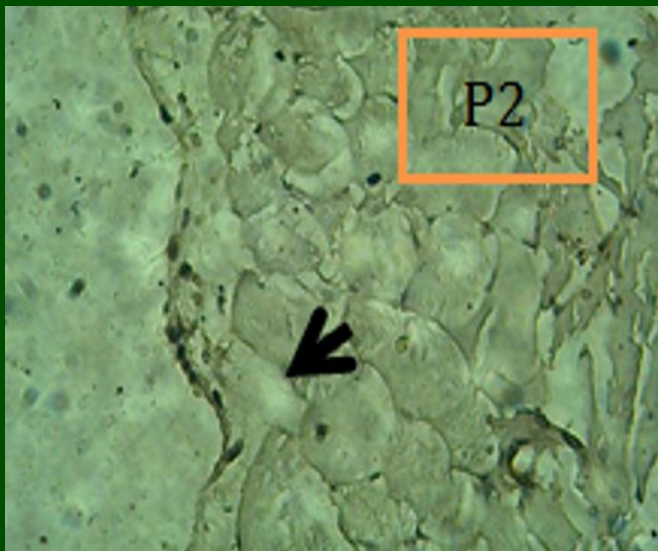


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**NF-κB expression (arrow) in mouse models of endometriosis administered with red fruit**

## Original Articles

- Different expression of NF-κB and endometrial implant width in the administration of red fruit (*Pandanus conoideus* Lam) and leuprolide
- Profile of pregnant women with preeclampsia and its termination method
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## Review Article

- Potential of trichloroacetic acid (TCA) for cervical precancerous lesions treatment in Indonesia

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## ORIGINAL ARTICLE

**Different expression of NF-κB and endometrial implant width in the administration of red fruit (*Pandanus conoideus* Lam) and leuprolide**Raudatul Hikmah<sup>1\*</sup>, Hendy Hendarto<sup>1</sup> , Widjiati<sup>2</sup> <sup>1</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia<sup>2</sup>Department of Embryology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia**ABSTRACT**

**Objectives:** This study aimed to prove the effect of different administration of red fruit (*Pandanus conoideus* Lam) extract and leuprolide on the expression of NF-κB and endometrial implant width in mouse models of endometriosis.

**Materials and Methods:** This study used completely randomized design with pre-post separated sample. The sample size was 36 female mice (*Mus musculus*), which were divided into 3 groups randomly. They were given with cyclosporine A, estrogen and endometrial tissue to form endometriosis model.

**Results:** The mean expression of NF-κB in treatment group receiving leuprolide ( $4.13 \pm 0.70$ ) and red fruit ( $2.70 \pm 1.08$ ) were significantly lower than that in control group ( $6.94 \pm 1.007$ ). Whereas, in treatment group receiving red fruit ( $2.70 \pm 1.08$ ), it was significantly lower than in those receiving leuprolide ( $4.13 \pm 0.70$ ). Mean endometrial implant width in treatment group receiving leuprolide ( $13.62 \pm 3.21$ ) and red fruit ( $8.93 \pm 2.74$ ) were significantly lower than that in control group ( $28.89 \pm 8.28$ ). Whereas, in treatment group receiving leuprolide ( $13.62 \pm 3.21$ ), it was not significantly higher than in those receiving red fruit ( $8.93 \pm 2.74$ ).

**Conclusion:** The expression of NF-κB was significantly lower after the administration of red fruit than leuprolide. The width of endometrial implant was not significantly lower after the administration of red fruit than after the administration of leuprolide.

**Keywords:** Endometriosis; NF-κB; red fruit, leuprolide; lesion; maternal health

**ABSTRAK**

**Tujuan:** Membuktikan adanya perbedaan pemberian ekstrak buah merah (*Pandanus conoideus* Lam) dan leuprolide terhadap ekspresi NF-κB dan luas implan endometriosis pada mencit model endometriosis.

**Bahan dan Metode:** Desain penelitian eksperimental laboratorium rancangan acak lengkap dengan sampel sebelum dan sesudah perlakuan yang berbeda. Sampel terdiri atas 36 ekor mencit betina yang dibagi 3 kelompok secara acak. Model endometriosis dibuat dengan pemberian injeksi siklosporin A, injeksi estrogen dan jaringan endometrium.

**Hasil:** Rerata ekspresi NF-κB kelompok perlakuan leuprolide ( $4,13 \pm 0,70$ ) dan buah merah ( $2,70 \pm 1,08$ ) lebih rendah secara bermakna dibandingkan kelompok kontrol ( $6,94 \pm 1,007$ ). Sedangkan kelompok perlakuan buah merah ( $2,70 \pm 1,08$ ) lebih rendah secara bermakna dibandingkan kelompok perlakuan leuprolide ( $4,13 \pm 0,70$ ). Rerata luas implan endometriosis kelompok perlakuan leuprolide ( $13,62 \pm 3,21$ ) dan buah merah ( $8,93 \pm 2,74$ ) lebih kecil secara bermakna dibandingkan luas implan endometriosis kelompok kontrol ( $28,89 \pm 8,28$ ), sedangkan kelompok perlakuan leuprolide ( $13,62 \pm 3,21$ ) lebih tinggi tapi tidak bermakna dibandingkan kelompok perlakuan buah merah ( $8,93 \pm 2,74$ ).

**Simpulan:** Ekspresi NF-κB lebih rendah secara bermakna setelah mendapat ekstrak buah merah dibandingkan dengan yang mendapat leuprolide. Luas implan lebih rendah tapi tidak bermakna setelah mendapat ekstrak buah merah dibandingkan dengan yang mendapat leuprolide.

**Kata kunci:** Endometriosis; ekspresi; NF-κB; buah merah; leuprolide; lesi; kesehatan ibu

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## INTRODUCTION

Current management of endometriosis is still controversial. The European Society of Human Reproduction and Embryology (ESHRE) guidelines are still stuck in hormonal modulation and/or surgical removal of the lesion.<sup>1</sup> Both of these approaches have many drawbacks. Hormonal modulation creates a hypoestrogenic environment with hormonal contraceptives, progestogens, anti-progestogens, GnRH agonists and aromatase inhibitors.<sup>2</sup> Creation of a hormonal environment by inhibiting ovulation can temporarily suppress ectopic implants and reduce inflammation and associated painful symptoms. This approach is not appropriate for endometriosis patients with infertility who wish to conceive normally.<sup>1</sup> After the discontinuation of hormonal therapy, the recurrence rate is also high. Patients also experience intolerable side effects, and sometimes do not respond or are resistant to therapy. On the other hand, surgical intervention often leads to complications and the outcome is highly dependent on surgical ability. Recurrence due to incomplete resection or the presence of hidden endometriosis is common.<sup>3</sup> All of these pose difficult clinical challenges in the management of endometriosis, especially for symptomatic deep infiltrating endometriosis (DIE) lesions. Therefore, new therapeutic options are needed.

Altered ability of the microenvironment in endometriosis to support endometriotic cells is transmitted by kinase signaling pathways and has the potential to establish kinase-dependent lesional growth. Drugs targeting these kinases have proven successful in the treatment of other tumors and are increasingly being investigated as potential endometriosis treatments, particularly in the treatment of DIE lesions.<sup>3</sup> NF- $\kappa$ B may represent a potential therapeutic target because it has constitutive activation in peritoneal endometriosis lesions. There have been many studies on the design of pharmacological methods that contribute to the activity of NF- $\kappa$ B.<sup>4</sup> Several previous studies in mice showed

that the expression of NF- $\kappa$ B decreased when red fruit extract was given.<sup>5</sup> This study aimed to compare the administration of red fruit extract and leuprolide, which have been widely used in the treatment of endometriosis, on the expression of NF- $\kappa$ B and the width of endometrial implants.

## MATERIALS AND METHODS

This research was a laboratory experimental study with a completely randomized design with pre- and post-separated sample. This study used a sample of 36 mice which were divided into three groups randomly. Then the mouse model of endometriosis were made by the injection of cyclosporine A, the injection of 0.1 ml endometriosis isolate and the injection of ethinyl-estradiol at a dose of 30 gr/kgBW. Group A was a positive control group, sacrificed on day 14 (before treatment). Group B received a single dose of leuprolide injection of 100 mcg/kg BW, sacrificed on day 14, and group C received red fruit extract of 0.05 ml per day per sonde for 14 days. Groups B and C were sacrificed on day 28. All three groups were examined for the width of endometrial implant and NF- $\kappa$ B expression. During the study 7 mice died.

## RESULTS

[Table 1](#) shows that the mean expression of NF- $\kappa$ B in leuprolide ( $4.13 \pm 0.70$ ) and red fruit ( $2.70 \pm 1.08$ ) treatment groups is lower than NF- $\kappa$ B expression in control group ( $6.94 \pm 1.007$ ). Analysis with Anova test showed that the expression of NF- $\kappa$ B in the treatment group was significantly lower than in the control group ( $p < 0.05$ ). Meanwhile, the expression of NF- $\kappa$ B in the treatment group that received red fruit was significantly lower ( $p < 0.05$ ) than in the treatment group receiving leuprolide.

Table 1. Expression of NF- $\kappa$ B in mice groups receiving leuprolide, red fruit, and control

c	n	Groups	NF $\kappa$ B expressions				p
			$\bar{x}$	SD	Min	Max	
Control $6.94 \pm 1.007$	10	Leuprolide	4.13	0.70	2.80	5.20	0.000
		Red fruit	2.70	1.08	1.40	4.00	0.000
Leuprolide $4.13 \pm 0.70$	9	Control	6.94	1.007	5.6	8.20	0.000
		Red fruit	2.70	1.08	1.40	4.00	0.003
Red fruit $2.70 \pm 1.08$	10	Control	6.94	1.007	5.6	8.20	0.000
		Leuprolide	4.13	0.70	2.80	5.20	0.003

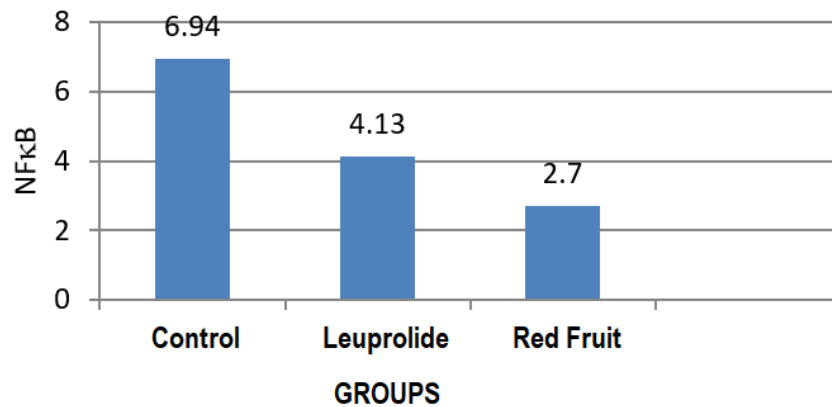


Figure 1. Expression of NF-κB in control, leuprolide and red fruit groups.

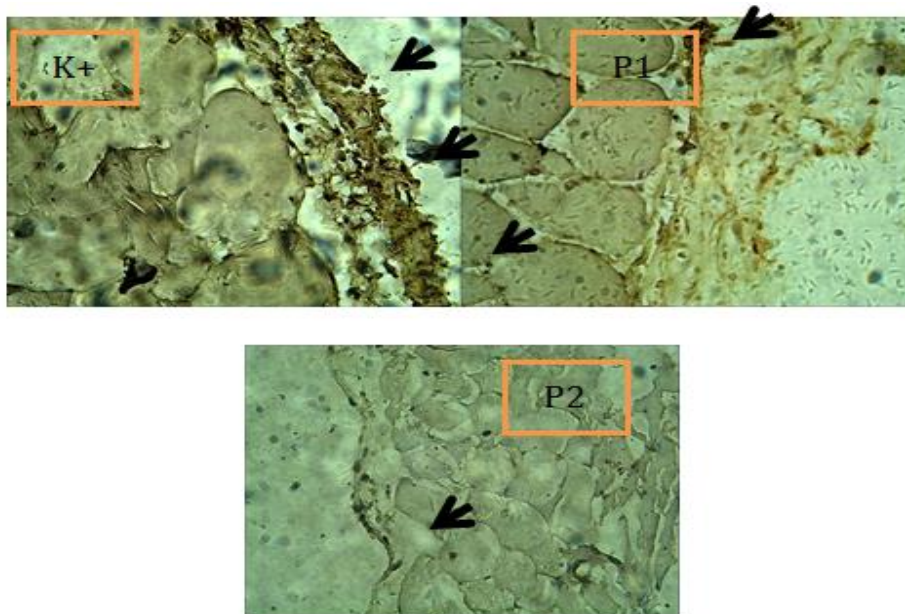


Figure 2. Differences in NF-κB expression (arrows) between K+, P1 (leuprolide) and P2 (red fruit) groups.

It was found that the expression of NF-κB in K+ group was stronger than in the other treatment groups, while the expression in P1 (leuprolide) group appeared to be stronger than in the other treatment groups. Its

expression in P1 (leuprolide) group appeared to be stronger than in P2 (red fruit) group (Immunohistochemical staining, 400x magnification, Nikon Eclipse Ci, OptilabViewer 2.2, Image raster 3.0).

Table 2. The width of mice endometrial implant in leuprolide, red fruit and control groups.

Implant Width	n	Groups	Implant Width				P
			x	SD	Min	Max	
28.89 ± 8.28	10	Leuprolide	13.62	3.21	9.34	17.54	0.000
		Red fruit	8.93	2.74	5.40	12.56	0.000
13.62 ± 3.21	9	Leuprolide	28.89	8.28	17.96	43.64	0.000
		Red fruit	8.93	2.74	5.40	12.56	0.074
8.93 ± 2.74	10	Control	28.89	8.28	17.96	43.64	0.000
		Leuprolide	13.62	3.21	9.34	17.54	0.074

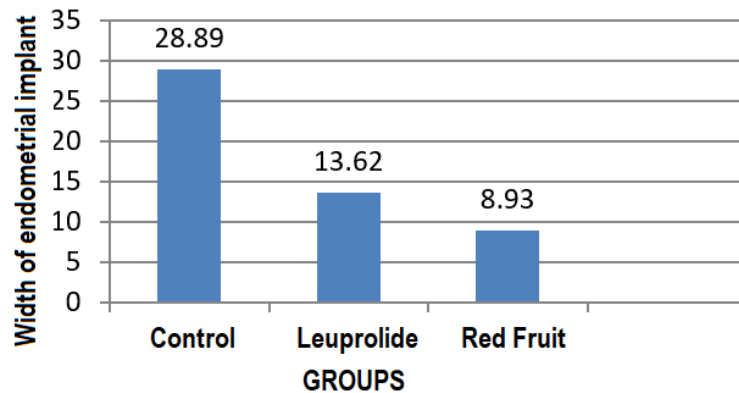


Figure 3. The size of endometrial lesions in control, leuprolide and red fruit groups.

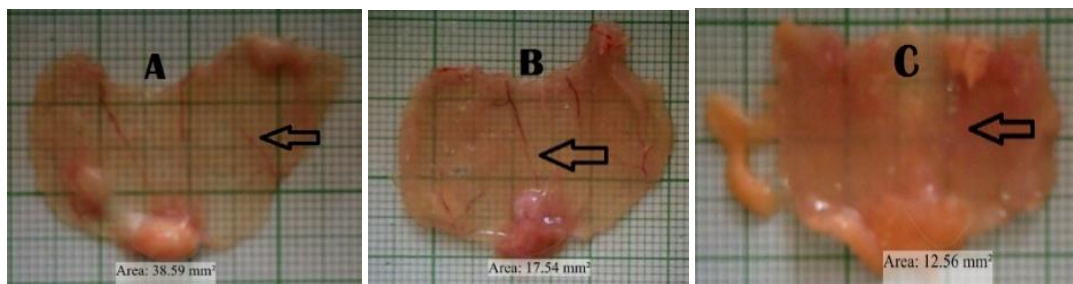


Figure 4. Profile of hypervascularization and implant width in the peritoneum of mouse model of endometriosis in control group (A), treatment group receiving leuprolide (B), and treatment group receiving red fruit (C).

[Table 2](#) shows that the mean width of endometrial implants in leuprolide ( $13.62 \pm 3.21$ ) and red fruit ( $8.93 \pm 2.74$ ) treatment groups was smaller than the width in control group ( $28.89 \pm 8.28$ ). Anova test showed that the width of endometrial implants in treatment group was significantly smaller than the width in the control group ( $p < 0.05$ ), while the implant width in the leuprolide treatment group was higher but not significant ( $p > 0.05$ ) than in the treatment group receiving red fruit.

## DISCUSSION

This study used a heterotransplantation technique, in which the tissue that was transplanted into the mice was derived from human endometrium. These implant fragments and endometriotic-like lesions resembled those found in the patients, both macroscopically and histologically, whereas the phase of the menstrual cycle at the time of tissue collection in humans did not appear to have an impact on the development of the ectopic lesions. Reservation of estrogen and progesterone receptors and estrogen responsiveness has been demonstrated in human ectopic tissue. Angiogenesis

ensures maintenance of transplanted and systemic transport of administered drugs to human endometrial tissue. Vessel formation in mice occurs 4 days after the transplanted, independent of the ectopic lesion. When it is randomly inoculated into the peritoneal cavity, adhesion occurs within 2 days after implantation. The implantation site is mainly in the intestines of the abdominal wall muscles, liver and fat around the abdominal wall.<sup>6</sup> In a heterologous mouse model, human tissue is transplanted into the mice. Tissue maintenance in order to remain intact and well maintained requires a limited period of time. In most studies that have been performed, human endometrial cultures in mice have not exceeded 4 weeks. Three weeks after inoculation onwards, lymphocyte infiltration and other changes occur.<sup>6</sup> Therefore, in this study the process and intervention carried out on the mouse models did not exceed a period of 4 weeks.

### Differences in NF- $\kappa$ B expression in mouse models of endometriosis in red fruit, leuprolide, and control groups

In endometriosis there is a chronic inflammatory process. Cytokines, as proinflammatory mediators such

as TNF- $\alpha$ , and IL-1 $\beta$ , will activate NF- $\kappa$ B through a canonical pathway. Stimulation of the canonical NF- $\kappa$ B pathway leads to IKK $\beta$  phosphorylation. IKK $\beta$  is part of the IKK complex along with IKK $\alpha$  and IKK $\gamma$  and activated IKK $\beta$  to phosphorylate the inhibitory protein I $\kappa$ B at p50-p65, removing it from the complex and targeting it for proteasomal degradation. The unbound p50-p65 complex translocate into the nucleus and stimulates gene transcription.<sup>3</sup>

### Differences in NF- $\kappa$ B expression in red fruit and control groups

This study showed that the mean expression of NF- $\kappa$ B in the treatment group that received red fruit ( $2.70 \pm 1.08$ ) was significantly lower than the expression of NF- $\kappa$ B in control group ( $6.94 \pm 1.007$ ). Many laboratory studies proved that various antioxidants had the ability to inhibit NF- $\kappa$ B activation with various mechanisms from phorbol ester to TNF- $\alpha$ , to hydrogen peroxide. These evidences prove the involvement of ROS in the NF- $\kappa$ B activation pathway.<sup>7</sup> Vitamin E derivatives inhibit TNF- $\alpha$  which induces NF- $\kappa$ B activation in human Jurkat T cells. Incubation of cells with different concentrations of  $\alpha$ -tocopherol acetate or  $\alpha$ -tocopherol succinate can inhibit NF- $\kappa$ B activation.<sup>7</sup> Only with 10  $\mu$ M pentamethyl hydroxy chromane, a vitamin E derivative without a phytyl tail is able to completely inhibit NF- $\kappa$ B activation.  $\alpha$ -tocopherol succinate not only inhibits the activation and translocation of NF- $\kappa$ B to the nucleus, but also inhibits in vitro binding of the active protein to  $\kappa$ B DNA.<sup>8</sup>

The components of vitamin E that have this activity are tocopherols and tocotrienols. The tocopherol group has a saturated isoprene side chain and is divided into alpha, beta, gamma and sigma tocopherols. The tocotrienol group has an unsaturated isoprene side chain and is divided into alpha, beta, gamma, and sigma tocotrienols.<sup>9</sup> The biological activity of tocopherols is alpha>beta>gamma>sigma. The biological activity of vitamin E is related to its function in the body. Broadly speaking, the main function of tocopherols in vivo is antioxidant, that is by protecting the unsaturated fatty acids in cell membranes from peroxidative degradation. The action of vitamin E as an antioxidant can be demonstrated by two different mechanisms, ie. 1) vitamin E reacts directly with singlet oxygen and 2) vitamin E acts by capturing radicals derived from unsaturated fatty acids and stop autoxidation.<sup>9</sup>

The results of Selly's research<sup>10</sup> showed that the tocopherol content in red fruit was very high of 22940.35 ppm, and  $\alpha$  tocopherol was 481.48 ppm. Research by Irawan<sup>11</sup> showed that the total tocopherol

content of red fruit extract was 11000 ppm. Meanwhile, Susanti's research<sup>12</sup> showed that the total tocopherol and  $\alpha$ -tocopherol in red fruit extract could reach 10832 ppm and 1368.26 ppm, respectively. In addition to containing high total tocopherols and  $\alpha$ -tocopherols, red fruit extract also contains oleic acid, linoleic acid, linolenic acid and decanoic acid, all of which are active compounds to inhibit TNF- $\alpha$  which induces NF- $\kappa$ B activation in Jurkat T cells, inhibiting activation and translocation of NF- $\kappa$ B to the nucleus, and inhibited in vitro binding of the active protein to  $\kappa$ B DNA. All of these activities cause the expression of NF- $\kappa$ B to decrease.

