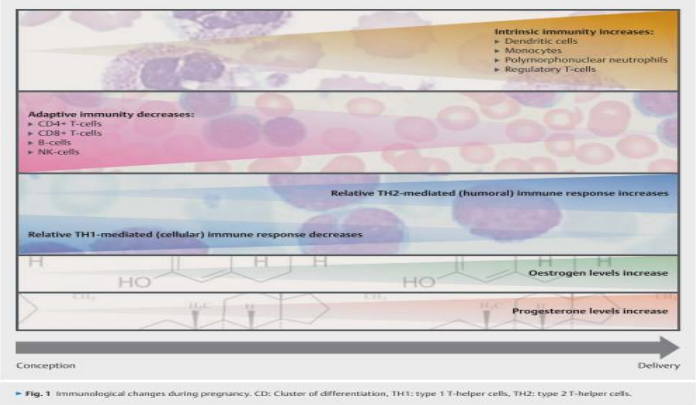

Fig 5. Immunological changes during pregnancyClick or tap here to enter text.

c) Breast Tuberculosis

Tuberculosis of the breast is a rare form of extrapulmonary tuberculosis. It is usually found in developing countries such as Africa and Asia where the prevalence of tuberculosis is still high. Breast tuberculosis is generally suffered by women of reproductive age between 21 and 20 years. The most common symptoms of breast tuberculosis are painless unilateral abscesses or masses.39 The most

common location of breast tuberculosis lumps is in the middle quadrant and/or upper quadrant of the breast.[40]

There are several ways of tuberculosis infection in the breast, namely; (i) hematogenous, (ii) lymphatic, (iii) spread from adjacent organs, (iv) direct inoculation, and (v) ductal infection. The path of spread from lung disease to breast tissue is through the tracheobronchial, paratracheal, mediastinal lymph and internal breast glands.[40]

The gold standard for diagnosing breast tuberculosis is detection of mycobacterium tuberculosis using BTA examination with Ziehl Neelsen or culture.[41]

The main therapy still refers to the national guidelines for tuberculosis treatment (Regulation of the Minister of Health of the Republic of Indonesia No. 67 of 2016) accompanied by conservative surgery (local excision of the mass). The average success rate of treatment is up to 95% using a 6-month treatment guideline (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol/4 months of isoniazid and rifampicin). Some authors also recommend 9-month therapy (2 months of isoniazid, rifampicin, ethambutol, pyrazinamide/7 months of isoniazid and rifampicin) due to the high relapse rate.[40]

IV. CONCLUSION

The prevalence of tuberculosis is higher in men than in women. Many factors influence the difference in the number of tuberculosis cases. Women have difficulty accessing tuberculosis services, experience stigma and discrimination from both society and family, and female prisoners have difficulty getting tuberculosis services.

Another factor that plays a role in women's tuberculosis is a biological factor explained through the X chromosome. The presence of two X chromosomes provides an advantage for women in terms of resistance to infection attacks, especially tuberculosis infections. In addition, sex hormones, namely estrogen and progesterone in women of productive age are very beneficial in the female immune system.

Tuberculosis also attacks female organs such as genitals and breasts. Genital and breast tuberculosis are extrapulmonary tuberculosis that rarely occurs in women. Symptoms of extrapulmonary tuberculosis are not specific, making it difficult to establish a diagnosis. Diagnosis is still done using BTA examination, culture, or molecular rapid test.

Tuberculosis problems also occur in vulnerable populations, namely pregnant women and women with tuberculosis-HIV. A fairly high mortality rate occurs in women with tuberculosis-HIV. In pregnant women, transmission of tuberculosis germs to the fetus occurs, so that the fetus can have latent tuberculosis.

Understanding tuberculosis in women can help achieve the 2030 tuberculosis elimination target. Gender equality and women's active participation in the planning, implementation and care of health services can be an effective way to address the problems of difficulty in accessing tuberculosis services, stigma and discrimination, and various existing barriers.

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