### Differences in the expression of NF- $\kappa$ B in leuprolide and control groups

This study showed that the mean expression of NF- $\kappa$ B in leuprolide treatment group ( $4.13 \pm 0.70$ ) was significantly lower than in control group ( $6.94 \pm 1.007$ ). The positive interaction between ER and the NF- $\kappa$ B signaling pathway is explained by the finding that estradiol induces cell proliferation by an NF- $\kappa$ B-dependent mechanism, which is enhanced by the presence of TNF- $\alpha$  and the formation of a complex containing ER, P65 and the ras-related C3 botulinum substrate 3 (RAC 3) coactivator. In endometrial stromal cells, estradiol increases TNF- $\alpha$ -induced IL8 production through NF- $\kappa$ B activation.<sup>4</sup> A laboratory experiment conducted by Stice et al.<sup>13</sup> stated that E2 causes activation of p50 NF- $\kappa$ B. I $\kappa$ B degradation was also detected with E2. The p50 and p65 binding and nuclear translocations increased. The activation of NF- $\kappa$ B by E2 is through ERK 1/2. ERK 1/2 knockdown inhibits NF- $\kappa$ B activation by E2, which supports the notion that ERK 1/2 phosphorylation is the point of convergence for the upstream signaling pathway for NF- $\kappa$ B activation by E2. Leuprolide induces medical menopause by decreasing the hypothalamic-pituitary GnRH receptor, resulting in decreased gonadotropin secretion, suppression of ovulation and a significant decrease in serum estrogen levels.<sup>14</sup> Under hypoestrogen conditions, the expression of NF- $\kappa$ B will decrease.

### Differences in NF- $\kappa$ B expression in red fruit and leuprolide groups

This study showed that the mean expression of NF- $\kappa$ B in red fruit treatment group ( $2.70 \pm 1.08$ ) was significantly lower than in leuprolide group ( $4.13 \pm 0.70$ ). Red fruit extract contains high total tocopherol and  $\alpha$ -tocopherol and in addition it also contains oleic acid, linoleic acid, linolenic acid and decanoic acid, all of which are active compounds that will inhibit TNF- $\alpha$  to induce NF- $\kappa$ B activation in Jurkat T cells, inhibiting

activation and translocation of NF-κB to the nucleus, and inhibiting in vitro active protein binding to κB DNA. This activity is able to suppress the expression of NF-κB more strongly than leuprolide.

### **Differences in the width of endometrial implants in mouse model of endometriosis in red fruit, leprolide and control groups**

The extent of endometriosis lesions was obtained by measuring the area of hyperemia in the form of red lesions on the peritoneal wall of the mice. This hyperemia area indicates the angiogenesis process to support the life and development of endometrial tissue in the peritoneum. There are some data to suggest that suppressed cytotoxic functions in the peritoneum may allow ectopic endometrial cells to survive and implant on the peritoneal surface. NK cells are cytotoxic lymphocytes with the ability to lyse target cells. Peritoneal NK cells are involved in retrograde menstrual clearance and endometriosis patients show decreased NK cell cytotoxicity. A study by Aoki et al.<sup>15</sup> using subcutaneously implanted human endometrial tissue in a mouse model of endometriosis, demonstrated the importance of NK cells in the formation of endometrial lesions. Lesions were found in only 40% of untreated mice, but were found in 100% of mice treated with NK inhibitors. In endometriosis there is a change in the immune system in the form of an immune system deficiency. Research on patients with endometriosis has shown changes in several immunological components in the peritoneal fluid, including macrophages, NK monocytes, T lymphocytes, B cells, inflammatory mediators such as complement and cytokines, and endometrial destroying cells that allow attachment, migration and angiogenesis.<sup>16</sup> Women with endometriosis have higher macrophage activity. This can be seen through an increase in size, an increase in the number of complement C3 and C4 and an increase in the secretion of lysosomal phospholipase. This phospholipase acts on the phospholipid membrane, releasing arachidonic acid which is then used for the synthesis of prostaglandins. This causes an increase in peritoneal prostaglandins in women with endometriosis and causes pain.

Macrophages play a role in the initiation, development and growth of endometriosis. Macrophages are also involved in the process of adhesion of endometrial cells to the peritoneum by secreting fibronectin which plays a role in changing cell stages in the cell cycle, so that they become cells that are sensitive to growth factors, and estrogen is one of the growth factors. Increased activation of macrophages accompanied by hyper-estrogenism is a factor in the proliferation of endometrial implant cells.<sup>17</sup> Red endometriotic lesions

and surrounding peritoneum were shown to have the greatest number of macrophages compared to black and white lesions, a finding consistent with the observation that red lesions are more inflamed and this may explain the difference in macrophage numbers seen in different studies. An increase in the number of macrophages can lead to a more inflammatory environment and increased production of inflammatory cytokines that will not only affect the endometriotic lesion, but also the surrounding area. The inflammatory response can lead to disease progression by stimulating cell proliferation, increasing cell adhesion protein expression and promoting neovascularization. Chronic inflammation within the peritoneum can also cause a fibrotic response and may be associated with progression to white fibrotic endometrial lesions. Retrograde menstrual blood can initiate an inflammatory response and macrophage recruitment but it is also possible that the inflammatory response precedes endometriosis and contributes to disease progression and sustaining its development.<sup>18</sup>

In this study, the mean width of the endometrial implant was found to be quite large in the leuprolide group, red fruit and control group. This shows that the statistical distribution of the width of endometrial implant in the leuprolide, red fruit and control groups each had a deviation that was far from the mean value. This condition could be caused by the process and the degree of occurrence of endometriosis lesions in each different mice, so that each sample started at a different level of endometriosis lesions. The level of immunity of each mouse was different, causing the level of endometriosis lesions formed was also different. In this study, randomization and strict control were carried out.

### **Difference in the width of endometrial implants in red fruit and control groups**

In this study, the mean width of endometrial implant in the red fruit group ( $8.93 \pm 2.74$ ) was significantly smaller than the control group ( $28.89 \pm 8.28$ ). This research used red fruit that had passed a standardized extraction process. Red fruit, in addition to containing tocopherol, also has a high content of carotene. According to Budi,<sup>19</sup> red fruit contains 59.7 ppm β-carotene. The results of Susanti's research<sup>12</sup> showed that the total carotene content of red fruit extract extracted by modification method 2 could reach 21,430 ppm with β-carotene of 4,583 ppm. The high carotene content in red fruit can be seen from the color of the red fruit extract (in the form of oil) which is dark red. Red fruit, in addition to containing α-carotene and β-carotene, also contains oleic acid, linoleic acid, linolenic acid and decanoic acid, all of which are active compounds that have the potential as antioxidants and boost immunity. Natural substances that act as antioxidants can function

in preventing the development of cancer cells as well as regulating the balance of hormones that play a role in causing cancer.

In addition, the interaction of  $\beta$  carotene with protein is known to increase the production of antibodies in the body's immune system.<sup>20</sup>  $\beta$  carotene is able to increase the number of natural killer cells and increase the activity of T cells and lymphocytes. This will suppress free radicals, carcinogenic compounds, and the presence of cancer cells. Tocopherol plays a role in improving the immune system and reducing tissue cell mortality, while unsaturated fatty acids are easily digested and absorbed by the body so as to facilitate metabolic processes.<sup>19</sup> As we know that the development of endometrial implants outside the uterine cavity endometrium is associated with a chronic inflammatory process. In endometriosis, there is a decrease in the phagocytosis of macrophages, the number of NK cells and lymphocytes. The administration of red fruit extract which has a very high carotene content has been shown to increase macrophage phagocytosis, increase the number of NK cells and lymphocyte proliferation. In the final result, the width of endometrial implants in mouse model of endometriosis receiving red fruit extract was smaller than that in control.

#### **Differences in the width of endometrial implants in leuprolide and control groups**

In this study, the mean width of endometrial implants in the leuprolide group ( $13.62 \pm 3.21$ ) was significantly smaller than the width of endometrial implant area in control group ( $28.89 \pm 8.28$ ). Estradiol is a biologically active estrogen that is produced mainly at three sites in the body of women with endometriosis. In all these sites, the expression of aromatase enzyme is critical for the production of estradiol. In addition, several other steroidogenic proteins are expressed and complement aromatase activity for estradiol production. The classic site for estrogen production is the ovary. Theca and granulosa cells of the preovulatory follicle convert cholesterol to estradiol which is actively released into the circulation in a cyclic manner. The second group of the body collectively referred to as the peripheral tissues, includes large tissues such as fat, skin, and skeletal muscle, all of which express aromatase. In these peripheral tissues, circulating androstenedione is converted to estrone, which is further converted to estradiol. Peripheral tissues do not secrete estradiol in the classical sense, but, because of their large quantity, can produce sufficient levels of estradiol to increase blood levels, especially in obese women. The third site for estradiol production is the endometriotic tissue itself. Endometriotic stromal cells uniquely express a full complement of genes in the steroidogenic cascade,

which is sufficient to convert cholesterol to estradiol.<sup>21</sup> A constant supply of estrogen from multiple sources is essential for the growth and persistence of endometriotic implants. As mentioned above, endometrial implants have intrinsic aromatase activity, which leads to the conversion of cholesterol to estradiol. The endometrium is rich in PG-E2 receptors and activation of the PG receptor subtype EP-2 leads to the activation of cyclic AMP, which increases steroidogenic gene expression, and aromatase activity ultimately leads to increased production of estradiol. Simultaneously, the intrinsic aromatase activity of estradiol produced from ovarian and peripheral fat also reaches the site of endometriosis. This continuous supply of estrogen is essential for the continued growth and survival of the endometrial implants.<sup>22</sup>

In another study, in endometriosis tissue there was an increase in the expression of the aromatase enzyme and a decrease in the expression of the  $17\beta$ -hydroxysteroid dehydrogenase ( $17\beta$ -HSD) type 2 enzyme. This indicated an increase in the bioavailability of the estradiol concentration. Estradiol stimulates the production of prostaglandin E2 (PGE2) which then stimulates aromatase activity,<sup>23</sup> while leuprolide is the drug most widely used for medical treatment of endometriosis. Prolonged administration of leuprolide suppresses gonadotropin secretion and suppresses steroidogenesis. Leuprolide binds to the receptor for a long time and induces a prolonged period of down-regulation. Leuprolide is 200 times more potent than natural GnRH. Long-term use of leuprolide produces many endocrine effects. Serum estrone, estradiol, testosterone, and androstenedione levels decreased significantly. Total serum estrone and estradiol and serum estradiol concentrations are two to three times lower than those induced by long-term administration of danazol. Leuprolide therapy relieves symptoms in up to 90% of patients with endometriosis. Maximum therapeutic effect is seen with endometriotic spots smaller than 1 cm.<sup>24</sup> GnRHa can reduce inflammatory reactions and angiogenesis, induce apoptosis in tissues, and reduce proliferation in endometrial tissue.<sup>25</sup>

#### **Differences in the extent of endometriosis lesions in red fruit and leuprolide groups**

This study showed that the mean area of endometriosis implants in leuprolide treatment group ( $13.62 \pm 3.21$ ) was higher but not significantly different than that in red fruit group ( $8.93 \pm 2.74$ ). Anova test showed the results of  $p > 0.05$ . An in vitro study by Andini showed that red fruit has anti-proliferative activity against HeLa and K-562 cancer cells. Its anti-proliferative activity can approach, or even exceed, the activity of the positive control (doxorubicin) at higher concentrations.<sup>26</sup>



Endometriosis itself, although actually a benign disease, has features that resemble cancer cells, such as a tendency to invasion, uncontrolled growth, neoangiogenesis, and distant spread.<sup>27</sup>

In this study, red fruit extract was shown to suppress endometrial implants more strongly (but not statistically significant) compared to the effect of leuprolide. When compared to leuprolide, red fruit is cheaper and abundantly available in Indonesia, especially in Papua Island. The way leuprolide acts is through the hormonal pathway, so long-term use will cause many endocrine effects. Serum estrone, estradiol, testosterone, and androstenedione levels decreased significantly. The most common side effects of leuprolide are hot flushes, vaginal dryness, insomnia, etc. Decreased bone mineral density has been shown in the lumbar spine, but until now there have been no reports of endocrine effects in people who consume red fruit which until now is consumed freely by the Papuan people and is safe for long-term use. Research conducted by Widowati et al.<sup>28</sup> did not find any toxic effects as abnormal behavior or mortality in rats, which were given red fruit even at high doses, 5 ml/200 g body weight, or about 9.4 times the human dose. The expression of NF- $\kappa$ B in endometriosis model mice that received red fruit was significantly lower than in those receiving leuprolide, while the width of endometrial implant in the mouse models that received red fruit was found to be lower but not statistically significant than those receiving leuprolide. This is because the expression of NF- $\kappa$ B is a molecular change, while the implant area is a cellular change. Molecular changes are more sensitive and occur before cellular changes. Not all molecular changes are immediately followed by cellular changes. A certain amount of time is required for the cellular changes to follow.

## CONCLUSION

The expression of NF- $\kappa$ B was significantly lower in the group of mouse models of endometriosis receiving red fruit extract than in those receiving leuprolide. The width of endometrial implant was lower but not significant in the group of mouse models of endometriosis receiving red fruit extract compared to those receiving leuprolide.

## REFERENCES

1. Dunselman GA, Vermeulen N, Becker C, et al. European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. *Hum Reprod.* 2014;29(3):400-12. doi: 10.1093/humrep/det457. Epub 2014 Jan 15. PMID: 24435778.
2. Brown J, Farquhar C. Endometriosis: An overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2014;2014(3):CD009590. doi: 10.1002/14651858.CD009590.pub2. PMID: 24610050; PMCID: PMC6984415.
3. McKinnon BD, Kocbek V, Nirgianakis K, et al. Kinase signalling pathways in endometriosis: potential targets for non-hormonal therapeutics. *Hum Reprod Update.* 2016;22(3):382-403. doi: 10.1093/humupd/dmv060. Epub 2016 Jan 5. PMID: 26740585.
4. González-Ramos R, Rocco J, Rojas C, et al. Physiologic activation of nuclear factor  $\kappa$ -B in the endometrium during the menstrual cycle is altered in endometriosis patients. *Fertil Steril.* 2012 97(3):645-51. doi: 10.1016/j.fertnstert.2011.12.006. Epub 2011 Dec 22. PMID: 22196717.
5. Ramadass V, Vaiyapuri T, Tergaonkar V. Small molecule NF- $\kappa$ B pathway inhibitors in clinic. *Int J Mol Sci.* 2020;21(14):5164. doi: 10.3390/ijms21145164. PMID: 32708302; PMCID: PMC7404026.
6. Laganà AS, Garzon S, Franchi M, et al. Translational animal models for endometriosis research: a long and windy road. *Ann Transl Med.* 2018;6(22):431. doi: 10.21037/atm.2018.08.24. PMID: 30596061; PMCID: PMC6281523.
7. Hsieh CY, Hsiao G, Hsu MJ, et al. PMC, a potent hydrophilic  $\alpha$ -tocopherol derivative, inhibits NF- $\kappa$ B activation via PP2A but not I $\kappa$ B $\alpha$ -dependent signals in vascular smooth muscle cells. *J Cell Mol Med.* 2014;18(7):1278-89. doi: 10.1111/jcmm.12277. Epub 2014 Apr 13. PMID: 24725826; PMCID: PMC4124013.
8. Dai F, Du YT, Zheng YL, Zhou B. Inhibiting NF- $\kappa$ B-mediated inflammation by catechol-type diphenylbutadiene via an intracellular copper- and iron-dependent pro-oxidative role. *J Agric Food Chem* 2020;68(37):10029–35. doi: 10.1021/acs.jafc.0c04399
9. Hunyadi A. The mechanism(s) of action of antioxidants: from scavenging reactive oxygen/nitrogen species to redox signaling and the generation of bioactive secondary metabolites. *Medicinal Research Reviews.* 2019;39(6):2505-33.
10. Selly AJ. Karakterisasi sifat fisiko-kimia dan pengujian antiproliferasi ekstrak buah merah (*Pandanus conoideus Lam.*) terhadap sel kanker HeLa dan k-562 secara in vitro [In vitro chemico-physical characterization and antiproliferative test of red fruit extract on HeLa and k-562 cancer cells] [Undergraduate thesis]. Bogor, Indonesia: Fakultas Teknologi Pertanian. Institut Pertanian Bogor. 2008.



11. Irawan D. 2006. Mengenal buah merah yang semakin populer [Red fruit, a more and more popular fruit] [internet]. Available from: <http://www.waspada.co.id/serbaserbi/>
12. Susanti. Karakterisasi ekstrak buah merah (*Pandanus conoideus Lam*) dan uji biologis terhadap proliferasi sel limfosit mencit [Red fruit extract characterization and biological test on mice lymphocyte proliferation]. Bogor, Indonesia: Fakultas Teknologi Pertanian. 2006.
13. Stice JP, Mbai FN, Chen L, Knowlton AA. Rapid activation of nuclear factor  $\kappa$ B by 17 $\beta$ -estradiol and selective estrogen receptor modulators: pathways mediating cellular protection. *Shock*. 2012 Aug;38(2):128-36. doi: 10.1097/SHK.0b013e31825da754. PMID: 22683727; PMCID: PMC3401555.
14. Collinet P, Fritel X, Revel-Delhom C, et al. Management of endometriosis: CNGOF/HAS clinical practice guidelines - short version. *J Gynecol Obstet Hum Reprod*. 2018;47(7):265-274. doi: 10.1016/j.jogoh.2018.06.003. Epub 2018 Jun 18. PMID: 29920379.
15. Aoki D, Katsuki Y, Shimizu A, Kakinuma C, Nozawa S. Successful heterotransplantation of human endometrium in SCID mice. *Obstet Gynecol*. 1994;83(2):220-8. PMID: 8290184.
16. Wang XM, Ma ZY, Song N. Inflammatory cytokines IL-6, IL-10, IL-13, TNF- $\alpha$  and peritoneal fluid flora were associated with infertility in patients with endometriosis. *Eur Rev Med Pharmacol Sci*. 2018;22(9):2513-2518. doi: 10.26355/eurrev\_201805\_14899. PMID: 29771400.
17. Liu H, Wang J, Wang H, et al. Correlation between matrix metalloproteinase-9 and endometriosis. *Int J Clin Exp Pathol*. 2015;8(10):13399-404. PMID: 26722547; PMCID: PMC4680492.
18. Young VJ, Brown JK, Saunders PT, Horne AW. The role of the peritoneum in the pathogenesis of endometriosis. *Hum Reprod Update*. 2013;19(5):558-69. doi: 10.1093/humupd/dmt024. Epub 2013 May 29. PMID: 23720497.
19. Budi, IM. 2002. Kajian kandungan zat gizi dan sifat fisiko kimia berbagai jenis buah merah (*Pandanus conoideus Lam*). Hasil ekstraksi secara tradisional di Kabupaten Jayawijaya Provinsi Irian Jaya [Analysis of nutrient and physico-chemical characteristics of several red fruit types. Traditional extraction at Jayawijaya District of the Province Irian Jaya] [Thesis]. Bogor, Indonesia: Institut Pertanian Bogor; 2002.
20. Cicero AFG, Colletti A. Effects of carotenoids on health: are all the same? Results from clinical trials. *Curr Pharm Des*. 2017;23(17):2422-7. doi: 10.2174/1381612823666170207095459. PMID: 28176669.
21. Bulun SE, Monsavais D, Pavone ME, et al. Role of estrogen receptor- $\beta$  in endometriosis. *Semin Reprod Med*. 2012;30(1):39-45. doi: 10.1055/s-0031-1299596. Epub 2012 Jan 23. PMID: 22271293; PMCID: PMC4034571.
22. Rafique S, Decherney AH. Medical management of endometriosis. *Clin Obstet Gynecol*. 2017 Sep;60(3):485-496. doi: 10.1097/GRF.0000000000000292. PMID: 28590310; PMCID: PMC5794019.
23. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril*. 2012;98(3):511-9. doi: 10.1016/j.fertnstert.2012.06.029. Epub 2012 Jul 20. PMID: 22819144; PMCID: PMC3836682.
24. Bedaiwy MA, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. *Fertil Steril*. 2017;107(3):537-548. doi: 10.1016/j.fertnstert.2016.12.024. Epub 2017 Jan 27. PMID: 28139239.
25. DiVasta AD, Laufer MR. The use of gonadotropin releasing hormone analogues in adolescent and young patients with endometriosis. *Curr Opin Obstet Gynecol*. 2013;25(4):287-92. doi: 10.1097/GCO.0b013e32836343eb. PMID: 23770813.
26. Andini, Y. 2008. Karakterisasi sifat fisiko-kimia dan pengujian antiproliferasi ekstrak buah merah (*Pandanus conoideus Lam.*) terhadap sel kanker HeLa dan k-562 secara in vitro [In vitro chemico-physical characterization and antiproliferative test of red fruit extract on HeLa and k-562 cancer cells] [Undergraduate thesis]. Bogor, Indonesia: Fakultas Teknologi Pertanian. Institut Pertanian Bogor. 2008.
27. Chen C, Zhou Y, Hu C, et al. Mitochondria and oxidative stress in ovarian endometriosis. *Free Radic Biol Med*. 2019 May 20;136:22-34. doi: 10.1016/j.freeradbiomed.2019.03.027. Epub 2019 Mar 27. PMID: 30926565.
28. Widowati L, Pudjiastuti P, Mudahar H. Karakterisasi dan toksisitas akut pada minyak buah merah [Characterization and acute toxicity in red fruit oil]. *JKI [Internet]*;1(1):18-4. Available from: <https://ejournal2.litbang.kemkes.go.id/index.php/jki/article/view/2835>

## ORIGINAL ARTICLE

## Profile of pregnant women with preeclampsia and its termination method

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## ABSTRACT

**Objectives:** To determine the symptoms of pregnant women with preeclampsia through the method of pregnancy termination.

**Materials and Methods:** This study used a cross-sectional method for descriptive analysis. The total sample included 75 pregnant women with preeclampsia. The sampling techniques was carried out with purposive sampling. This study used auxiliary data in medical records of preeclampsia mothers who gave birth at Taman Husada Regional Hospital, Bontang, Indonesia, in 2019.

**Results:** The results showed that most preeclampsia mothers delivered by cesarean section (CS). Among mothers who gave birth by cesarean section, there were severe symptoms of preeclampsia, 74.14% had severe hypertension with systolic blood pressure of  $\geq 160$  mmHg or diastolic blood pressure of  $\geq 110$  mmHg. Those with severe proteinuria with urine protein  $\geq 2$ g/24 hours or  $\geq +2$  were 82.76% and 60.35% of those complained visual impairment with blurred vision.

**Conclusion:** These data indicated that most mothers with preeclampsia gave birth by cesarean section and exhibited severe symptoms of preeclampsia.

**Keywords:** preeclampsia; termination method; cesarean section; hypertension; proteinuria; blurred vision; maternal health

## ABSTRAK

**Tujuan:** Untuk mengetahui gejala ibu hamil preeklampsia serta metode terminasi kehamilan.

**Bahan dan Metode:** Analisis deskriptif menggunakan metode cross-sectional. Sampel diambil sebanyak 75 ibu hamil preeklampsia dan menggunakan metode target sampling. Penelitian ini menggunakan data sekunder berupa rekam medis ibu preeklampsia yang melahirkan di RSUD Taman Husada, Bontang, Indonesia, tahun 2019.

**Hasil:** Hasil penelitian menunjukkan bahwa sebagian besar ibu preeklampsia melahirkan dengan operasi bedah sesar (SC). Pada ibu preeklampsia dengan operasi bedah sesar, ditemukan gejala preeklampsia berat (PEB): Hipertensi berat dengan tekanan darah sistolik  $\geq 160$  mmHg atau tekanan darah diastolik  $\geq 110$  mmHg yaitu 74,14%; proteinuria berat dengan protein urin  $\geq 2$ g/24 jam atau  $\geq +2$  sebanyak 82,76% dan 60,35% orang menderita penglihatan yang buruk.

**Simpulan:** Data menunjukkan bahwa sebagian besar ibu dengan preeklampsia melahirkan dengan operasi bedah sesar dan menunjukkan gejala preeklampsia yang parah.

**Kata kunci:** preeklampsia; metode terminasi; bedah sesar; hipertensi; proteinuria; gangguan penglihatan; kesehatan ibu

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## INTRODUCTION

Preeclampsia is a pregnancy-specific disease characterized by placental dysfunction and the maternal response to systemic inflammation through endothelial activation and coagulation. The diagnosis of preeclampsia is confirmed by the presence of hypertension caused by pregnancy and other organ system diseases that occur over 20 weeks of gestation.<sup>1</sup> Severe preeclampsia can be diagnosed with one or more of the following findings: systolic blood pressure of 160 mmHg or higher, diastolic blood pressure of 110 mmHg or higher, thrombocytopenia, and liver function impairment when liver enzyme levels are elevated. Patients with renal insufficiency have higher blood creatinine levels (1.1 mg/dL), pulmonary edema, and insufficiency in patients with brain and visual impairment.<sup>2</sup>

In a retrospective cohort study published in August 2017, 5506 women with preeclampsia underwent a cesarean section at 34 weeks of pregnancy. Among them, 5104 (92.7%) women received cesarean section, and 402 (7.3%) women received cesarean section. However, during the monitoring process, of the 5104 women undergoing labor induction, 3450 (67.6%) women gave birth vaginally and 1654 (32.4%) women continued cesarean section. Therefore, the total number of women with preeclampsia who underwent cesarean section was 2,057 women.<sup>3</sup>

Regardless of the indications considered, this number is high when considering the morbidity associated with cesarean section. The general belief that cesarean section is safe without side effects has shown contrasting evidence, especially in regard to future complications of subsequent pregnancy.<sup>2</sup> Therefore, it is necessary to take preventive measures so that the complications of cesarean section indications do not occur in preeclampsia. This is the role of health practitioners to identify risk factors for preeclampsia, provide control, and recognize the clinical symptoms of preeclampsia, so that early referral is possible, in an effort to prevent the deterioration of preeclampsia.<sup>1</sup>

Factors still associated with severe maternal morbidity include the diagnosis of hemolysis, elevated liver enzymes and postnatal syndrome of hemolytic liver enzyme low platelet elevation (HELLP) (nearly four times higher risk) and cesarean section (almost doubled increased risk). Pregnant women with severe preeclampsia are more likely to have cesarean section, but when it is significantly associated with postpartum maternal morbidity, induction of labor should be considered a better option for these women.<sup>2</sup> Another study stated that in women with preeclampsia at 34 weeks of gestation or later (172 women who underwent

induction labor and 21 women by planned cesarean), there was no statistically significant difference in the composite adverse maternal outcome (liver/renal failure, thrombocytopenia, disseminated intravascular coagulation, pulmonary edema, eclampsia, blood transfusion, stroke), but induced labor had a higher risk of ICU hospitalization than cesarean section (ICU hospitalization; 16.3% with induction and 9.5% with planned cesarean delivery).<sup>2</sup> Therefore, it is necessary to take preventive measures so that preeclampsia does not occur with complications that are an indication of cesarean section.

This study focused on understanding the profile of pregnant women using the pregnancy termination method at Taman Husada Regional Hospital in Bontang, Indonesia. Various indicators studied included blood pressure, urine protein, platelets, and visual disturbances which are signs of preeclampsia in pregnant women.

Various studies have shown that preeclampsia often results to a cesarean section. A study by Amorim et al. (2015) found that 59% of women with severe preeclampsia required a cesarean section.<sup>4</sup> Cesarean section is carried out to maintain the health of the fetus, avoid the risk of the fetus, and fetal death by using termination method.<sup>5</sup>

The American College of Obstetrics and Gynecology Task Force on Hypertension (ACOG) stated that the type of delivery should be determined by gestational age, fetal performance, cervical condition, and the condition of the mother and fetus.<sup>6</sup> Compared with induction of labor, planned cesarean section is not related to the increased risk of the main outcome (thromboembolism, blood transfusion, and hysterectomy), but it is related to the increased risk of entering the maternal intensive care unit and neonatal risk. Therefore, several other researchers support the recommendation that preeclampsia does not require cesarean section.<sup>7</sup>

On this basis, it is necessary to describe the symptoms of pregnant women with preeclampsia by means of termination of pregnancy. Therefore, pregnant women with preeclampsia have a higher risk of cesarean section, which can be detected early and treated immediately, so preeclampsia will not worsen and vaginal delivery can be performed.

This study may increase the knowledge and role of health practitioners in identifying and controlling the risk factors for preeclampsia, as well as recognizing the its clinical symptoms, so that it is possible to make referrals for early treatment in an effort to prevent

worsening preeclampsia conditions to reduce morbidity and mortality of the mothers.

## MATERIALS AND METHODS

In this study, a cross-sectional descriptive analysis method based on medical records was used to determine the symptoms of pregnant women with preeclampsia by means of pregnancy termination. The population of the study included pregnant women with preeclampsia who gave birth at the Taman Husada Regional Hospital in Bontang, Indonesia, in 2019. The sampling method was carried out with a targeted sampling method, and a sample of 75 mothers was obtained. This study used auxiliary data in the form of maternal medical records. The inclusion criteria were all pregnant women with preeclampsia who gave birth at Taman Husada Regional Hospital in Bontang, Indonesia, singleton pregnancy, and no comorbidities and obstetric diseases.

The research was performed through several steps. The initial stage was to obtain research permits from the Faculty of Medicine, Universitas Airlangga, Surabaya and Taman Husada Regional Hospital, Bontang, Indonesia, and then to obtain research subjects in the form of medical records and registration data records from the medical records department. The functional medical staff of the Obstetrics and Gynecology Department of Taman Husada Regional Hospital, Bontang, Indonesia, checked the patients' medical records in the emergency room, especially in the delivery room, from January 1, 2019 to December 31, 2019. After all the data had been collected, data processing was performed.

Statistical data analysis was carried out descriptively with a frequency distribution table for each symptom variable for preeclampsia mothers (hypertension status, proteinuria and visual disturbances) who underwent vaginal delivery and cesarean section. Vaginal delivery data were also displayed so as not to bias the cesarean section data. Ethical clearance number: 202/EC/KEPK/FKUA/2020 for this study was issued on Agustus 19, 2020, by Health Research Ethics Committee, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

## RESULTS AND DISCUSSION

Based on the registration of the Medical Record Department of Taman Husada Regional Hospital in Bontang, Indonesia, from January 1 to December 31, 2019, the total cases of preeclampsia was 82, 75 mothers gave birth by cesarean section, 17 mothers gave birth by vaginal delivery. There were 75 samples that fulfilled the inclusion and exclusion criteria, consisted of 58 samples in cesarean section and 17 cases in vaginal delivery. Eight mothers with preeclampsia did not fulfill the criteria due to fetal distress, history of cesarean section, and fetal position abnormalities.

Based on [Table 1](#), most preeclamptic mothers gave birth by cesarean section. The cesarean group (74.14%) had symptoms of severe hypertension with systolic blood pressure  $\geq 160$  mmHg or diastolic blood pressure  $\geq 110$  mmHg, while in group of preeclamptic women with vaginal delivery, most had mild hypertension symptoms. Groups of preeclamptic mothers with symptoms of hypertension and the method of delivery are described in [Figure 1](#).

Table 1. Frequency distribution of surveys based on hypertension symptoms at the Taman Husada Regional Hospital in Bontang, Indonesia, from January to December 2019.

Blood pressure	Frequency & percentage of each method of delivery (%)		Total & percentage (%)
	CS	Vaginal Delivery	
Mild hypertension (systolic blood pressure $\geq 140$ mmHg or diastolic blood pressure $\geq 90$ mmHg)	15 (25.86%)	14 (82.35%)	29 (45.33%)
Severe hypertension (systolic $\geq 160$ mmHg or diastolic $\geq 110$ mmHg)	43 (74.14%)	3 (17.65%)	46 (54.67%)
Total & percentage of method of deliveries	58 (100%)	17 (100%)	75 (100%)

Source: Medical records 2019

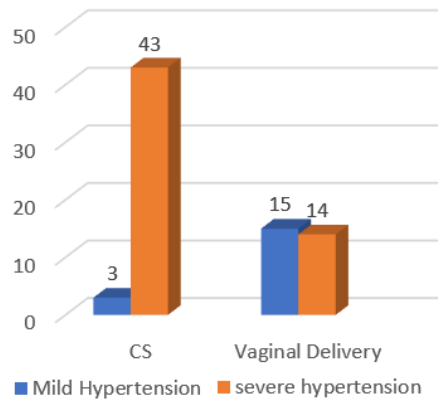


Figure 1. Symptoms of hypertension and method of delivery

Table 2. Frequency distribution of respondents based on proteinuria symptoms visited Taman Husada Regional Hospital, Bontang, Indonesia, from January to December 2019.

Urine protein	Frequency & percentage of each method of delivery (%)		Σ all PE mothers & percentage (%)
	CS	Vaginal Delivery	
Mild proteinuria (Urine protein 300 mg / 24 hours or +1)	10 (17.24%)	14 (82.35%)	24 (32%)
Severe proteinuria (urinary protein ≥ 2 g / 24 hours or ≥ +2)	48 (82.76%)	3 (17.65%)	51 (68%)
Total & Percentage of method of delivery	58 (100%)	17 (100%)	75 (100%)

Source: Medical record in 2019

Table 2 shows that mothers with preeclampsia who underwent cesarean section had symptoms of severe proteinuria, as many as 48 patients (82.76%) and mild proteinuria as many as 10 patients (17.24%), while

preeclamptic mothers who underwent vaginal delivery mostly had mild proteinuria symptoms. Groups of preeclamptic mothers with symptoms of proteinuria and the method of delivery are described in Figure 2.

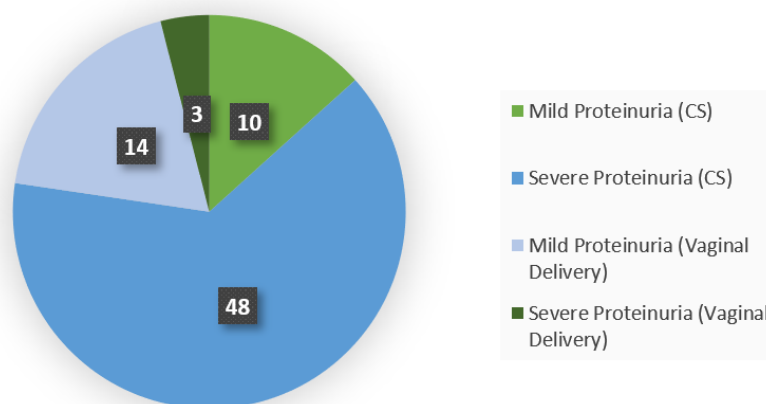


Figure 2. Symptoms of proteinuria and methods of delivery

Table 3. Frequency distribution of respondents based on visual impairment symptoms at Taman Husada Regional Hospital, Bontang, Indonesia, from January to December 2019

Visual Disturbance	Frequency & Percentage of Each Method of Delivery (%)		Total & Percentage (%)
	CS	Vaginal Delivery	
No visual disturbances present (No complaints of blurred vision)	23 (39.66%)	14 (82.35%)	37 (49.33%)
Visual disturbances present (in form of blurred vision)	35 (60.34%)	3 (17.65%)	38 (50.67%)
Total & percentage of method of deliveries	58 (100%)	17 (100%)	75 (100%)

Source: Medical record 2019

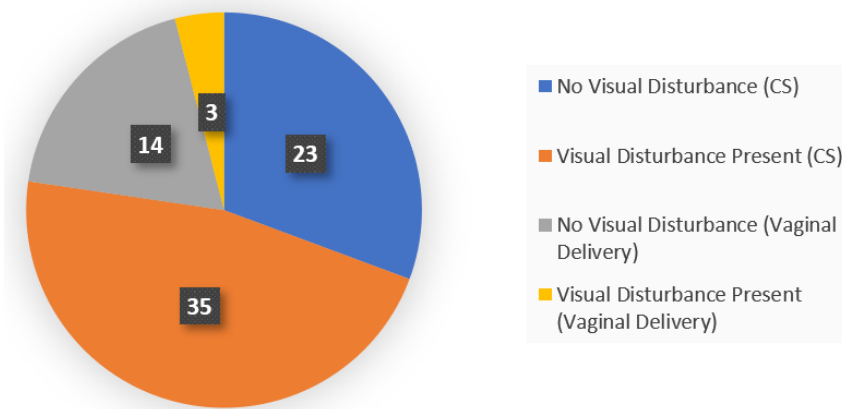


Figure 3. Symptoms of visual disturbance and method of delivery

Table 3 shows that preeclamptic mothers with cesarean section mostly experienced visual disturbances, in the form of blurred vision, as many as 35 mothers (60.34%) and the remaining 23 mothers (39.66%) had no complaints of blurred vision. Meanwhile, preeclamptic mothers that underwent vaginal delivery mostly did not have complaints of blurred vision. Preeclamptic mothers with symptoms of visual disturbances and the method of delivery are described in Figure 3.

The results of the study listed in Table 1 showed that most preeclamptic mothers who delivered using cesarean section had symptoms of severe hypertension. These data were consistent with a study carried out by O'Brien et al. after reviewing 178 cases of pregnant women during their imminent time of delivery and found that 58 (32.6%) of the patients were confirmed of having severe blood pressure. Of the 58 cases, 46 (79.3%) received a diagnosis of preeclampsia with severe features, and the majority of 38 (65.5%) patients underwent cesarean section.<sup>8</sup> Syahriana in his study stated that pregnant women with pregnancy-induced hypertension were at three times the risk of cesarean

section compared to mothers who had normal blood pressure.<sup>9</sup>

Hypertension conditions will force the kidneys to work harder, resulting in cell damage which is indicated by the presence of proteinuria. Proteinuria is the presence of protein in human urine whose level exceeds the normal limit, which is >150mg/24 hours.<sup>10</sup> When left untreated, this condition will not only cause kidney problems, but also kidney damage. Therefore, it is necessary to quickly and accurately treat preeclampsia with high proteinuria as one of the symptoms of severe preeclampsia.

Table 2 of all preeclamptic mothers who delivered using cesarean section, most mothers experienced symptoms of severe proteinuria. These results were in line with the study carried out by Ozkara et al. after evaluating preeclamptic mothers. The results of cesarean section rates in patients in group 1 (300-1,000 mg/day), group 2 (1,001-3,000 mg/day) and group 3 ( $\geq$  3,001 mg/day) were 87.5%, 75.7%, and 85.7% respectively, while the normal vaginal birth rates in the same group were found to be 12.5%, 24.3% and 14.3%, respectively.<sup>11</sup>

Another pregnancy complication that occurs in mothers with preeclampsia is visual disturbances. In [Table 3](#) we observe a high frequency of preeclamptic mothers with cesarean section experiencing blurred vision, indicating that visual disturbances are one of the symptoms of preeclamptic mothers with risk for cesarean section. This finding was also in line with the result of a study by research conducted by Radha Bai Prabhu et al. at the Special Government Hospital for Women and Children, Chennai, India, in which one of the rare complications of preeclampsia was the incidence of blindness. The incidence of blindness in women with preeclampsia and eclampsia was 0.17%. The causes of vision loss were cortical blindness in 14 patients and retinal detachment in two patients. Blindness was manifested mainly in the intrapartum and postpartum periods in 13/16 cases (81.25%). Seven patients (43.75%) were diagnosed with severe preeclampsia, and nine patients (56.25%) were diagnosed with eclampsia. Blindness that occurs during the antepartum period is an indication of immediate termination of pregnancy. In three of the patients, blindness occurred in the antepartum period, and they delivered by cesarean section within 12 hours.<sup>12</sup>

Increased blood pressure will affect blood flow, including in the eyes, resulting in vision problems. The common pathological change is swelling in the center of vision (macula). This occurs because of a leak in the lining of the eye nerve (retina), which then collects in the center of vision (central serous retinopathy). Generally, the symptom complained by the mother is a sharp decline in vision or a more blurred middle vision. This condition can improve on its own after childbirth. But in some cases, the vision does not return to normal condition, and there are even some cases of blindness.<sup>13</sup>

Another finding that was in line with our results was also carried out at the Medical Record Installation of Dr. M. Djamil, Padang, Indonesia, in December 2018-January 2019 with a sample of 77 preeclamptic mothers. From this study, it was found the highest levels of proteinuria in patients with preeclampsia and eclampsia were +2 with a percentage of 39.0%. In this group, 43.3% had normal ocular fundus, and 56.7% had positive ocular fundus changes. Mild preeclamptic ocular fundus was the most common finding in the +2 proteinuria group, as much as 50%.<sup>14</sup>

This study revealed that among all mothers with preeclampsia, most received cesarean section and a small percentage received a vaginal delivery. Most of the mothers with preeclampsia who gave birth through cesarean section had symptoms of severe preeclampsia, ie. severe hypertension, severe proteinuria, and visual impairment with poor vision.

The data of this study were in accordance to an observational study by Amorim which showed that from 500 mothers with severe preeclampsia, 110 mothers (22.0%) had spontaneous labor, 141 mothers (28.2%) had induced labor, while 249 (49.8%) underwent elective cesarean section. However, of the mothers with induced labor, 95 (67.4%) gave birth vaginally, while the rest experienced failed induction and performed cesarean section instead. In total, 295 mothers underwent cesarean section or 59% of all severe preeclamptic mothers. Amorim argued that caesarean section was common in women with severe preeclampsia and was associated with significant postpartum maternal morbidity.<sup>15</sup>

One possible treatment for preeclampsia is childbirth. In theory, the benefits of immediate termination of pregnancy by cesarean section would be even greater. When severe preeclampsia occurs before 34 weeks and the cervix is not supported, a longer induction time can be expected. At the same time, maternal complications may appear or worsen. The health of the fetus is also worrying, because abnormal placental function may lead to fetal distress and fetal death.<sup>5</sup>

However, there was another study whose results did not support the finding of this study. It was a population-based case-control study conducted in eight Brazilian states. The research was derived from a large-scale birth study in Brazil (the 2011 national survey that included 9221 postpartum women). It was found that the postpartum mortality risk of cesarean section women was nearly three times higher than that of vaginal delivery. This was mainly due to mortality and complications of anesthesia caused by postpartum hemorrhage.<sup>15</sup>

The researchers' of the study believed that it was important to consider the level of morbidity and mortality when determining the delivery management of preeclampsia. The symptoms of preeclampsia are not only exacerbated, leading to other comorbidities, but future complications caused by the birth process and subsequent pregnancy must also be considered.

In this study, the number of cases of preeclampsia was high. This was because the study site was a referral hospital, and most patients had experienced obstetric complications, on which medical decisions for the obstetric indications were based.

## CONCLUSION

Most pregnancy of the mothers with preeclampsia at Taman Husada Regional Hospital in Bontang,



Indonesia, were terminated by cesarean section, while a small percentage of mothers terminated their pregnancy through vaginal delivery. Most mothers with preeclampsia who gave birth by cesarean section have descriptions of the symptoms of severe preeclampsia, that is, severe hypertension, severe proteinuria, and visual impairment caused by poor vision. The results of this study can be used as a reference for formulating prevention plans and solving preeclampsia problems, such as screening and early detection of preeclampsia symptoms to better manage the disease, thereby reducing morbidity, mortality and delivery with cesarean section.

### CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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### REFERENCES

1. Indonesian Society of Obstetrics and Gynecology (POGI). PNPk Diagnosis dan Tatalaksana Preeklampsia [Preeclampsia, Diagnosis and Management]; 2016. p. 1–48.
2. Amorim MM, Souza ASR, Katz L. Planned caesarean section versus planned vaginal birth for severe pre-eclampsia. *Cochrane Database Syst Rev.* 2017;10(10):CD009430. doi: 10.1002/14651858.CD009430.pub2. PMID: 29058762; PMCID: PMC6485640.
3. Kawakita T, Bowers K. Maternal and neonatal outcomes of induction of labor compared with planned cesarean delivery in women with preeclampsia at 34 weeks' gestation or longer. *Am J Perinatol.* 2018;35(1):95-102. doi: 10.1055/s-0037-1606185. Epub 2017 Aug 24. PMID: 28838008.
4. Amorim MM, Katz L, Barros AS, et al. Maternal outcomes according to mode of delivery in women with severe preeclampsia: a cohort study. *J Matern Fetal Neonatal Med.* 2015;28(6):654-60. doi: 10.3109/14767058.2014.928689. Epub 2014 Jun 30. PMID: 24866351.
5. Norwitz ER, Repke JT. Preeclampsia prevention and management. *Journal of the Society for Gynecologic Investigation.* 2000;7(1):21-36. doi:10.1177/107155760000700105
6. Coviello EM, et al. Early preterm preeclampsia outcomes by intended mode of delivery. *American Journal of Obstetrics and Gynecology.* 2019;220(1): 100.e1-100.e9. doi: 10.1016/j.ajog.2018.09.027.
7. Wisner K. Gestational hypertension and preeclampsia. *MCN The American Journal of Maternal/Child Nursing,* 2019;44(3):170. doi: 10.1097/NMC.000000000000523.
8. O'Brien L, et al. Management of hypertension on the labor and delivery unit: delivering care in the era of protocols and algorithms *The Permanente Journal.* 2018;22: 17–170. doi: 10.7812/TPP/17-170.
9. Syahriana S, et al. Type of delivery and length of stay in hypertension patients. *Global Journal of Health Science.* 2018;10:158. doi: 10.5539/gjhs.v10n6p158.
10. Sinta. Gambaran proteinuria pada penderita hipertensi [Proteinuria profile in hypertensives] [Undergraduate Thesis]. Jombang, Indonesia: Sekolah Tinggi Ilmu Kesehatan Insan Cendekia; 2017
11. Ozkara A et al. Proteinuria in preeclampsia: Is it important? *Ginekologia Polska.* 2018;89. doi: 10.5603/GP.a2018.0044.
12. Radha Bai Prabhu T. Serious visual (ocular) complications in pre-eclampsia and eclampsia. *Journal of Obstetrics and Gynaecology of India.* 2017;67(5):343–348. doi: 10.1007/s13224-017-0975-6
13. Solahuddin G. Gangguan mata rentan dialami ibu hamil, inilah penyebab dan solusinya. [Internet] Gridhealth; 2019. (cited 2020 Nov 19). Available from <https://health.grid.id/read/351641362/gangguan-mata-rentan-dialami-ibu-hamil-inilah-penyebab-dan-solusinya?page=all>
14. Putri FA, Hendriati, Almurdi. Gambaran fundus okuli pada pasien preeklampsia dan eklampsia di RS M. Djamil Padang Periode 2015-2017 [Ocular fundus in preeclamptic and eclamptic patients at M Djamil Hospital, Padang, 2015-2017]. *Jurnal Kesehatan Andalas,* 2020;9(Supplement 1):119–27.
15. Esteves-Pereira AP et al. Caesarean delivery and postpartum maternal mortality: A population-based case control study in Brazil. *PLoS ONE.* 2016;11(4):1–13. doi: 10.1371/journal.pone.0153396.



## ORIGINAL ARTICLE

**Maternal and perinatal outcomes of pre-referral magnesium sulfate treatment in severe preeclampsia patients**Rizki Amalia Sari<sup>1</sup>, Sulistiawati<sup>2\*</sup>, Ernawati<sup>3</sup>

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**ABSTRACT**

**Objectives:** This study analyzed the association between pre-referral magnesium sulfate administration and maternal and perinatal outcomes in severe preeclampsia patients.

**Materials and Methods:** This was a retrospective observational analytic study using cross-sectional design. Samples were 132 pregnant women with preeclampsia referred to dr. Saiful Anwar, Hospital Malang, Indonesia in 2019. Data were taken from the patients' medical records. Maternal outcomes measured in this study were the incidence of eclampsia, ICU care, and maternal mortality, while the perinatal outcomes included the incidence of asphyxia, NICU care, and perinatal mortality.

**Results:** Patients' history of magnesium sulphate administration significantly associated with the incidence of eclampsia with p-value 0.035 and odds ratio (OR) 2.413, thus consumption of magnesium sulphate could reduce the risk of seizures. However, it did not associate with either maternal ICU care outcomes (p-value 0.087, OR 2.028), or maternal mortality (p-value 0.573). No relationship was found neither between history of magnesium sulphate administration in pregnant women with severe preeclampsia and perinatal outcomes nor with the incidence of asphyxia (p-value 0.577, OR 0.795), with NICU treatment (p-value 0.205, OR 0.579), and with perinatal mortality (p-value 0.153, OR 3.259).

**Conclusion:** Magnesium sulfate reduced the risk of eclampsia, yet it did not affect either the rate of ICU care, maternal mortality, incidence rate of perinatal asphyxia, the rate of NICU care, or perinatal mortality.

**Keywords:** Pre-referral; magnesium sulfate; severe preeclampsia; maternal outcomes; perinatal outcomes; maternal health

**ABSTRAK**

**Tujuan:** Penelitian ini bertujuan untuk menganalisis hubungan pemberian magnesium pra rujukan sulfat dengan luaran maternal dan perinatal pada pasien preeklampsia berat.

**Bahan dan Metode:** Metode penelitian ini adalah analitik observasional retrospektif dengan rancangan penelitian cross sectional. Sampel adalah 132 ibu hamil dengan preeklampsia yang dirujuk ke RSUD dr. Saiful Anwar, Malang, Indonesia, tahun 2019. Data diambil dari rekam medis pasien. Luaran maternal yang diteliti adalah kejadian eklampsia, perawatan ICU, dan kematian maternal. Luaran perinatal yang diteliti adalah kejadian asfiksia, perawatan NICU, dan kematian perinatal.

**Hasil:** Riwayat pemberian magnesium sulfat berhubungan signifikan dengan kejadian eklampsia p-value=0.035 dengan odds ratio (OR) 2.413. sehingga pemberian magnesium sulfat dapat menurunkan risiko kejadian kejang pada ibu dengan preeklampsia. Namun tidak terdapat hubungan dengan luaran maternal perawatan ICU (p-value 0.087, odds ratio (OR) 2.028). dan kematian maternal (p value 0.573). Tidak ada hubungan antara pemberian magnesium sulfat pra rujukan pada ibu hamil preeklampsia berat dengan luaran perinatal, antara lain kejadian asfiksia (p-value=0.577, odds ratio (OR) 0.795), perawatan NICU (p-value=0.182, odds ratio (OR) 0.579). dan kematian perinatal (p-value=0.153, odds ratio (OR) 3.259).

**Simpulan:** Penelitian ini menunjukkan magnesium sulfat pra rujukan dapat menurunkan risiko kejadian eklampsia namun tidak mempengaruhi tingkat perawatan ICU, kematian maternal. kejadian asfiksia perinatal, tingkat perawatan NICU dan kematian perinatal.

**Kata kunci:** Pra-rujukan; magnesium sulfat; preeklampsia dengan gejala berat; luaran maternal; luaran perinatal; kesehatan ibu

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## INTRODUCTION

Preeclampsia-eclampsia is a pregnancy complication that has been the main cause of maternal and perinatal mortality and morbidity. Preeclampsia-eclampsia contributes to 14% of global maternal mortality.<sup>1</sup> In Indonesia, 25.25% of total maternal mortality rate is caused by preeclampsia-eclampsia, 31.15% of which occurred in East Java in 2019.<sup>2</sup>

Maternal mortality and morbidity rates can be lowered through the prevention of eclampsia occurrence. Nearly half of the total maternal mortality rate is due to eclampsia which should be preventable through the administration of precise treatment.<sup>3</sup>

WHO has recommended the consumption of magnesium sulfate in the prevention against eclampsia.<sup>4</sup> The MAGPIE Trial research showed magnesium sulfate administration to mothers with severe preeclampsia was effective in reducing the risk of eclampsia by more than 50%.<sup>3</sup> Magnesium sulfate can reduce maternal mortality,<sup>5</sup> maternal complications, need for intensive care and prevents long hospital stay due to eclampsia.<sup>6</sup>

The administration of magnesium sulfate to pregnant women with severe preeclampsia can prevent fetal brain injury due to hypoxia and prevent brain cell death.<sup>7</sup> However, Jordan (2003) found exposure to magnesium sulfate increased the risk of asphyxia in newborns due to its hypotonic effect that inhibited the blood flow to the fetus. This situation can bring complications such as asphyxia and death in newborns.<sup>8</sup> Furthermore, asphyxia has been the most dominant cause of the need for NICU care.<sup>9</sup> Thus, the administration of magnesium sulfate is assumed to increase the need for NICU. On the other hand, Shepherd et al. (2019) reported no significant gap in asphyxia prevalence between infants with mothers given magnesium sulfate and those were not.<sup>10</sup>

Magnesium sulfate is one of the standard services for the prevention and management of severe preeclampsia in Indonesia. Mothers who are diagnosed with severe preeclampsia must immediately consume magnesium sulfate, including those who will be referred.<sup>11</sup>

Health facilities that are unable to provide holistic magnesium sulfate treatment are required to give only loading dose before referring the patient to more advanced health facilities.<sup>11</sup> Pre-referral magnesium sulfate administration is the key to prevent fatalities to mothers and babies which might occur due to longer referral process to more advanced health facilities.<sup>12</sup>

dr. Saiful Anwar Hospital, Malang, Indonesia, is a tertiary hospital which is a main referral hospital for maternal and neonatal patients in East Java. In Java, pre-eclampsia/eclampsia was the top cause of maternal death in 2019. In this year, 95% of pregnant patients with severe preeclampsia were referred to dr. Saiful Anwar Hospital from other health facilities. However, some patients had not been given pre-referral magnesium sulfate due to various considerations, one of which was due to the fear of harmful drug reactions.<sup>13</sup> Analysis on quality of maternal and perinatal outcomes of patients with severe preeclampsia given pre-referral magnesium sulfate will improve the awareness regarding the importance of pre-referral of magnesium sulfate administration. The results of the analysis also provide a valuable insight in developing proper strategies to reduce maternal mortality and morbidity rates due to preeclampsia.

## MATERIALS AND METHODS

This study was a retrospective observational analytic study with cross-sectional design in pregnant women with severe preeclampsia at dr. Saiful Anwar Hospital, Malang, Indonesia. The study population was pregnant women with severe preeclampsia who were referred to dr. Saiful Anwar Hospital from 1 January to 31 December 2019. The inclusion criteria were gestational age longer than 28 weeks, single pregnancy, and complete medical records. The exclusion criteria were pregnant women suffering from pre-eclampsia with contraindications to magnesium sulfate administration. The research sample was all pregnant women with severe preeclampsia who were referred to dr. Saiful Anwar Hospital from January 1, 2019 to December 31, 2019 who met the research requirements. Data used in this study were secondary data taken from the patient's medical records.

Pre-referral magnesium sulfate refers to the administration of magnesium sulfate by health facilities that referred the patients to dr. Saiful Anwar Hospital based on the standards of service. The history of magnesium sulfate administration was seen from the referral records in the medical records.

The maternal outcomes included the incidence of eclampsia, level of ICU care, and maternal incidence. The perinatal outcomes studied were incidence of asphyxia in newborn infants, rate of NICU care, and perinatal mortality. Data obtained were then processed, analyzed by statistical tests which results were presented in tables and narration.

## RESULTS AND DISCUSSION

Table 1. Characteristics of pregnant women with severe pre-eclampsia referred to dr. Saiful Anwar Hospital, Malang, Indonesia, between 1 January and 31 December 2019.

Characteristic	Total (n=132)	Percentage
Age (y.o)		
< 20	8	6.1
20-35	94	71.2
> 35	30	22.7
Education		
Elementary	38	28.8
Secondary	77	58.3
High	17	12.9
Parity		
Primipara	49	37.1
Multipara	75	56.8
Grandemulti	8	6.1
Referrer		
Doctor's Clinics	2	1.5
Health Care Center	16	12.1
Midwife Independent Service	24	18.2
Hospital	90	68.2
Eclampsia		
Yes	35	26.5
No	97	73.5
ICU care		
Yes	38	28.2
No	94	71.2
Maternal Death		
Yes	4	3.0
No	128	97.0
Asphyxia		
Yes	44	33.3
No	88	66.7
NICU Care		
Yes	41	31.1
No	91	68.9
Perinatal Death		
Yes	18	13.6
No	114	86.4

Medical records obtained from dr. Saiful Anwar Hospital from 1 January to 31 December 2019 showed that there were 132 samples that met the research criteria. [Table 1](#) shows the characteristics of pregnant women with severe preeclampsia referred to dr. Saiful Anwar Hospital, Malang. Severe preeclampsia was mostly experienced by mothers of productive age between 20-35 years, as many as 94 mothers (71.2%), followed by 30 mothers aged >35 years, as many as 30 (22.7%). The lowest case occurred in the age group <20 years with 8 samples (6.1%).

In this study, pregnant women with severe preeclampsia were mostly secondary school graduates, 77 mothers (58.3%), followed by 38 primary school graduates (28.8%), and the least were 17 mothers with high school degrees (12.9%).

Based on parity, this study found that preeclampsia was mostly experienced by multiparous mothers amounting to 75 mothers (56.8%), followed by primiparous with a total of 49 mothers (37.1%), and grandemultipara as many as 8 mothers (6.1%). This study found that the highest number of patients with preeclampsia were referred from hospitals amounting to 90 mothers (68.2%). There were 24 mothers referred by independent midwife services (18.2%), followed by 16 mothers referred from public health centers (12.1%), then the lowest were 2 mothers referred from physicians' clinic (1.5%).

Most of mothers with severe preeclampsia (97 mothers) who were referred did not experience eclampsia (73.5%). Whereas, most of 94 mothers were not admitted to the ICU (71.2%), and 4 mothers died from severe preeclampsia (3%) ([Table 1](#)). [Table 1](#) also shows that most newborns of mothers with severe preeclampsia did not experience asphyxia (88 babies or 66.7%), most of them (91 babies) were not referred to NICU (68.9%), and there were 18 newborns who died (86.4%).

Table 2. Relationship between pre-referral magnesium sulfate administration and maternal outcomes at dr. Saiful Anwar Hospital, Malang, Indonesia

Outcomes	Magnesium Sulfate Administration		<i>p</i> -value	Odds ratio (OR)	Relative Risk (RR)	
	Yes (n=97)	No (n=35)				
Eclampsia						
Yes	21	14	0.035	2.413	1.848	<i>Confidence Interval (CI) 95%</i>
No	76	21				
ICU Care						
Yes	24	14	0.87	2.028		
No	73	21				
Maternal Death						
Yes	4	0	0.573	-		
No	93	35				

[Table 2](#) shows the statistical test results of the relationship between pre-referral magnesium sulfate administration with eclampsia incidence using the chi-square test with p-value  $0.035 \leq 0.05$  with odds ratio (OR) 2.413 and RR value 1.848 (95% CI). These values indicated relationship between the history of magnesium sulfate administration with eclampsia. Mothers who did not receive pre-referral magnesium sulfate had a 2.413 greater risk of developing eclampsia than mothers who did not receive magnesium sulfate.

For ICU care variable, chi-square test revealed p-value of 0.087 with odds ratio of 2.028, which is higher than 0.05. Therefore, no relationship between the history of pre-referral magnesium sulfate administration and ICU care was found. Among pre-eclamptic pregnant women who received magnesium sulfate, 4 mothers died, while mothers who did not receive magnesium sulfate survived. Chi-square test with p-value = 0.573 indicated no relationship between the history of pre-referral magnesium sulfate administration and maternal mortality.

This study confirmed no relationship between magnesium sulfate administration in pregnant women with severe preeclampsia and perinatal outcomes. The details are presented in [Table 3](#). [Table 3](#) shows the results of bivariate analysis between pre-referral magnesium sulfate administration in preeclamptic pregnant women and perinatal outcomes. For the asphyxia variable, the chi-square analysis resulted in a p-value of 0.577 with an odds ratio=0.795, indicating that there was no relationship between pre-referral magnesium sulfate administration and the incidence of asphyxia in newborns of mothers with severe preeclampsia.

[Table 3](#) also shows that the number of newborns of mothers who were given pre-referral magnesium sulfate admitted to the NICU was lesser than that of newborns from mothers who were not given magnesium sulfate. The chi-square analysis showed p-value 0.182 with odds ratio 0.579, so as the p-value was greater than 0.05, no relationship was found between the history of pre-referral magnesium sulfate administration with the level of NICU care among newborns of severe preeclamptic mothers.

The number of newborns of mothers with severe preeclampsia receiving magnesium sulfate who died was higher than those of newborns of mothers who were not given magnesium sulfate. The chi-square analysis obtained p-value 0.153 with odds ratio 3.259. Since the p-value was higher than 0.05, it indicated no relationship between magnesium sulfate administration for pregnant women with severe preeclampsia and perinatal mortality.

In this study, it was found that 26.5% of women with severe preeclampsia were not given magnesium sulfate before being referred, while magnesium sulfate administration as prevention of eclampsia had been a standard of care in severe preeclampsia management. This result was still better than the one of a study conducted in South Konawe, Indonesia, where 100% of severe preeclampsia patients were not given magnesium sulfate before being referred. The fear of side effects and drug reactions had made health workers reluctant to administer magnesium sulfate to women with severe pre-eclampsia.<sup>13</sup>

Table 3. The relationship between pre-referral magnesium sulfate administration and perinatal outcomes at dr. Saiful Anwar Hospital, Malang, Indonesia

Outcomes	Magnesium Sulfate Administration		p-value	Odds Ratio (OR)
	Yes (n=97)	No (n=35)		
Asphyxia				
Yes	31	13	0.577	0.795
No	66	22		
NICU Care				
Yes	27	14	0.182	0.579
No	70	21		
Perinatal Death				
Yes	16	2	0.153	3.259
No	81	33		

Magnesium sulfate is an anticonvulsant and neuro-protective drug that is the first recommendation for the prevention of eclamptic seizures in severe preeclampsia.<sup>4</sup> The specific mechanism of action of magnesium sulfate in preventing seizures in patients with severe preeclampsia is not yet well-known. Magnesium sulfate prevents seizures through its vasodilator properties that reduce the blood pressure. This vasodilator property is temporary, especially during loading the dose. Magnesium sulfate is a natural antagonist of calcium. An increase in magnesium levels in cells can reduce calcium levels needed for contraction.<sup>14</sup> Magnesium sulfate decreases the activity of N-methyl D-aspartate (NMDA) receptors that are associated with seizures. Hence, magnesium sulfate prevents seizures or eclampsia in mothers with severe preeclampsia.<sup>15</sup> Magnesium sulfate has been proven to significantly reduce the incidence of seizures and recurrent seizures compared to other anti-seizures such as phenytoin and nimodipine.<sup>16</sup>

The results of the chi-square analysis indicated a relationship between pre-referral magnesium sulfate administration with the incidence of eclampsia. Mothers who did not receive pre-referral magnesium sulfate had a higher risk of eclampsia (RR 1.848 95% CI), while mothers who received magnesium sulfate had a lower risk of eclampsia (RR 0.766 CI 95%). This finding was consistent with the results of The Magpie Trial which showed that magnesium sulfate administration for mothers with severe preeclampsia reduced the risk of eclampsia by half.<sup>3</sup> Another study done in Finland measuring the incidence of eclampsia in 2006-2010 also showed a very low incidence of eclampsia due to increased use of magnesium sulfate.<sup>6</sup>

Eclampsia is one of factors that worsens the condition of patients with severe preeclampsia who require intensive care. Magnesium sulfate administration is expected to reduce the level of intensive care requirement.<sup>17</sup> However, in this study, the history of magnesium sulfate administration was found to have no relationship with the level of ICU care. The results of studies done by Duley (2002) and Gordon et al. (2014) also showed that magnesium sulfate administration did not significantly associate with ICU care.<sup>3,12</sup> This study found that the number of patients admitted to the ICU exceeded the number of eclamptic patients, meaning that there were patients who did not experience eclampsia but requiring ICU care. Other factors might influence the need for ICU care in patients, such as the modes of delivery. Aryana and Manuaba (2015) stated that ICU deliveries in severe preeclampsia patients are the most common cause of ICU care in obstetric cases.<sup>18</sup>

Preeclampsia is one of the top causes of global maternal death. In developing countries, in which resources are limited, maternal mortality rate is mostly affected by eclampsia, seizures that cause severe maternal hypoxia, trauma, and aspiration pneumonia.<sup>3</sup> Prevention against eclampsia through magnesium sulfate administration is expected to reduce maternal mortality. The Magpie Trial study noted lower maternal mortality among patients with preeclampsia who received magnesium sulfate than in patients who did not. The study also found that magnesium sulfate administration did not affect maternal mortality since no maternal deaths were found in patients who were not given magnesium sulfate while 4% of patients given magnesium sulfate died.<sup>3</sup>

Such condition may occur due to other factors that can reduce the risk of maternal death, such as advanced health facilities.<sup>19</sup> dr. Saiful Anwar Hospital, Malang, Indonesia, is a tertiary hospital with better and more complete facilities. However, more accurate studies which involve greater number of subjects are needed to analyze factors that can reduce the risk of maternal death in mothers with severe preeclampsia.

The chi-square analysis showed no relationship between magnesium sulfate administration and perinatal outcome, including the incidence of asphyxia, NICU care, and perinatal mortality. Hallak and Cotton in their study on animals found that magnesium sulfate could enter fetal blood brain barrier through the placenta.<sup>20</sup> Greater intracellular magnesium concentration inhibits the calcium from entering the cells, which can block calcium channels and lead to decreased uterine contractions or hypotonia. The effect of hypotonia reduces the blood flow to the fetus and cause fetal hypoxia. Fetal output, that is the sign of fetal hypoxia prior to delivery, is the occurrence of metabolic acidosis, asphyxia, and complications that can lead to fetal death.<sup>8</sup>

The chi-square analysis performed in this study indicated no relationship between magnesium sulfate administration and the incidence of perinatal asphyxia. Other studies also found that magnesium sulfate administration did not affect the incidence of asphyxia in newborns.<sup>3,10</sup> Severe preeclampsia itself is one of the risk factors for asphyxia in newborns. The risk increases 4 times higher in pregnant women with severe preeclampsia than preeclamptic pregnant women without severe symptoms.<sup>21</sup> In other words, even without magnesium sulfate administration, newborns of mothers with severe preeclampsia have higher risk of experiencing asphyxia.

Asphyxia is the most common factor that makes newborns required to be admitted to NICU.<sup>9</sup>

Theoretically, magnesium sulfate may increase the risk of developing asphyxia, thereby increasing the need for intensive care for newborns. However, in this study, the results of the chi-square analysis showed that pre-referral administration of magnesium sulfate did not affect the level of NICU care. Similarly, other studies also showed no association between magnesium sulfate administration and NICU treatment levels.<sup>3,10</sup>

One of the factors that can reduce the level of NICU care is good quality neonatal resuscitation. Proper asphyxia management can minimize the need for NICU care.<sup>9</sup> On the other hand, other factors can also increase the need for NICU care including preeclamptic pregnant women who deliver by sectio caesaria, babies with low birth weight, and prematurity.<sup>23</sup>

The use of magnesium sulfate is accused of increasing the incidence of perinatal mortality, but some other studies have shown no relationship between the use of magnesium sulfate in pregnant women with preeclampsia and the perinatal mortality rate.<sup>3,10</sup> Meanwhile, in this study, chi-square analysis showed no relationship between magnesium sulfate administration and the incidence of perinatal mortality. Therefore, other factors might influence perinatal mortality including quality of newborn management. Proper resuscitation can help reduce the risk of perinatal death.<sup>22</sup>

Other factors also possibly influence perinatal maternal outcome in patients with severe preeclamptic patients. However, this study only investigated their association with magnesium sulfate administration. The quality of referrals, including response time, the tiered referral system, and the quality of antenatal care can also affect the quality of maternal and perinatal outcomes. Secondary data sources in this study could be biased due to the possibility of documentation error. Therefore, further and more accurate research is needed.

## CONCLUSION

Pre-referral injection of magnesium sulfate reduced the risk of eclampsia, yet it did not affect either the rate of ICU care or maternal mortality. Pregnant women with preeclampsia who did not get pre-referral infection of magnesium sulfate had a higher risk of eclampsia, while pregnant women with magnesium sulfate preeclampsia had a lower risk of eclampsia. The administration of pre-referral magnesium sulfate to pregnant women with severe preeclampsia neither affected the incidence rate of perinatal asphyxia, the rate of NICU care, nor the perinatal mortality. Health workers at the primary health facility level are recommended to continue giving

magnesium sulfate prior to hospital referrals to prevent eclampsia from occurring during the referral process. Future researchers are encouraged to involve larger sample size in order to obtain more comprehensive results.

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## REFERENCES

1. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323-33. doi: 10.1016/S2214-109X(14)70227-X. Epub 2014 May 5. PMID: 25103301.
2. Ministry of Health, Republic of Indonesia. Data dan informasi profil kesehatan Indonesia 2019 [Data and information on health profile Indonesia 2019]. 2019.
3. Duley L. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: A randomised placebo-controlled trial. *Lancet*. 2002;359(9321):1877-90. doi: 10.1016/S0140-6736(02)08778-0
4. ACOG, Gestational hypertension and preeclampsia, *Obstetrics & Gynecology*. 2020;135(6):e237-e260 doi: 10.1097/AOG.0000000000003891.
5. Mawarti Y, Utarini A, Hakimi M. Maternal care quality in near miss and maternal mortality in an academic public tertiary hospital in Yogyakarta, Indonesia: a retrospective cohort study. *BMC Pregnancy Childbirth*. 2017;17(1):149. doi: 10.1186/s12884-017-1326-4. PMID: 28532393; PMCID: PMC5440944.
6. Jaatinen N, Ekholm E. Eclampsia in Finland; 2006 to 2010. *Acta Obstet Gynecol Scand*. 2016;95(7): 787-92. doi: 10.1111/aogs.12882
7. RCOG. Magnesium sulphate to prevent cerebral palsy following preterm birth. *RCOG Sci Impact Pap*. 2011;(29).
8. Jordan S. Farmakologi kebidanan [Midwifery Pharmacology]. Hartono A, translator. Ester M, editor. Jakarta: EGC 2003.
9. Yelamali BC, Panigatti P, Pol R, et al. Outcome of newborn with birth asphyxia in tertiary care hospital - a retrospective study. *Medica Innovatica*. 2014;3(2):59-64.
10. Shepherd E, Salam RA, Manhas D, et al. Antenatal magnesium sulphate and adverse neonatal out-



- comes: A systematic review and meta-analysis. *PLoS Med.* 2019;16(12):e1002988. doi: 10.1371/journal.pmed.1002988. PMID: 31809499; PMCID: PMC6897495.
11. Ministry of Health, Republic of Indonesia. Buku saku pelayanan kesehatan ibu di fasilitas kesehatan dasar dan rujukan. Pedoman bagi tenaga kesehatan [Pocketbook on maternal healthcare in first and referral health facilities. Guidelines for healthcare workers]. 1st ed. Moegni EM, Ocviyanti D, editors. 2013.
  12. Gordon R, Magee LA, Payne B, et al. Magnesium sulphate for the management of preeclampsia and eclampsia in low and middle income countries: a systematic review of tested dosing regimens. *J Obstet Gynaecol Can.* 2014;36(2):154-163. doi: 10.1016/S1701-2163(15)30662-9. PMID: 24518915.
  13. Pardomuan DY, Prasetyo B, Pranadyan R. Pre-referral management of patients with severe preeclampsia and eclampsia in a district hospital, Southeast Sulawesi, Indonesia. *Maj Obstet Ginekol.* 2020;28(3):104. doi: 10.20473/mog.V28I32020.104-108
  14. Pribadi A. Preeklampsia “Stoppable.” Jakarta: Sagung Seto; 2019.
  15. Chiarello DI, Marín R, Proverbio F, et al. Mechanisms of the effect of magnesium salts in preeclampsia. *Placenta.* 2018;69:134-139. doi: 10.1016/j.placenta.2018.04.011. Epub 2018 Apr 24. PMID: 29716747.
  16. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anti-convulsants for women with pre-eclampsia. *Cochrane Database Syst Rev.* 2010;2010(11):CD000025. doi: 10.1002/14651858.CD000025.pub2. PMID: 21069663; PMCID: PMC7061250.
  17. MacDonald EJ, Lepine S, Pledger M, et al. Preeclampsia causing severe maternal morbidity - A national retrospective review of preventability and opportunities for improved care. *Aust N Z J Obstet Gynaecol.* 2019;59(6):825-830. doi: 10.1111/ajo.12971. Epub 2019 Mar 18. PMID: 30883684.
  18. Aryana M, Manuaba I. Pendidikan dokter berkelanjutan obstetri dan ginekologi [Continuing medical education on obstetrics and gynecology]. In: *PKB Obstetri dan Ginekologi Ke-7.* 2015. p. 129-44.
  19. Alexander JM, Gary Cunningham F. Clinical management [Internet]. Fourth Edition. *Chesley's Hypertensive Disorders in Pregnancy, Fourth Edition.* Elsevier Inc.; 2014. 439-464 p. Available from: <http://dx.doi.org/10.1016/B978-0-12-407866-6.00020-1>
  20. Hallak M, Cotton DB. Transfer of maternally administered magnesium sulfate into the fetal compartment of the rat: Assessment of amniotic fluid, blood, and brain concentrations. *Am J Obstet Gynecol [Internet].* 1993;169(2 PART 1):427-31. Available from: [http://dx.doi.org/10.1016/0002-9378\(93\)90101-N](http://dx.doi.org/10.1016/0002-9378(93)90101-N)
  21. Wijayanti, Ernawati. Luaran maternal dan neonatal pada preeklampsia berat perawatan konservatif di RSUD Dr. Soetomo Surabaya [Maternal and neonatal outcomes in severe preeclampsia patient with conservative treatment at Dr. Soetomo Surabaya Hospital]. *Indones J Obstet Gynecol Sci.* 2019;2(2):128-36. doi: 10.24198/obgynia.v2n2.143
  22. Anggraini A, Sumadiono S, Wandita S. Faktor risiko kematian neonatus dengan penyakit membran hialin [Mortality risk factors among neonates with hyaline membrane disease]. *Sari Pediatr.* 2016;15(2):75. doi: 10.14238/sp15.2.2013.75-80
  23. Quinn CE, Sivasubramaniam P, Blevins M, et al. Risk factors for neonatal intensive care unit admission in Amman, Jordan. *East Mediterr Health J.* 2016;22(3):163-74. doi: 10.26719/2016.22.3.163. PMID: 27334073.



## ORIGINAL ARTICLE

### Preeclampsia correlates with maternal and perinatal outcomes in Regional Public Hospital, Madiun, Indonesia

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#### ABSTRACT

**Objectives:** This research aimed to find correlation between preeclampsia and maternal as well as perinatal outcomes in Regional Public Hospital, Madiun, Indonesia, from 1 January 2017 to 30 September 2020.

**Materials and Methods:** An observational analysis was applied in this study with a cross-sectional design. This study used secondary data from medical records of Regional Public Hospital, Madiun, Indonesia, with retrospective sampling and total sampling methods. Samples were 250 preeclamptic mothers with or without severe symptoms.

**Results:** Of 250 preeclamptic mothers, only 216 samples could participate in this study. Maternal outcomes included spontaneous PV delivery (12.22%), SC (87.78%), antepartum hemorrhage (0.45%), postpartum hemorrhage (6.33%), eclampsia (0.45%), HELLP syndrome (0.90%), and maternal mortality (0.45%), while perinatal outcomes covered IUGR (7.69%), LBW (33.94%), preterm birth (12.67%), perinatal mortality (2.71%), and asphyxia neonatorum (13.12%).

**Conclusion:** There was a significant correlation between preeclampsia with or without severe symptoms and maternal outcomes, which was the delivery process, and perinatal outcomes, which were the IUGR, LBW, and preterm birth. However, there was no significant correlation for antepartum hemorrhage, postpartum hemorrhage, eclampsia, HELLP syndrome, maternal mortality (maternal outcomes), perinatal mortality and neonatal asphyxia (perinatal outcomes).

**Keywords:** preeclampsia; maternal outcomes; perinatal outcomes; maternal mortality

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#### ABSTRAK

**Tujuan:** Mengetahui adanya hubungan kehamilan dengan preeklampsia terhadap maternal outcomes dan perinatal outcomes di RSUD Kota Madiun, Indonesia, periode 1 Januari 2017 sampai 30 September 2020.

**Bahan dan Metode:** Penelitian ini menggunakan metode analitik observasional dengan rancangan penelitian cross-sectional. Penelitian ini menggunakan data rekam medik di RSUD Kota Madiun, Indonesia, dengan pengambilan sampel retrospektif serta metode total sampling sejumlah 250 ibu dengan preeklampsia tanpa ataupun dengan gejala berat.

**Hasil:** Terdapat 250 ibu preeklampsia dari 4636 ibu bersalin (5,39%). Namun hanya 216 sampel yang termasuk dalam penelitian ini. Maternal outcomes meliputi proses persalinan dengan pervaginam (12,22%), SC (87,78%), terjadi perdarahan antepartum (0,45%), perdarahan postpartum (6,33%), eklampsia (0,45%), sindrom HELLP (0,90%), kematian maternal (0,45%), IUGR (7,69%), BBLR (33,94%), kelahiran preterm (12,67%), kematian perinatal (2,71%), asfiksia neonatorum (13,12%).

**Simpulan:** Didapatkan hubungan yang bermakna antara preeklampsia dengan atau tanpa gejala berat terhadap maternal outcome yaitu proses persalinan, dan perinatal outcomes yaitu IUGR, BBLR, kelahiran preterm. Hubungan yang tidak bermakna pada perdarahan antepartum, perdarahan postpartum, eklampsia, sindrom HELLP, kematian maternal (maternal outcomes), kematian perinatal dan asfiksia neonatorum (perinatal outcomes).

**Kata kunci:** preeklampsia; luaran maternal; luaran perinatal; kematian ibu

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## INTRODUCTION

Preeclampsia is a hypertension or high blood pressure in pregnancy with systolic per diastolic pressure at or above 140/90 mmHg which occurs after 20 weeks of gestational age followed by proteinuria of quantitatively 300 mg protein in the urine for 24 hours or semi-quantitatively equal to  $\geq 1$  + dipstick or by other organ system symptoms.<sup>1</sup> The cause of preeclampsia is still unknown that Zweifel in 1916 called it “the disease of theories.” The prevalence of preeclampsia occurrences in Indonesia has reached 3-10% of pregnancies, specifically 23.6 preeclampsia occurrences per 1,000 births.<sup>2</sup> Preeclampsia and its complications hold a significant role for maternal outcomes, such as maternal mortality which remains one of the world’s health problems. According to WHO, every day in 2017, approximately 810 women died from pregnancy and labor complications which could have been prevented.<sup>3</sup>

The prevalence of maternal mortality with eclampsia resulting from preeclampsia in developed countries is from 0.4% to 7.2%. Meanwhile, inadequate tertiary medical services in developing countries result in deaths from eclampsia up to more than 25%.<sup>3</sup> On the other hand, the percentage of maternal mortality from preeclampsia in East Java reached 31.32%, based on the the data from Public Health Office of East Java Province, Indonesia, in 2018.<sup>4</sup> According to Sarwono Prawirohardjo, there are four main causes of maternal, fetal, and newborn mortalities from the perspectives of obstetrics: bleeding, infection and sepsis, hypertension in pregnancy (preeclampsia/eclampsia), and dystocia.<sup>5</sup>

Infant mortality rate in East Java is still rather high. As proven by the data from the Health Department of Republic of Indonesia in 2009 in East Java, the infant mortality resulted from asphyxia neonatorum (23.14%), premature birth (21.3%), low birth weight (16.4%), infection (9.2%), and congenital abnormalities (4.6%).<sup>4</sup> Preeclampsia causes one of the above outcomes. Even though preeclampsia is a disease in pregnancy with great impacts to perinatal outcomes, it can actually be diagnosed and prevented from possible mortality and morbidity.

## MATERIALS AND METHODS

This research used analytical observational method with retrospective sampling. The design used in this research was cross-sectional. The research was conducted in the Medical Record and Maternity Room at the Regional Public Hospital, Madiun, Indonesia from October to December 2020 with secondary data taken from the medical records at the hospital.

Total sampling method was used in this study with inclusion criteria: all age groups of mothers who gave birth with all types of preeclampsia (preeclampsia without severe symptoms or preeclampsia with severe symptoms) recorded in the medical records within the period from January 1, 2017 to September 30, 2020 at Regional Public Hospital, Madiun, Indonesia. The exclusion criteria in this study were mothers with gemellary pregnancy who were not completely recorded in the medical records of the hospital. Finally, there were 216 mothers included in this study.

The analysis of this study used Chi-square and Fisher Exact Test on outcomes that did not fulfil the Chi-Square test requirements. The analysis used had a significance level of 95% and p value of 0.05.

## RESULTS AND DISCUSSION

In this study, 250 preeclampsia mothers were found from 4636 mothers who gave birth at the Regional Public Hospital, Madiun, Indonesia, from January 1, 2017 to September 30, 2020 (5.39%). This was also found in a previous study where the incidence of preeclampsia in Indonesia was around 3-10% of all pregnancies, with 23.6 cases per 1,000 births.<sup>2</sup> The frequency of pregnant women with preeclampsia in this study was 216 mothers of 4636 women who gave birth at the Regional Public Hospital, Madiun, in the period from January 1, 2017, to September 30, 2020 (4.65%) with the frequency of preeclampsia without and with severe symptoms were 104 mothers (48.15%) and 112 mothers (51.85%) respectively. The frequency of preeclampsia with severe symptoms was higher than the preeclampsia without severe symptoms, while the distribution of the types of preeclampsia with severe symptoms was predominantly found in a study by Ika (2017) in Dr. H Abdul Moeloek Regional General Hospital in Lampung Province, Indonesia, where 58.4% of 154 preeclampsia mothers had severe symptoms.<sup>6</sup>

Some of the risk factors for preeclampsia include gravida, age of pregnant women, history of previous chronic diseases, obesity, pregnancy with more than one baby (gemellary) and previous history of preeclampsia.<sup>7</sup> The age of pregnant women can be a risk factor for causing complications in pregnancy, including preeclampsia. According to previous studies, pregnant women of less than 20 years easily have increased blood pressure and tends to cause seizures quickly, while age of more than 35 years is also a predisposing factor for the occurrence of pre-eclampsia.<sup>7,8</sup> Age distribution the preeclampsia women were 20-35 years in as many as 140 mothers (64.81%) (Table 1). The highest frequency

at that age proves the possibility of increasing public awareness of getting pregnant at a physiological age of 20 to 35 years. This is because the age of 20-35 years is the period of regulating pregnancy, which is also a fertile age for pregnancy and childbirth. However, in this productive age, they are also in the active period of activity, causing mothers to pay less attention to her pregnancy, resulting in less regular antenatal care.<sup>8</sup>

Table 1. Distribution of preeclamptic mothers characteristics

Characteristics of pregnant mothers		
Mothers' age	Frequency (n)	Percentage (%)
<20 years	2	0.93
20-35 years	140	64.81
>35 years	74	34.26
Gravide		
1	69	31.94
2-5	145	67.13
>6	2	0.93
Parity		
0	71	32.87
1-4	143	66.20
>5	2	0.93
History of disease		
Hypertension	17	7.87
Diabetes melitus	8	3.70
No history of disease	191	88.43
Pregnancy interval		
Gravide 1	69	31.94
<2 years	4	1.85
2-10 years	106	49.07
>10 years	37	17.13
Body mass index		
Underweight (<18.5)	1	0.46
Normal (18.5-22.9)	6	2.78
Overweight (23-24.9)	23	10.65
Obesity 1 (25-29.9)	84	38.89
Obesity 2 (>30)	102	47.22
Total	216	100.00

Based on previous research, gravida had an influence on pregnancy and childbirth in pregnant women due to a higher risk for disturbances during pregnancy, especially in the first pregnancy or primigravida. This was due to the imperfect formation of antibody blocking against placental antigens. In the first pregnancy, the antigenic location of the placenta was wider than the number of antibodies, so it causes an immune response that is detrimental to the histoincompatibility of the placenta.<sup>8</sup> In this study, the frequency of primigravida was 31.94%, comprising 69 mothers. According to a previous study by Windaryani, such primigravida frequency can be regarded as high. Primigravida often experience stress in dealing with pregnancy and childbirth. This stress can trigger the release of CRH and causes increasing cortisol. The effect of cortisol is to prepare the body to respond to various stressors by increasing sympathetic responses, including responses to increased cardiac output and blood pressure.<sup>9</sup>

Parity also affects the incidence of preeclampsia, for example, in nulliparity and pregnant women who give birth more than three times. In multiparous mothers, there is excessive uterine stretching and can effect in excessive ischemia which can lead to preeclampsia.<sup>9</sup> Multiparity is a woman who has given birth between 2 and 4 times, while grande-multipara is a woman who has given birth 5 times or more. The multiparous mothers have a 1% risk of developing preeclampsia. It based on the results of this research where there were 68 nulliparous mothers (31.48%), 68 multiparous mothers (31.48%), and grandemultipara 2 mothers (0.93%).

In addition, preeclampsia is more common in women with risk factors for autoimmune disease, hydatidiform mole, parity, diabetes and gestational diabetes, twin pregnancies/gemelli, chronic hypertension, history of preeclampsia, age, kidney disease. A study found that a mothers with a history of hypertension comprised 17 cases (7.87%) and diabetes mellitus was cases (3.70%) and those without history of previous disease as many as 191 cases (88.43%).<sup>9</sup>

In our findings, 37 mothers (17.13%) gave birth with an interval more than 10 years. When the interval is more than equal to ten years, then the risk for these mothers to experience preeclampsia is the same as nulliparous mothers or those who have never given birth before.<sup>10</sup> While those with an interval of less than 2 years, the number was 4 mothers (1.85%). Pregnant women with a birth interval of less than 2 years have a twice greater risk of experiencing complications during pregnancy or during childbirth compared to longer birth intervals. Therefore, the recommended interval of pregnancy is at least 2 years or more for women to recover after pregnancy, childbirth and lactation. Roberts et al. (2011) stated that the risk of preeclampsia became three times higher in obese women. Cardiovascular disorders that arise due to obesity are the cause of preeclampsia in pregnant women.<sup>11</sup>

There was a significant result relationship ( $p=0.00$ ) between preeclampsia with severe symptoms or without severe symptoms on the childbirth process in this study, which was in line with Basri's study (2020) that there is a significant relationship between preeclampsia and the childbirth process (spontaneous vaginal and caesarean section).<sup>12</sup> The results of this study obtained 189 mothers from 216 preeclampsia mothers (87.5%) who were terminated by caesarean section (Table 2). The high incidence of pregnancy termination by caesarean section is indicated if the mother and the fetus were in emergency, such as fetal position abnormalities, fetal distress, eclampsia and preeclampsia, narrow pelvis, old parturition, premature rupture of membranes, macrosomia, cephalopelvic disproportion, oligohydramnios.

Table 2. Childbirth process

Variables	Spontaneous Vaginal N=27 (%)	Caesarean Section N = 189 (%)	<i>p</i> *
Degree of preeclampsia			
Without severe symptoms	20 (9.26)	84 (38.89)	0.00
With severe symptoms	7 (3.24)	105 (48.61)	

In this study, there was no significant relationship between preeclampsia with or without severe symptoms and antepartum bleeding cases ( $p=0.48$ ) (Table 3). The results of this study were in line with Hartanto's study (2021) which concluded that there was no significant relationship between preeclampsia with or without severe symptoms and placental abruption.<sup>13</sup> Based on the development theory, placental abruption occurs as a result of less strong vascular relationship between maternal and fetal vasculature in preeclampsia due to abnormal trophoblastic invasion which causes easy separation of the placenta from the mother's basal decidua cell layer, so that it causes placental abruption easily.<sup>14</sup>

Table 3. Antepartum bleeding

Variables	No Antepartum Bleeding N=215 (%)	Antepartum Bleeding N = 1 (%)	<i>p</i> *
Degree of preeclampsia			
Without severe symptoms	103 (47.69)	1 (0.46)	0.48
With severe symptoms	112 (51.85)	0 (0.00)	

In this study, there were 14 cases of postpartum hemorrhage with 9 mothers experiencing preeclampsia without severe symptoms, and 5 of them had preeclampsia with severe symptoms. There was an insignificant relationship between preeclampsia without or with severe symptoms when it was associated with postpartum hemorrhage ( $p=0.21$ ) (Table 4). In this research, uterine atony was found as the most common cause of postpartum hemorrhage, as it was explained in Julizar's research (2019) that the use of MgSO<sub>4</sub> (magnesium sulfate) was indicated in pre-eclampsia or severe eclampsia and it was known that magnesium sulfate had a tocolytic effect that contributed to uterine atony.<sup>15</sup>

Table 4. Postpartum bleeding

Variables	No Postpartum Bleeding N=202 (%)	Postpartum Bleeding N = 14 (%)	<i>p</i> *
Degree of preeclampsia			
Without severe symptoms	95 (43.98)	9 (4.17)	0.21
With severe symptoms	107 (49.54)	5 (2.31)	

According to Sarwono Prawirohardjo, eclampsia is a complication of pregnancy with preeclampsia with manifestations of generalized seizures or coma.<sup>1</sup> In this study, there was an insignificant relationship between preeclampsia without severe symptoms or with severe symptoms if it was associated with the incidence of eclampsia ( $p=1.00$ ) (Table 5).

Table 5. Eclampsia

Variables	Not Eclampsia N=202 (%)	Eclampsia N = 14 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	104 (48.15)	0 (0.00)	1.00
With severe symptoms	111 (51.39)	1 (0.46)	

Although it was not statistically significant, there was a tendency for severe preeclampsia to become eclampsia clinically. Before a patient with severe preeclampsia becomes eclampsia, symptoms such as severe headache, vomiting, epigastric pain, visual disturbances, and a progressive increase in blood pressure are known as impending eclampsia. This is due to vascular disorders that occur in the cerebral cortex, so that it causes hypersynchronization and hyperactivity of electrical activity that can cause seizures.<sup>1</sup>

Table 6. HELLP syndrome

Variables	No HELLP Syndrome N=214 (%)	HELLP Syndrome N = 2 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	104 (48.15)	0 (0.00)	0.50
With severe symptoms	111 (50.39)	2 (0.93)	

HELLP syndrome is a complication of pregnancy with pre-eclampsia accompanied by the onset of hemolysis, liver dysfunction characterized by an increase in liver enzymes, and thrombocytopenia.<sup>1</sup> In this study, there was a non-significant relationship between preeclampsia without severe symptoms or with severe symptoms in relations to the incidence of HELLP syndrome ( $p=0.50$ ), indicating that the incidence of HELLP syndrome is not affected by the degree of preeclampsia with or without severe symptoms (Table 6). Although it was not significant statistically, there is a tendency for severe preeclampsia to develop into the HELLP syndrome clinically. There is an uncertain mechanism related to the occurrence of HELLP syndrome in preeclampsia, but most believe that this is caused by systemic arterial vasoconstriction causing blood accumulation in the veins, one of which is in the hepatic veins, which causes enlargement of the liver, and stretching of the liver capsule which causes damage and dysfunction in the liver, leading to hemolysis, increased liver enzymes and thrombocytopenia and activation of nociceptors so that it induces pain in the right upper quadrant of the

abdomen. The results of this study were in line with Kinay's research (2015) that there is the same level of morbidity between mothers with HELLP syndrome and severe preeclampsia at the same gestational age. Therefore, the management of severe preeclampsia and HELLP syndrome must be carried out properly in order to simultaneously reduce maternal morbidity and perinatal outcomes.<sup>16</sup>

Table 7. Maternal death

Variables	No Maternal Death N=215 (%)	Maternal Death N = 1 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	103 (47.69)	1 (0.46)	0.48
With severe symptoms	112 (51.85)	0 (0.00)	

In this study, there was an insignificant relationship between preeclampsia without severe symptoms or with severe symptoms in relations to the incidence of maternal death ( $p=0.48$ ) (Table 7). Mothers with preeclampsia are more likely to experience hemodynamic disturbances when compared to women without preeclampsia with the same amount of bleeding. Based on the previous studies, more than 90% of maternal deaths were due to obstetric complications which have been predicted during pregnancy. Most of these complications occur at or around childbirth. However, there are also mother who are not categorized as at risk, but they are actually experience complications.<sup>7,17</sup> This was also found in our study that maternal deaths occurred precisely in women with preeclampsia without severe symptoms. Therefore, the recommended approach is to assume all pregnancies are at risk and that every pregnancy is considered risky and pregnant women have an access to safe childbirth assistance and obstetric services.

Low frequency maternal outcomes, such as antepartum bleeding, eclampsia, HELLP syndrome and maternal deaths, that occurred in pregnant women with preeclampsia at Regional Public Hospital Madiun from January 1, 2017 to September 30, 2020 might be affected by referral system implemented at this hospital. As a type C hospital, it refers patients to referral hospitals with higher type. Another factor that might have caused low incidence of preeclampsia complications in this hospital was the control and management of preeclampsia that had been carried out properly that resulted in the low incidence found in this study.

In a previous study, pre-eclampsia mothers with severe symptoms have a 4.5 times greater chance of giving birth to babies with complications than pre-eclamptic mothers without severe symptoms.<sup>18</sup> Based on the PNPk diagnosis and management of preeclampsia in 2016, IUGR or Intra Uterine Growth Restriction is an

indicator of impaired organ function, especially disruption of uteroplacental circulation that occurs in preeclampsia.<sup>19</sup> In this study, the relationship between preeclampsia with or without severe symptoms when associated with IUGR ( $p=0.01$ ) was found to be significant (Table 8).

Table 8. IUGR (Intra Uterine Growth Restriction)

Variables	No IUGR N=199 (%)	IUGR N = 17 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	101 (46.76)	3 (1.39)	0.01
With severe symptoms	98 (45.37)	14 (6.48)	

In this study, there was a significant relationship between preeclampsia without severe symptoms or with severe symptoms in relations to the incidence of Low Birth Weight (LBW) ( $p=0.00$ ) (Table 9). The results of this study were in line with Dewi's research (2018) which indicated that there was a significant relationship with an odd ratio of 2.042, indicating an increased risk of mothers with preeclampsia to give birth to babies with low birth weight, especially in those with severe preeclampsia with an increased risk of 2.042 times higher than preeclampsia without severe symptoms. This is because in women with preeclampsia there are physiological and pathological alterations, such as alterations in the placenta and uterus, which result in decreased blood flow to the placenta and cause inadequate nutrition for the fetus, leading to Low Birth Weight.<sup>20</sup>

Table 9. LBW (Low Birth Weight)

Variables	No LBW N=145 (%)	LBW N = 71 (%)	<i>p</i> *
Degree of preeclampsia			
Without severe symptoms	81 (37.50)	23 (10.65)	0.00
With severe symptoms	64 (29.63)	48 (22.22)	

Table 10. Preterm birth

Variables	No Preterm Birth N=189 (%)	Preterm Birth N = 27 (%)	<i>p</i> *
Degree of preeclampsia			
Without severe symptoms	98 (45.37)	6 (2.78)	0.00
With severe symptoms	91 (42.13)	21 (9.72)	

In this study, there were 216 women with preeclampsia and 27 women who gave preterm birth with 6 of them being women with preeclampsia without severe symptoms and 21 women with preeclampsia with severe symptoms. ( $p=0.00$ ) (Table 10). These results were in line with those found in Faiza et al. study which indicated that mothers with severe preeclampsia had a risk of 3.303 times and 4.5 times for preterm childbirth compared to women without severe preeclampsia. It has been recognized that in severe preeclampsia premature



birth can occur due to vasospasm of blood vessels which will reduce blood flow to the placenta, so that there was impaired placental function. If vasospasm lasts for a long time, then it will interfere with fetal growth. If there is an increase in uterine tone and sensitivity to stimulation, it can result in premature childbirth.<sup>21</sup>

Table 11. Perinatal death

Variables	No Perinatal Death N=210 (%)	Perinatal Death N = 6 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	103 (47.69)	1 (0.46)	0.21
With severe symptoms	107 (49.54)	5 (2.31)	

In this study, there was no significant relationship between preeclampsia without severe symptoms or with severe symptoms in relations to perinatal mortality (p=0.21) (Table 11). These findings were also in line with those of Faiza et al. which indicated that mothers with severe preeclampsia did not have a significant relationship with perinatal mortality or Intra Uterine Fetal Death (IUFD). Although the finding in this study was not statistically significant, there was a tendency for infants born to mothers with severe preeclampsia to experience complications in the form of perinatal death clinically, in this case IUFD and severe asphyxia. There were other factors affect the occurrence of Intra Uterine Fetal Death (IUFD) such as placental abruption, DM, breech position, congenital abnormalities.<sup>21</sup>

The occurrence of perinatal death in mothers with preeclampsia is supported by a notion that there are four causalities of maternal, fetal and neonatal death from an obstetric perspective, ie. hemorrhagic, sepsis and infection, high blood pressure and preeclampsia or eclampsia and obstructed childbirth. The occurrence of spasm in the arteriolar blood vessels in preeclampsia will then cause compensation as a way to overcome the increase in peripheral pressure so that oxygen can still reach all tissues adequately. As a result, blood flow to the placenta will decrease and cause in disturbances in fetal growth and due to lack of oxygen, it can cause fetal distress or fetal distress.<sup>1,22</sup>

Table 12. Asphyxia neonatorum

Variables	No Asphyxia Neonatorum N=188 (%)	Asphyxia Neonatorum N = 28 (%)	<i>p</i>
Degree of preeclampsia			
Without severe symptoms	93 (43.06)	11 (5.09)	0.31
With severe symptoms	95 (43.98)	17 (7.87)	

In this study, there was no significant relationship between preeclampsia with or without severe symptoms on the incidence of asphyxia neonatorum (p=0.31),

although it was not statistically significant but there was a tendency for infants born to mothers with severe preeclampsia to have severe preeclampsia complications in the form of asphyxia neonatorum clinically (Table 12). The results in this study were in line with a previous study by Heriyanti that there were no statistically significant relationship found between severe preeclampsia and neonatorum asphyxia at Dr. Moewardi Hospital, Surakarta, Indonesia.<sup>23</sup> According to Sunarsih's research (2014) preeclampsia mothers tended to give birth to asphyxia babies, although statistically it was not significant.<sup>4</sup> Asphyxia can occur in infants with pre-eclampsia mothers due to preeclampsia, and spiral artery spasms occur which cause disruption of uteroplacental circulation so that fetal hypoxia occurs and continues to be asphyxia neonatorum.<sup>23,24</sup>

**CONCLUSION**

There is a significant relationship between preeclampsia with or without severe symptoms and maternal outcome, namely the childbirth process, while there is a non-significant relationship between preeclampsia with or without severe symptoms on maternal outcomes, namely antepartum hemorrhage, postpartum hemorrhage, eclampsia, HELLP syndrome, and maternal death. There is a significant relationship between preeclampsia with or without severe symptoms and perinatal outcomes, ie. Intra Uterine Growth Restriction (IUGR), Low Birth Weight (LBW), and preterm birth, while there is a non-significant relationship between preeclampsia with or without severe symptoms on perinatal outcomes of perinatal mortality and neonatal asphyxia. Precautions for maternal and perinatal outcomes must still be carried out, considering some outcomes do not have a significant relationship to the severity of preeclampsia, meaning that these outcomes can still occur even in preeclampsia without severe symptoms.

**REFERENCES**

1. Prawirohardjo S. Ilmu kebidanan: Hipertensi pada kehamilan [Midwifery. Hypertension in pregnancy]. 4<sup>th</sup> edition. Jakarta: Yayasan Bina Pustaka Prawirohadjo; 2018.p.531-55.
2. Silomba W, Wantania J, Kaeng J. Karakteristik dan luaran preeklampsi di RSUP Prof. Dr. RD Kandou Manado [Preeclampsia characteristics and outcome in Prof Dr RD Kandou Hospital Manado]. E-Biomedik; 2013.



3. World Health Organization. Maternal Mortality in 2017. 2019. Available from: <https://www.who.int/news-room/fact-sheets/detail/maternal-mortality>.
4. Sunarsih. Hubungan preeklampsia terhadap kejadian asfiksia pada bayi baru lahir di RSUD Kota Madiun [Correlation between preeclampsia and asphyxia incidence in newborns]. *Warta Bhakti Husada Mulia*. 2014;1(1):10-5.
5. Prawirohardjo S. Ilmu kebidanan: Prinsip dasar penanganan kegawatdaruratan [Midwifery: Basic principles of emergency treatment]. 4<sup>th</sup> edn. Jakarta: Yayasan Bina Pustaka Sarwono Prawirohadjo; 2018. p. 391.
6. Manik IN, Sari RDP, Wulan AJ. Hubungan status preeklampsia dengan kejadian perdarahan postpartum pada ibu bersalin di RSUD Dr H Abdul Moeloek Provinsi Lampung Periode 1 Juli 2014-30 Juni 2015 [Correlation between preeclampsia and postpartum bleeding in mothers delivered at Abdul Moeloek Hospital, Lampung]. *Jurnal Majority*. 2017;6(3):51-7.
7. Palupi DD, Indawati R. Faktor risiko kematian ibu dengan preeklampsia/eklampsia dan perdarahan di Provinsi Jawa Timur [Risk of fatality among mothers with preeclampsia/eclampsia and bleeding in East Java]. *Jurnal Biometrika dan Kependudukan*. 2014;3(2):107-13.
8. Indriani N. Analisis faktor-faktor yang berhubungan dengan preeklampsia pada ibu bersalin di RSU Daerah Kardinah Kota Tegal tahun 2011 [Analysis of factors related to preeclampsia in partus mothers], Depok: Faculty of Public Health, Universitas Indonesia, Midwifery Program; 2012.
9. Pratiwi I, Wantonoro W. Hubungan paritas dengan kejadian preeklampsia pada ibu hamil di RSUD Wonosari [Correlation between parity and preeclampsia incidence] [Dissertation]. STIKES Aisyiyah: Yogyakarta; 2015
10. Simarmata OS, Armagustini Y, Bisara D. Determinan kejadian komplikasi persalinan di Indonesia (Analisis data sekunder Survei Demografi dan Kesehatan Indonesia tahun 2007) [Determinant of delivery complications incidence in Indonesia (Secondary data analysis)]. [Undergraduate Thesis]. Depok: Indonesia. Postgraduate Program, Faculty of Public Health, Universitas Indonesia; 2010.
11. Roberts JM, Bodnar LM, Patrick TE, Powers RW. The role of obesity in preeclampsia. *Pregnancy Hypertens*. 2011;1(1):6-16. doi: 10.1016/j.preghy.2010.10.013. PMID: 21532964; PMCID: PMC3082136.
12. Basri NF, Apriyanto DR, Sulistiyana CS. Hubungan antara jenis persalinan dengan kondisi janin saat lahir pada kejadian preeklampsia pada ibu bersalin di RSUD Waled Kabupaten Cirebon tahun 2017 [Correlation between delivery type and preeclampsia among delivering mothers]. *Tunas Medika Jurnal Kedokteran & Kesehatan*. 2020; 6(1).
13. Hartanto AI, Kusumosih TAR, Indrarto W. Luaran kehamilan dan persalinan pada ibu dengan preeklampsia berat di RS Panti Wilasa, Citarum, Semarang [Pregnancy and delivery outcome among mothers with severe preeclampsia]. *Obgynia*. 2021;4(1):20-27. doi: 10.24198/obgynia/v4n1.240
14. Chotimah C. Hubungan antara preeklampsia/eklampsia dengan kejadian solusio plasenta di RSUD Prof. Dr. Margono Soekardjo Purwokerto Tahun 2012 [Correlation between preeclampsia/eclampsia and placental abruption incidence]. Cirebon, Indonesia. Stikes YLPP Repository. 2013.
15. Julizar M, Sukandar H. Analisis faktor risiko atonia uteri [Risk factor analysis of uterine atony]. *Care: Jurnal Ilmiah Ilmu Kesehatan*, 2019. 7(3), p.108-117. doi: 10.33366/jc.v7i3.1399
16. Kınay T, Küçük C, Kayıçioğlu F, Karakaya J. Severe preeclampsia versus HELLP syndrome: Maternal and perinatal outcomes at <34 and ≥34 weeks' gestation. *Balkan Med J*. 2015;32(4):359-63. doi: 10.5152/balkanmedj.2015.15777. Epub 2015 Oct 1. PMID: 26740894; PMCID: PMC4692334.
17. Cunningham FG, Leveno KJ, Bloom SL, et al. Hipertensi dalam kehamilan [Hypertension in pregnancy]. In: Williams Obstetrics vol. 2. 23 ed.: New York: Mc Graw Hill; 2010. p.740-7.
18. Noni HS. Hubungan preeklampsia berat dengan komplikasi neonatal di ruang rawat inap kebidanan RSUP di Dr. M. Djamil Padang tahun 2016 [Correlation between severe preeclampsia and neonatal complications in maternity ward]. [Dissertation]. Padang, Universitas Andalas.2017
19. Noroyono W, Irwinda R, Frisdiantiny E, et al. Pedoman nasional pelayanan kedokteran. Diagnosis dan tatalaksana pre-eklampsia [Medical care national guidelines. Pre-eclampsia diagnosis and management]. Perkumpulan Obstetri dan Ginekologi Indonesia. Himpunan Kedokteran Feto Maternal.2016. p. 6-21.
20. Dewi PSR. Hubungan tingkat preeklampsia dengan kejadian bayi berat lahir rendah (BBLR) di RSUD Dr. H. Abdul Moeloek Provinsi Lampung. [Correlation between preeclampsia rate and LBW incidence]. *Proceeding of Konas Perinasia*; 2018 October 15-16.
21. Faiza MMR, Ngo NF, Fikriah I. Hubungan preeklampsia berat dengan komplikasi pada janin di RSUD Abdul 2 Wahab Sjahranie Samarinda 3 Tahun 2017-2018 [Correlation between severe preeclampsia and fetal complications]. *Jurnal Kebidanan Mutiara Mahakam*. 2019;7(2):74-84. doi: 10.36998/jkmm.v7i2.59



22. Djaja S. Hubungan preeklamsia berat (PEB) dengan kejadian Intra Uterine Fetal Death (IUFD) di Ruang Teratai I BLUD RSUD Kota Banjar Tahun 2016 [Correlation between severe preeclampsia and IUFD incidence]. *Jurnal Kesehatan Mandiri Aktif*. 2019; 2(2):64-9.
23. Heriyanti O. Hubungan antara preeklampsia berat dengan asfiksia perinatal di RSUD Dr Moewardi Surakarta [Correlation between severe preeclampsia and perinatal asphyxia]. Universitas Negeri Sebelas Maret, Indonesia. Repository. 2009.
24. Prihatini IJ. Hubungan antara preeklampsia dengan kejadian BBLR dan asfiksia neonatorum di VK IRD RSUD Dr. Soetomo Surabaya [Correlation between preeclampsia and LBW incidence and neonatal asphyxia] [Dissertation] Surabaya, Indonesia. Universitas Airlangga; 2013.



## ORIGINAL ARTICLE

**Eclampsia as the leading cause of maternal death at Prof. dr. R.D. Kandou Hospital, Manado, Indonesia****Hermie MM Tendean<sup>1</sup>\*, Joice MM Sondakh, Anastasia M Lumentut, Reni Ch Ibrahim**

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**ABSTRACT**

**Objectives:** To determine the characteristics of maternal deaths at Prof. dr. R.D. Kandou Hospital, Manado, Indonesia, from January 1 to December 31, 2019.

**Materials and Methods:** This was a retrospective descriptive study. Data were taken from the patient's medical record at Prof. dr. R.D. Kandou Hospital, Manado, in the period of January 1, to December 31, 2019.

**Results:** From January 1 to December 31, 2019 in Prof. dr. R.D. Kandou Hospital, Manado, there were 1.215 single live births, with maternal mortality of 22 cases. In the distribution of characteristics based on age, most patients had age range of 20-34 years with a total of 15 patients (68.18%) and parity 2 - 4 with a total of 21 patients (95.45%), Antenatal Care (ANC) of 1 - 3 times visit in a total of 11 cases (50%), and most came from outside the city of Manado with a total of 12 patients (54.54%). The most common cause of maternal death was due to eclampsia, comprising 8 cases (36.36%).

**Conclusion:** Maternal death cases in Obstetrics and Gynecology Department of Prof. dr. R.D. Kandou Hospital, Manado, Indonesia, in 2019 reached 22 cases per 1.215 live births. Eclampsia was still the leading cause of maternal death.

**Keywords:** maternal mortality rate, maternal death, eclampsia

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**ABSTRAK**

**Tujuan:** Mengetahui karakteristik kematian maternal di Bagian Obstetri dan Ginekologi RSUP Prof. dr. R.D. Kandou Manado, Indonesia, 1 Januari - 31 Desember 2019.

**Bahan dan Metode:** Deskriptif retrospektif. Data diambil dari rekam medik di Bagian Obstetri dan Ginekologi RSUP Prof. dr. R.D. Kandou Manado selama 1 Januari - 31 Desember 2019.

**Hasil:** Terdapat 22 kasus kematian maternal dari 1.215 kelahiran hidup tunggal pada periode 1 Januari - 31 Desember 2019 di RSUP Prof. dr. R.D. Kandou Manado. Usia 20 - 34 tahun memiliki persentase terbanyak dengan jumlah 15 kasus (68.18%), paritas 2 - 4 dengan jumlah 12 kasus (54.54%), riwayat Antenatal Care (ANC) terbanyak 1 - 3 kali dengan jumlah 11 kasus (50%) dan terbanyak berasal dari luar kota Manado dengan jumlah 12 kasus (54.54%). Penyebab kematian maternal terbanyak disebabkan karena eklampsia dengan jumlah 8 kasus (36.36%).

**Simpulan:** Kasus kematian maternal di Bagian Obstetri dan Ginekologi RSUP Prof. dr. R.D. Kandou Manado tahun 2019 mencapai 22 kasus per 1.215 kelahiran hidup. Eklampsia masih merupakan penyebab terbanyak kematian maternal.

**Kata kunci:** angka kematian ibu, kematian maternal, eklampsia

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## INTRODUCTION

Maternal mortality is one indicator to observe the progress of a country's health, specifically in association with maternal and children health problems.<sup>1</sup> Maternal mortality may be categorized into proximate determinants, intermediate determinants, and contextual determinants. Proximate determinants are directly associated with maternal mortality, namely obstetrics disorders; meanwhile, intermediate determinants are associated with health factors, for instance, maternal health, maternal reproductive status, access to healthcare facilities, and healthcare facilities utilization behaviors. In addition to those determinants, contextual determinants are those associated with demographical and sociocultural factors. The attempts to decrease maternal death are accomplished through obstetrics complication management with providing standardized coverage and definitive treatments by a competent healthcare worker in primary and referral healthcare facilities.<sup>2,3</sup>

From the year 1990 to 2015, reducing the Maternal Mortality Rate (MMR) has been the fifth goal of the Millennium Development Goals (MDGs). With Sustainable Development Goals (SDGs), World Health Organization (WHO) has aimed to reduce global MMR as low as 70 cases out of 100.000 live birth in 2030.<sup>4</sup> According to Survei Antar Sensus (SUPAS), in 2015, Indonesia's MMR was as high as 305 cases out of 100.000 live birth. This number accounts for Indonesia as a country with the second-highest MMR in the South East Asia region, preceded by Laos with MMR as high as 357 cases out of 100.000 live birth.<sup>5</sup> This study aimed to investigate the characteristics of maternal deaths in Prof. dr. R.D Kandou Hospital, Manado, Indonesia, in 2019.

## MATERIALS AND METHODS

This study was designed as a retrospective descriptive study. Data was taken from medical records of patients in Obstetrics and Gynecology Department at Prof. dr. R.D. Kandou Hospital, Manado, Indonesia, dated from January 1 to December 31, 2019.

## RESULTS AND DISCUSSION

According to the Obstetrics and Gynecology Department study at Prof. dr. R.D. Kandou Hospital, Manado, in January 1 to December 31, 2019 period, 1.215 cases of single live birth were registered, 22 cases of which were maternal death. Characteristics of maternal deaths are shown in the following tables.

Table 1. Characteristics of maternal deaths according to age and parity

Characteristics	N	%
Age		
< 20	2	9.09
20 – 34	15	68.18
≥ 35	5	22.73
Parity		
1	9	40.91
2 – 4	12	54.54
≥ 5	1	4.55
Total	22	100

Table 1 presents the highest number of patients were from 20 – 34 years of age group, comprising 15 patients (68.18%), whereas the highest parity ranged from 2 – 4, comprising 12 patients (54.54%). In contrast, <20 years old of age group and ≥ 5 parities has the lowest number of patients, in each amounting to 2 patients (9.09%) and 1 patient (4.55%).

Table 2. Antenatal care (ANC) number of visit

ANC Number of Visit	N	%
0	2	9,09
1 – 3 times	11	50
≥ 4 times	9	40,91
Total	22	100

Table 2 presents the number of visits to Antenatal Care (ANC) in which the highest number of visitations ranged from 1 – 3 times, amounting to 11 cases (50%).

Table 3. Distribution of referral origin in maternal mortality cases

Referral Origin	N	%
Manado City	10	45.46
Outside of Manado City	12	54.54
Total	22	100

Table 3 presents the highest number of patients which originated from outside of Manado City, comprising 12 patients (54.54%).

Table 4. Maternal mortality causes

Causes of Mortality	N	%
Hemorrhage	6	27.27
Sepsis	6	27.27
Eclampsia	8	36.36
Amniotic Fluid Embolism	1	4.55
Heart Failure	1	4.55
Total	22	100

Table 4 presents hospital admission cases in which the most frequent cause of maternal mortality was eclampsia, amounting to 8 cases (36.36%). Sepsis and hemorrhage each accounted for 6 cases (27.27%), respectively, whereas amniotic fluid embolism and heart failure were each responsible for 1 case (4.55%). Whereas, total maternal mortality cases at Prof. dr. R.D. Kandou General Hospital Manado was up to 22 cases out of 1.215 live birth.

## DISCUSSION

Based on research conducted at the Obstetrics and Gynecology Department of Prof. dr. R.D. Kandou, Hospital, Manado for January 1 to December 31, 2019 [Table 1](#) presents the highest number of mortalities at the age of 20 – 34 years old, consisting of 15 people (68.18%). This finding is in accordance with a study conducted by Blanc et al. in 2013 in a total of 38 countries, which stated that the 20 - 34 years of age group had the highest maternal mortality cases due to such age group being the most frequent age of women to give birth; therefore, preventive measures that are directed towards this age group to reduce the numbers of mortality would effectively be beneficial.<sup>6</sup>

In terms of parity, 2–4 parities accounted for the highest number of patients as high as 12 patients (54.54%); meanwhile,  $\geq 5$  parities held the least patient, which was only in 1 patient (4.54%). These findings were consistent with a study conducted by Aeni in 2013 and Zein in 2014 regarding risk factors for maternal death, which stated that there was no correlation between parity and mortality risk.<sup>7,8</sup> However, these results were inconsistent with 4T theory about pregnancy risk factors categorized as 'too much', which explains that too many births contribute to maternal mortality. Based on this inconsistency, another potential cause that may not have been studied, namely the period between pregnancies, might potentially influence maternal mortality besides the number of parity.

Regarding the number of Antenatal Care (ANC) visits, 1–3 ANC visits held the highest number of maternal mortalities with 11 cases (50%). The World Health Organization (WHO) ANC recommendation uses the Four-visit focused ANC (FANC) model, which has been replaced by the 2016 WHO ANC model, namely 8 visits to improve the quality of ANC and reduce maternal and perinatal mortality. In 2016, WHO recommends ANC with a minimum of 8 visits, with the first visit accomplished within the first trimester ( $> 12$  weeks), 2 visits within the second trimester (20-26 weeks), and 5 visits within the third trimester (30, 34, 36, 38, and 40 weeks).<sup>9</sup>

Based on the referral's origin, most of the admitted patients were from outside of Manado City, accounting for 12 patients (54.54%), compared to within the city that covered up to 10 patients (45.45%). The fact that Prof. dr. R.D. Kandou Hospital is a type A referral center hospital in North Sulawesi, Indonesia, might justify a large number of patients that originated from outside of Manado City. According to a study conducted by Laili in 2013, a well-established and well-planned obstetric referral system would reduce maternal mortality. This is due to the referral system being a part of health attempts that fall within the national health system's scope, aiming to improve maternal and children's welfare. This referral is associated with the patient's visit to the health center, in this matter, namely community health centers, doctors' practices, and hospitals. The implementation of referrals, in this matter, is the referral timing following operational standards, which may assist in the early management of obstetric cases. In addition, patients with poorly educated knowledge about their health condition or pregnancy risk factor may lead to negligent behavior towards the pregnancy and tend to have their pregnancy less likely to be checked. Economic burden and delayed management in healthcare facilities by healthcare workers may also appear as promoting factors that lead to an inability to maximally treat obstetrics cases.<sup>10,11</sup>

Based on maternal mortality causes, this study's results indicated that the most frequent maternal mortality was due to eclampsia, which was in 8 cases (36.36%). Sepsis and bleeding covered up to 6 cases (27.27%), respectively, whereas amniotic fluid embolism and heart failure covered up to 1 case (4.54%). This result was consistent with the preceding research at Prof. dr. R.D. Kandou Hospital regarding the cause of maternal mortality in 2013 - 2015, which found that eclampsia was the highest cause of maternal mortality.<sup>12</sup>

According to the research conducted by Ghulmiyyah in 2012, eclampsia increases the risk of maternal death in developing countries. High maternal mortality may occur, especially in patients who have had multiple seizures outside the hospital and those who did not undergo prenatal care. In addition, this high mortality rate can be attributed to the lack of resources and intensive care facilities needed to manage maternal complications of eclampsia. Pregnancy complications with eclampsia were also associated with increased maternal mortality, such as placental abruption, DIC, pulmonary edema, aspiration pneumonia, and cardiopulmonary arrest.<sup>13</sup> However, this finding was inconsistent with maternal mortality causes according to the data from the Indonesian Ministry of Health 2014, namely hemorrhage during the 2010 – 2013 period.<sup>1</sup>

In this study, 22 cases of maternal death out of 1215 single live births were recorded. The number of maternal mortality cases in 2019 has decreased by 24 cases compared with those in 2018. Overall maternal mortality may be caused by low public awareness towards pregnancy health, despite the fact that many factors remain to be considered regarding this matter.

The mortality that occurs is due to common indications as hemorrhage, eclampsia, abortion, and infection. However, other factors are also essential; for example, lack of women's empowerment, educational background, family socioeconomic factor, community environment, political settings, and policies are likewise influencing factors. Men are also expected to actively participate in all reproductive matter problems in a more responsible manner. Apart from medical matters, a high number of maternal mortalities may also result from gender inequality issues, cultural values, economic matters, and lack of men's attention towards pregnancy and childbirth. Therefore, perspectives that consider pregnancy as a natural occasion must be adjusted in a sociocultural way, that such adjustment might lead women to gain more consideration from society. An attempt to improve maternal care is required by the government, private sector, and society, especially men.<sup>14,15</sup>

## CONCLUSION

Maternal death cases in Obstetrics and Gynecology Department of Prof dr. R.D. Kandou Hospital, Manado, Indonesia, in 2019 were as high as 22 cases out of 1.215 live birth cases. Eclampsia remained the most frequent cause responsible for maternal mortality cases.

## REFERENCES

1. Ministry of Health, Republic of Indonesia. Situasi kesehatan ibu [Maternal health situation]. Infodatin. Jakarta. 2014.
2. Ministry of Health, Republic of Indonesia. Profil kesehatan Indonesia 2015 [Health profile of Indonesia 2015]. Jakarta; 2015.
3. Ministry of Health, Republic of Indonesia. Rencana aksi percepatan penurunan angka kematian ibu di Indonesia [Action plan for accelerating reduction of maternal death rate]. Jakarta; 2015.
4. WHO. Trends in Maternal Mortality: 1990 to 2015. Geneva: World Health Organization. 2015
5. Badan Pusat Statistik (BPS) [Statistics Indonesia]. Profil penduduk Indonesia hasil SUPAS 2015. Jakarta: Badan Pusat Statistik. 2015
6. Blanc AK, Winfrey W, Ross J. New finding for maternal mortality age patterns: Aggregated result for 38 countries. PLoS ONE. 2013;8(4):23-5. doi: 10.1371/journal.pone.0059864
7. Aeni N. Faktor risiko kematian ibu [Risk factors of maternal death]. Kesmas: Jurnal Kesehatan Masyarakat Nasional (National Public Health Journal), [e-journal]. 2013;7(10):453-9. doi: 10.21109/kesmas.v7i10.4
8. Zein F, Budiman, Yulianto FA. Hubungan tingkat pendidikan dan jumlah paritas dengan kematian ibu di Kabupaten Bandung tahun 2014 [Correlation between level of education and number of parity with maternal death]. Bandung: Universitas Islam Bandung Repository; 2015.
9. WHO. WHO recommendations on antenatal care for positive pregnancy experience. Geneva: World Health Organization. 2016.
10. Laili F. Hubungan faktor risiko kegawatdaruratan obstetri menurut Rochjati dengan pelaksanaan rujukan oleh bidan di RSUD Gambiran Kediri. Bandung [Correlation between risk factor of obstetric emergency according to Rochjati and referral implementation]. Jurnal Pendidikan dan Pelayanan Kedokteran Indonesia. 2014;23-7. doi: 10.24198/ijemc.v2i2.11
11. Karlsen S, Say L, Souza JP, et al. The relationship between maternal education and mortality among women giving birth in health care institutions: Analysis of the cross sectional WHO Global Survey on Maternal and Perinatal Health. BMC Public Health 2011;(11)606. doi: 10.1186/1471-2458-11-606.
12. Lumbanraja, MS, Tendean HM, Loho M. Gambaran kematian maternal di RSUP Prof. Dr. R.D. Kandou Manado [Profile of maternal death in Prof. Dr. RD Kandou Hospital]. Jurnal e-Clinic (eCl), [e-journal]. 2015;4(2): 1-5. doi: 10.35790/ecl.v4i2.14595
13. Ghulmiyyah L, Sibai B. Maternal mortality from preeclampsia/eclampsia. Semin Perinatol. 2012;36 (1):56-9. doi: 10.1053/j.semperi.2011.09.011. PMID: 22280867.
14. Puti SH, Hapsari S, Dharmayanti I, et al. Faktor-faktor yang berpengaruh terhadap risiko kehamilan "4 Terlalu (4-T)" pada wanita usia 10-59 tahun (Analisis Riskesdas 2010) [Risk factors of pregnancy risk of "Four Too's" in women aged 10-59 years]. Media Litbangkes. 2014;24(3):143-52.
15. Mundayat AA, Noerdin E, Agustini E, et al. Target MDGs menurunkan angka kematian ibu tahun 2015 sulit dicapai [MDGs target to reduce maternal death rate in 2015 is hard to reach]. Woman Research Institute, 2015.

## ORIGINAL ARTICLE

## Hot herbal compresses as therapy for reducing labor pain levels in the first stage of active phase in primigravida

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## ABSTRACT

**Objective:** To prove the effect of providing hot herbal compresses as a therapy for reducing the level of labor pain in the first stage of the active phase of primigravida

**Materials and Methods:** This was a true experimental study using pretest and posttest designs with control group. There was an intervention group (n=19) which was provided with hot herbal compress therapy for 20 minutes with a temperature between 37-51.5°C and a control group (n=19) receiving breathing exercise therapy. Respondents were selected by inclusion and exclusion criteria and randomization was carried out to determine whether the respondents were included in the intervention or control group by drawing lots.

**Results:** Hot herbal compress therapy reduced the level of labor pain in the first active phase at the 1st hour treatment by 49.3% (p=0.000), the 2nd hour by 50.3% (p=0.000), and the third hour by 22.4% (p=0.009).

**Conclusion:** Hot herbal compresses have an effect as a therapy for reducing pain levels of labor in the first stage of the active phase of primigravida.

**Keywords:** hot herbal compress; labor pain; maternal health

## ABSTRAK

**Tujuan:** Membuktikan pengaruh pemberian kompres hot herbal sebagai terapi pengurangan tingkat nyeri persalinan kala I fase aktif primigravida

**Bahan dan Metode:** Penelitian true experiment dengan desain pretest and posttest with control group. Terdapat kelompok intervensi (n=19) yang diberikan terapi kompres hot herbal selama 20 menit dengan suhu antara 37-51,5°C dan kelompok kontrol (n=19) yang diberikan terapi latihan napas. Penentuan responden dengan kriteria inklusi dan eksklusi serta dilakukan randomisasi untuk menentukan responden masuk kelompok intervensi atau kontrol dengan cara diundi.

**Hasil:** Terapi kompres hot herbal menurunkan tingkat nyeri persalinan kala I fase aktif pada perlakuan jam ke-1 sebesar 49,3% (p=0,000), jam ke-2 sebesar 50,3% (p=0,000), dan jam ke-3 sebesar 22,4 % (p=0,009).

**Simpulan:** Kompres hot herbal berpengaruh sebagai terapi pengurangan tingkat nyeri dan durasi persalinan kala I fase aktif primigravida.

**Kata kunci:** kompres hot herbal; nyeri persalinan; kesehatan ibu

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## INTRODUCTION

Labor pain is one of the physiological events that occurs during labor, but this pain is reported that was the most severe degree of pain experienced by women during their lives.<sup>1</sup> It is reported that about 60% of primigravida and 40% multigravida women experience very severe pain levels.<sup>2</sup> The results of another studies showed that, in 21 primigravida respondents who experienced mild pain level were only 4.8%, the majority of 47.6% had severe pain and those with very severe pain were 47.6%.<sup>3</sup> In addition, other studies have shown that the average level of pain in the first stage of primigravida was 3.97, much more severe than multigravida, which was 2.69.<sup>4</sup> Labor pain continuously increases maternal anxiety and can stimulate the sympathetic nervous system so that the amount of catecholamines increases. Increased of catecholamines causes the decrease of blood flow to the uterus due to vasoconstriction and will interfere uterine contractions, inadequate oxygenation of the baby up to fetal distress, and also prolonged labor.<sup>5</sup> For several reasons, it is necessary to take action to reduce pain in labor.

Pharmacological methods such as intravenous analgesic drugs (morphine and fentanyl), inhaled analgesics, and nerve block methods can cause side effects to the mother such as the risk of aspiration, dizziness, nausea and adverse effects on the fetus, especially respiratory depression. Another pharmacological method is the use of epidural analgesia, but this method requires a large cost. In addition, the results of the study showed side effects in the form of prolonged labor, increased incidence of delivery with the help of devices such as cesarean section due to fetal distress, increased risk of hypotension, fever, and increased breastfeeding problems.<sup>6</sup>

Hot herbal compress is a traditional medicine from Thailand and is a non-pharmacological method that creates a feeling of warmth, analgesic and aromatherapy effects for relaxation from the herbal ingredients contained in it, namely bangle, turmeric, *temu putih*, lemongrass, kaffir lime peel, camphor, and salt. The herbs are natural ingredients that are often found in Indonesia. Previous research has proven that hot herbal compresses can reduce the intensity of breast engorgement with an average decrease in pain intensity was 5.9 compared to only warm compresses which was 3.1 ( $p < 0.001$ ) and there are no reports of respondents who experienced side effects.<sup>7</sup> In addition, hot herbal compresses can reduce myofascial pain on day 16 of the treatment compared to warm compresses and the use of topical diclofenac.<sup>8</sup> Another study showed that hot herbal compresses were effective in reducing the height

of uterine fundus, lochia volume and intensity of afterpains in postpartum with  $p < 0.05$ .<sup>9</sup>

Until October 2020, the number of deliveries with live births in the city of Semarang, Indonesia, was 16,321, with the highest number of live births being in public health centers in the areas of Bandarharjo, Bangetayu, Tlogosari Kulon, and Sronдол. Those public health centers did not use hot herbal compresses to reduce pain levels during the active phase of the first stage of labor and there was no research on this. This study aimed to identify effect of hot herbal compresses to reduce pain levels and duration of labor in the first stage of the active phase.

## MATERIALS AND METHODS

This study used true experimental design with pretest and posttest and control group. The study was conducted at the Public Health Centers of Sronдол, Ngesrep, Halmahera, Bangetayu, Tlogosari Kulon, PMB Hj. Thoiffah, Klinik Esti Husada and PMB Eka Tlogosari, all in Semarang, Indonesia, from March to April 2021. There were 2 groups in this study, the intervention group and the control group. The population in this study was an infinite population with criteria for primigravida mothers aged between 20-35 years with gestational age 37 - 42 weeks with normal pregnancy. The sampling technique used in this study was simple random sampling. The number of respondents in the intervention group was 19 respondents and those in the control group was also 19.

The intervention group was provided with hot herbal compress therapy and the control group only received breathing exercise therapy as standard care. Hot herbal compresses was steamed for 15 minutes to bring out the active ingredients contained in the hot herbs. The respondent's pain scale was observed with the VAS (pretest) and the time when the intervention began was recorded. After steaming for 15 minutes, the hot herbal was re-coated using a clean and dry cloth so as not to cause heat irritation to the skin and the temperature of the hot herbal was first adjusted to 51.5°C using a thermometer. Compression was given to the respondent starting from the opening of 4-5 cm in the first stage of the active phase for 20 minutes at the point of the mother's sacrum. Then the pain scale was re-observed after the hot herbal compress (posttest) was provided. The herbal hot compress was provided again for 20 minutes after 1 hour from the previous intervention. Interventions were provided until complete opening was reached.

Table 1. Characteristics of respondents based on age, parity, anxiety, family support, and contraction scores in the intervention and control group

Characteristics	Groups						p
	Intervention			Control			
	n	(%)	Mean ± SD	n	(%)	Mean ± SD	
Age							
20 – 35 year	19	100	25.11 ± 2.536	19	100	23.21 ± 2.594	0.852 <sup>a</sup>
Parity							
Primigravida	19	100	-	19	100	-	1,000 <sup>a</sup>
Anxiety							
Mild anxiety	16	84.2	11.21 ± 5.062	13	68.4	15.05 ± 4.249	0.661 <sup>a</sup>
Moderate anxiety	3	15.8		6	31.6		
Contraction							
Normal	15	78.9	-	4	21.1	-	1.000 <sup>a</sup>
Abnormal	4	21.1		15	78.9		
Baby Birth Weight	-	-	3084.21 ± 177.21	-	-	3000.00 ± 200.00	0.989 <sup>a</sup>
Family support							
Moderate	3	15.8	47.21 ± 6.696	1	5.3	47.11 ± 4.280	0.119 <sup>a</sup>
High	16	84.2		18	94.7		

<sup>a</sup>: Levene's test statistic

This study had been approved by the ethics commission of Sultan Agung Islamic University, Semarang, Indonesia, No. 37/II/2021/Komisi Bioetik. Respondents' data were kept confidential and informed consent was used to obtain the respondents' consent. Paired t-test and independent t-test were used for data with normal distribution, and to determine the effectiveness of the intervention (magnitude of influence) the repeated ANOVA test was used. Data were analyzed with SPSS type 22.0.

## RESULTS AND DISCUSSION

### Confounding variable analysis

Table 1 shows that the data on age, parity, age of pregnancy, anxiety scores, contraction strength, baby weight, and family support had a p value > 0.05 so that there was no statistically significant difference between the intervention group and the control group or, in other words, the two groups had the same data variance (homogeneous). The magnitude of the effect of the administration of hot herbal compresses in reducing labor pain in the first stage of the active phase is shown in Table 2.

Table 2. The effectiveness of herbal hot compresses on reducing labor pain levels in the active phase

Labor pain	Mean Difference	p <sup>a</sup>	Effect size (%) <sup>b</sup>
Pretest 1 vs. Post 1	1.956	0.000	49.3
Post 1 vs. Post 2	0.287	0.000	50.3
Post 2 vs. Post 3	0.056	0.009	22.4

<sup>a</sup>: Repeated Anova

<sup>b</sup>: Eta Squared

The results of the analysis in Table 2 shows that the level of pain from pretest 1 to posttest treatment at first hour, posttest treatment at 1st hour to posttest treatment at 2nd hours, and from posttest treatment at 2nd hours to posttest treatment at 3rd hours had a p-value <0.05 so showing that the administration of hot herbal compress therapy was effective in reducing the level of labor pain in the active phase of the first stage at pretest 1 to post 1, post 1 to post 2, and post 2 to post 3, ranging from 22.4% to 50.3%. The most remarkable effect occurred in posttest 1 to posttest 2, which was 50.3%.

### Relationship of confounding variables to dependent variables

#### Age

A good, healthy and safe reproductive age is 20-35 years. The age of the mother determines her health status and it also relates to the maturity of the reproductive organs and psychological conditions. High risk may be present if the pregnant woman is < 20 years old or > 35 years old. A mother aged <20 years is biologically and emotionally not optimal and tends to be more unstable. In this study, the majority of the new mothers were in this age range. They had their first experience in giving birth so it caused anxiety in dealing with childbirth and resulted in more severe pain felt. Meanwhile, pregnant women aged >35 years feel anxious because they may have more risks in the process of pregnancy and childbirth. Research shows that the age factor is significantly related to labor pain with a p-value <0.05.<sup>10,11</sup>

## Parity

Previous childbirth experience will help the mother in dealing with pain because in this case the mother's body already has a coping mechanism for pain. Mothers who have given birth for the first time will experience more anxiety and worry when facing labor because they have not experienced labor pain before. This will make the perception of pain higher in the first labor than in the second or more labor. In the second or more labor it does not mean that the mother does not feel pain, but because the mother has had previous experiences or even pleasant experiences, it will affect the perception of the mother's pain to be reduced and make the mother feel more comfortable in dealing with her delivery.

The results showed that mothers who had never had a previous birth experience or were primigravida experienced more severe pain intensity in the first stage than multigravida mothers. Of the 21 primigravida respondents, only 4.8% experienced mild pain intensity, the majority were 47.6% severe pain and 47.6% very severe pain.

## Family support

The majority of the respondents, both in intervention and control groups, received high family support. Respondents between the intervention and control groups had the same or homogeneous family support data variance ( $p > 0.05$ ). Family support, especially from the husband when giving birth will affect the mother's level of anxiety in the form of inner peace, feelings of calm, security and comfort so that the anxiety felt by the mother will be reduced. This will trigger catecholamine levels in the blood to drop to normal. This normal level of catecholamines will cause smooth muscles to relax and trigger vasodilation of blood vessels so that blood and oxygen flow increases to the uterus and the pain that the mother feels is reduced.<sup>12,13</sup>

## Anxiety

The anxiety experienced by the majority of respondents was mild anxiety. Respondents between the intervention and control groups had the same variance or homogeneous anxiety score data ( $p > 0.05$ ). Anxiety and fear will increase muscle tension and interfere with blood flow to the brain and muscles. Anxiety in labor will cause tension in the pelvic muscles, uterine muscle tension or uterine contractions are disrupted. Muscle tension that lasts for a long time will cause the mother to be tired and the mother's power factor will be lost during the second stage so that it will increase the perception of pain and reduce the mother's ability to

control her pain.<sup>14</sup> Anxiety and pain can cause stress in the mother so that it triggers the release of the hormone adrenaline. This will cause vasoconstriction of blood vessels so that the blood flow that carries oxygen to the uterus is reduced and results in decreased uterine contractions and the duration of labor becomes longer.<sup>15</sup>

## Baby birth weight

The average birth weight in the intervention group was 3084.21 grams, not much different from the control group average, which was 3000 grams. It can be seen that the birth weight variable has the same or homogeneous data variance between the intervention group and the control group ( $p > 0.05$ ). Birth weight can affect the delivery process because the greater the birth weight of a baby, it will affect the mother's pushing power and the risk of delivery due to shoulder dystocia. Macrosomic babies will trigger labor with shoulder dystocia which is characterized by no progress in the labor process so that the labor process takes a long time.<sup>16</sup>

## Contraction strength

The contraction strength variable had a homogeneous variance between the intervention group and the control group. The majority of respondents in the intervention group had normal contraction strength of 78.9% while in the control group it was only 21.1%. In the group that received hot herbal compresses, the majority of respondents had normal contractions because the active ingredients in the herbs used in hot herbs such as curcumin, naringenin and apigenin can play a role in reducing levels of matrix metalloproteinase-9 which causes the endometrium to contract so that it can cause its opening in the uterus, allowing the childbirth.<sup>17</sup>

## Hot herbal compresses in reducing the level of labor pain in the active phase

The results showed that the intervention group which received hot herbal compress therapy for 20 minutes until complete dilatation experienced a decrease in pain scale more than the group given breathing exercises until complete opening ( $p < 0.05$ ). The use of hot herbal compresses was effective in reducing the level of pain in the first stage of the active phase at 1, 2, and 3 hours of treatment when compared to the control group with the magnitude of the effect between 22.4-50.3%.

Previous research has shown that herbal hot compresses can be used as alternative analgesic therapy. It can reduce the level of breast swelling pain by 5.9 while the warm compress group only experienced a decrease of 3.1.7 In addition, other studies have proven that hot



herbal compresses given for 20 minutes every day for 10 days in postpartum women can accelerate the decrease in the intensity of afterpains than the group given uterine massage. Providing hot herbal compresses is effective in reducing the intensity of afterpains on days 1 to 4 of the postpartum period with an effect size of 10%-18.7%.<sup>9</sup>

This study proved that breathing exercises reduced labor pain less than hot herbal compresses. This was because hot herbal compresses had advantages over breathing exercises as it contains active ingredients from the herbs used, warm effects and aromatherapy effects from essential oils which are analgesic and relaxing so that they triggered the release of endorphins as pain impulse inhibitors.

The content of the active ingredients in hot herbal compresses will come out when heated, one of which is by steaming.<sup>18</sup> The content of active ingredients such as lipopolysaccharide, compound D or dimethoxyphenyl, curcumin, naringenin, apigenin, curcumenol, and steroids will act by inhibiting the action of COX-2 enzymes and substance P, where these enzymes act in synthesizing prostaglandins. Substance P and prostaglandins as pain mediators that are inhibited will interfere with the transmission of pain impulses to the brain.<sup>17,19-23</sup> Luteolin content acts in its analgesic activity by activating opioid receptors and inhibiting the release of inflammatory mediators.<sup>24</sup> Other ingredients such as eugenol which when used topically can activate Transient Receptor Potential Vanilloid 1 (TRPV 1). These receptors function as antinociceptive or inhibit pain sensors from being transmitted to C fibers.<sup>25</sup>

In addition to the herbal content that has an analgesic effect, herbal hot compresses also produce a warm effect. Heat stimulation received by receptors in the hypothalamus will trigger vasodilation, causing increased blood flow to tissues, especially those experiencing inflammation and pain, resulting in a decrease in pain.<sup>26</sup>

#### Research limitations

In this study, it was not possible to control the possibility of differences in the position of the mother during childbirth and the history of exercise or pregnancy exercise which could confound the duration of active phase I labor. In addition, the authors were unable to make the temperature used in hot herbal compresses to be stable at a certain desired temperature so that the decrease in the temperature of the compress was still very likely to be influenced by external factors such as room conditions and wind.

## CONCLUSION

Hot herbal compresses with temperatures between 51.5-37°C for 20 minutes applied to mother's sacrum at the 1st hour, 2nd hour, and 3rd hour treatment had an effect in reducing labor pain in the first stage of the active phase of primigravida by 49.3% at the 1st hour after treatment, 50.3% at the 2nd hour and by 22.4% at the 3rd hour. Future studies are recommended to develop hot herbal compress product to make it easier to use with a stable temperature level.

## REFERENCES

1. Ozgoli G, Sedigh Mobarakabadi S, Heshmat R, et al. Effect of LI4 and BL32 acupressure on labor pain and delivery outcome in the first stage of labor in primiparous women: A randomized controlled trial. *Complement Ther Med*. 2016;29:175-180. doi: 10.1016/j.ctim.2016.10.009. Epub 2016 Oct 15. PMID: 27912944.
2. Bobak Iea. *Keperawatan maternitas [Maternity nursing]*. Jakarta: EGC, 2012.
3. Ayu ES NGM. Karakteristik ibu bersalin kaitannya dengan intensitas nyeri persalinan kala I di kota Bogor [Characteristics of delivery mothers and labor pain intensity phase I]. *Jurnal Kebidanan Malahayati*. 2017;3: 204-10. doi: 10.33024/jkm.v3i4.629
4. Magfuroh A. Faktor-faktor yang berhubungan dengan nyeri persalinan kala I fase aktif di Ruang Bersalin Rumah Sakit Umum Kabupaten Tangerang Tahun 2012 [Factors related to labor pain active phase I]. Repository. Jakarta: UIN Syarif Hidayatullah; 2012.
5. Klomp T, de Jonge A, Hutton EK et al. Dutch women in midwife-led care at the onset of labour: which pain relief do they prefer and what do they use? *BMC Pregnancy Childbirth*. 2013;13:230. doi: 10.1186/1471-2393-13-230.
6. Jones L, Othman M, Dowswell T, et al. Pain management for women in labour: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2012;2012(3):CD009234. doi: 10.1002/14651858.CD009234.pub2. PMID: 2241 9342; PMCID: PMC 7132546.
7. Ketsuwan S, Baiya N, Paritakul P, et al. Effect of herbal compresses for maternal breast engorgement at postpartum: A randomized controlled trial. *Breastfeed Med*. 2018;13(5):361-365. doi: 10.1089/bfm.2018.0032. Epub 2018 Apr 24. PMID: 29688768.
8. Boonruab J, Nimpitakpong N, Damjuti W. The distinction of hot herbal compress, hot compress, and topical diclofenac as myofascial pain syndrome



- treatment. *J Evid Based Integr Med.* 2018;23: 2156587217753451. doi: 10.1177/ 21565872177 53451. PMID: 29405762; PMCID: PMC5871049.
9. Karimah N. Hot herbal compress sebagai terapi alternatif involusi uterus dan afterpains pada ibu nifas: Studi di kota dan Kabupaten Semarang [Hot herbal compress as alternative therapy for uterine involution and afterpains in postpartum mothers]. Prodi Magister Terapan Kebidanan. Semarang: Poltekkes Kemenkes Semarang, 2020.
  10. Afritayeni A. Hubungan umur, paritas dan pendamping persalinan dengan intensitas nyeri persalinan kala I [Correlation between age, parity and companion in labor with stage I pain intensity]. *Jurnal Endurance.* 2017;2:178-85. doi: 10.22216/jen.v2i2.1852
  11. Adam J. Hubungan antara umur, parietas dan pendamping suami dengan intensitas nyeri persalinan kala I fase aktif deselerasi di Ruang Bersalin RSUD Prof. Dr. H. Aloei Saboe Kota Gorontalo [Correlation between age, parity, and husband companion with pain intensity during active deceleration phase of stage I of labor]. *JIKMU.* 2015; 5.
  12. Manuaba I. Penuntun kepaniteraan klinik obstetri dan ginekologi [Guidelines for obstetric and gynecologic internship]. Jakarta: EGC, 2003.
  13. Yuliantanti T, Nurhidayati N. Pendampingan suami dan skala nyeri pada persalinan kala I fase aktif [Husband companion and pain scale during active phase I of labor]. *Bidan Prada: Jurnal Ilmiah Kebidanan.* 2013; 4:1-14.
  14. Tzeng YL, Yang YL, Kuo PC, et al. Pain, anxiety, and fatigue during labor: A prospective, repeated measures study. *J Nurs Res.* 2017 ;25(1):59-67. doi: 10.1097/jnr.000000000000165. PMID: 28072678.
  15. Soviyati, E. Faktor-Faktor yang Berhubungan dengan Lama Persalinan di RSUD'45 Kuningan Jawa Barat Tahun 2015. [Factors related to the duration of labor]. *Jurnal Bidan,* 2016;2(1):33-43.
  16. Ruqaiyah R, Asrianingsih D, Yusuf SY. Faktor yang berhubungan terhadap kejadian partus lama di Rumah Sakit AL Jala Ammari Makassar 2019 [Factors related to lengthy labor duration]. *Jurnal Kesehatan Delima Pelamonia.* 2019;3(2).
  17. Lim R, Barker G, Wall CA, Lappas M. Dietary phytochemicals curcumin, naringenin and apigenin reduce infection-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium. *Mol Hum Reprod.* 2013;19(7): 451-62. doi: 10.1093/molehr/gat015. Epub 2013 Mar 7. PMID: 23475986.
  18. Chotikamas S, Cheenkachorn K, Wongpanit B, et al. Chemical profiling analysis and identification the bioactivities of herbal compress extracts. *MATEC Web of Conferences* 2018; 187. doi: 10.1051/mateconf/201818701001.
  19. Koontongkaew S, Meesuk L, Aupaphong V, et al. Inhibitory effect of Zingiber cassumunar extracts on lipopolysaccharide-induced cyclooxygenase-2 and matrix metalloproteinase expression in human gingival fibroblasts. *J Periodontal Res.* 2013;48(4): 507-16. doi: 10.1111/jre.12033. Epub 2012 Dec 30. PMID: 23278498.
  20. Khemawoot P, Hunsakunachai N, Anukunwithaya T, et al. Pharmacokinetics of compound D, the major bioactive component of zingiber cassumunar, in rats. *Planta Med.* 2016;82(13):1186-91. doi: 10.1055/s-0042-104658. Epub 2016 Apr 28. PMID: 27124244.
  21. Kumar AD, Singh J, Anup. A review on spice of life curcuma longa (*turmeric*). *Int J Appl Biol Pharmaceut Tech.* 2011; 2: 371-9.
  22. Das K, Rahman MA. Analgesic and antimicrobial activities of Curcuma zedoaria. *International Journal of Pharmacy and Pharmaceutical Sciences.* 2021;4:322-8.
  23. Youkwon J, Sutthivaiyakit S, Sutthivaiyakit P. Citrusosides A-D and furanocoumarins with cholinesterase inhibitory activity from the fruit peels of Citrus hystrix. *J Nat Prod.* 2010;73(11): 1879-83. doi: 10.1021/np100531x. Epub 2010 Oct 21. PMID: 20964319.
  24. Garcia RF, Pinto Costa J, Santos G, et al. Evaluation of anti-inflammatory and analgesic activities of Cymbopogon citratus in vivo-polyphenols contribution. *Research Journal of Medicinal Plant.* 2015; 9: 1-13. doi: 10.3923/rjmp.2015.1.13
  25. Hamidpour R, Hamidpour S, Hamidpour M, Shahlari M. Camphor (*Cinnamomum camphora*), a traditional remedy with the history of treating several diseases. *International Journal of Case Reports and Images* 2013;4(2):86-89. doi: 10.5348/ijcri-2013-02-267-RA-1
  26. Tamsuri A. Konsep dan penatalaksanaan nyeri [Pain concept and management]. Jakarta: EGC, 2007.

## ORIGINAL ARTICLE

**Contraception method among pregnant women with HIV delivered in Cipto Mangunkusumo General Hospital, Jakarta, Indonesia****Junita Indarti<sup>1</sup> \*, Shinta Pangestu<sup>2</sup> , Adri Dwi Anggayana<sup>2</sup> , Cherysa Rifiranda<sup>2</sup> , Natasya Prameswari<sup>2</sup> , Kristian Alda<sup>2</sup> **

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**ABSTRACT**

**Objectives:** The aim of this study was to describe characteristics of contraceptive methods among women with HIV infection who delivered in a tertiary hospital.

**Materials and Methods:** This was a cross-sectional study. The inclusion criteria were pregnant women with HIV infection who delivered in Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia, from January 2016 to December 2020. Data were retrieved from medical records, registered HIV and laboratory result. The included data were demographic data, obstetric data, mode of delivery, contraception method, ARV history, and laboratory history of the mothers.

**Results:** From January 2016 to December 2020 there were 119 HIV patients who delivered at the RSCM. Most of the subjects were 35 years old (84%), had low education (52.9%) and worked as housewives (76.5%). A total of 79.8% of the subjects were gravida  $\geq 2$  and most of the subjects delivered by caesarean section (87.3%). The choice of contraceptive methods were IUD (72.4%), tubectomy (26.8%) and implants (0.8%). There was a statistically significant relationship between contraceptive method with age (p 0.040), gravida (p 0.016) and delivery method (p 0.049)

**Conclusion:** The most common contraceptive method was IUD. The choice of this method of contraception was related to age, gravida and method of delivery.

**Keywords:** Contraception; post-partum; HIV; IUD; gravida; method of delivery

**ABSTRAK**

**Tujuan:** Tujuan dari penelitian ini adalah untuk mendeskripsikan karakteristik metode kontrasepsi pada wanita dengan infeksi HIV yang melahirkan di sebuah rumah sakit tersier.

**Bahan dan Metode:** Penelitian ini merupakan penelitian *cross-sectional*. Kriteria inklusi adalah ibu hamil dengan infeksi HIV yang melahirkan di Rumah Sakit Cipto Mangunkusumo (RSCM), Jakarta, Indonesia, dari Januari 2016 sampai Desember 2020. Data diambil dari rekam medis, status HIV dan hasil laboratorium. Data yang disertakan adalah data demografi, data obstetri, metode persalinan, metode kontrasepsi, riwayat ARV, dan riwayat laboratorium pada ibu.

**Hasil:** Sejak Januari 2016 hingga Desember 2020 terdapat 119 pasien HIV yang melahirkan di RSCM. Sebagian besar subjek berusia  $\leq 35$  tahun (84%), berpendidikan rendah (52,9%) dan bekerja sebagai ibu rumah tangga (76,5%). Sejumlah 79,8% subjek adalah gravida  $\geq 2$  dan sebagian besar subjek melahirkan melalui operasi caesar (87,3%). Pemilihan metode kontrasepsi adalah IUD (72,4%), tubektomi (26,8%) dan implan (0,8%). Terdapat hubungan bermakna secara statistik antara metode kontrasepsi dengan umur (p 0.040), gravida (p 0.016) dan metode persalinan (p 0.049)

**Simpulan:** Metode kontrasepsi yang terbanyak adalah IUD. Pemilihan metode kontrasepsi ini berhubungan dengan usia, gravida dan metode persalinan.

**Kata Kunci:** Kontrasepsi; post-partum; HIV; IUD; gravida; metode persalinan

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## INTRODUCTION

In Indonesia, the number of people with HIV infection has also increased and also attacks young people. Until 2016, the number of HIV cases was 191,073 and AIDS 77,940.<sup>1</sup> There are more than 15 million pregnant women with HIV infection in developing countries and more than 500,000 HIV-infected babies were born every year. Based on previous studies, it was found that 2.5% of 21,103 pregnant women were diagnosed with HIV positive in 2011 in Indonesia.<sup>2</sup> Based on data in Cipto Mangunkusumo General Hospital (RSCM), Jakarta, Indonesia, in 2015-2019 there were 5.596 deliveries.<sup>3</sup> There were 20, 29, 21, 26 and 25 pregnant women diagnosed with HIV positive in those respective years with a total of 111 (1.9%) from 5.596 deliveries. In this study we observed data from 2016-2020 in which there were 119 HIV positive pregnancy deliveries.

In order to reduce HIV transmission from HIV positive mothers to their children, it is necessary to strengthen family planning programs and better integrate family planning and HIV services.<sup>4</sup> WHO sets the Medical Eligibility Criteria (MEC) category 1, in which there is no limit on the use of contraceptive methods, on the use of hormonal contraceptives, such as combined oral pills, combined contraceptive injection, patch, ring, pill and progestogen injection, as well as levonorgestrel and etonogestrel. Meanwhile, the use of LNG-IUD (levonorgestrel-intrauterine device) in HIV-positive women is classified as MEC category 2, which means that the benefits obtained are higher than the disadvantages of using contraception. Despite having lower MEC value, intrauterine devices (IUDs) is widely used in women with HIV positive cases, reaching 2.9% in women who are not infected with HIV.<sup>5</sup> HIV patients must use family planning to reduce the number of children.

## MATERIALS AND METHODS

This study design was a cross-sectional study. The population of the study was all pregnant and in labor women with HIV infection at RSCM from January 2016 up to December 2020. The inclusion criteria were pregnant women with HIV infection delivered at RSCM. The exclusion criteria were pregnant women with HIV infection who came to RSCM but did not deliver at RSCM. Respondents were recruited with total sampling method. Primary outcome of this study was contraception used by patients typically referred to our hospital due to their obstetric problem and/or their HIV status. Once the patients give birth, the obstetric care in coordination with HIV integrated service, especially for HIV, as well as co-morbidity and ARV treatment, offer the patients with some contraceptive methods. The aim

of this study was to observe the choice of contraception methods and the characteristic of each methods.

In the process of the study, we retrieved the registration book of pregnant patients who delivered in the delivery room. From these data, we obtained data on pregnant patients with HIV. The data was retrieved from medical records, HIV registry and laboratory results. Maternal demographic status observed consisting of age, education, and employment. The obstetric status comprised contraceptive method, the parity, gestational age at admission, delivery method, and neonatal outcome. HIV status of the mothers consisted of ARV consumption, CD4 level and viral load level. The collected data were presented as distribution and displayed in tables as number and percentage. Statistical analysis was performed using SPSS 23. Multiple Anova test was used for multiple variables. The level of significance was set to  $p < 0.05$ . This study had been approved by Ethical Committee of Faculty of Medicine Universitas Indonesia. No.: KET-169/UN2.F1/ETIK/ PPM.00.02/2021

## RESULTS AND DISCUSSION

There were a total of 119 pregnant women with HIV who delivered at RSCM from January 2016 to December 2020. Demographic data showed that most women were at  $\leq 35$  years old ( $n=100$ , 84%). Most of the subjects' last education was junior high school ( $n=55$ , 46.2%). Ninety-one pregnant women worked as housewife (76.5%).

On the obstetric status, most subjects had a history of multigravida  $\geq 2$  ( $n=95$ , 79.8%). They usually came at third trimester, with gestational age  $>36$  weeks ( $n=93$ , 78.2%) and delivered by cesarean section ( $n=104$ , 87.3%). For the contraception method, there were 86 subjects (72.4%) using IUD, 32 subjects (26.8%) underwent tubectomy during cesarean section and 1 subject (0.8%) using implant as contraception method. Among all babies born from the observed mothers, 118 were alive. Detailed data on distribution of maternal obstetric status can be seen on [Table 1](#). From 104 cesarean section, 31 (29.8%) patient used tubectomy as contraception method, while from 15 patient with vaginal delivery only 1 patient used tubectomy.

Ninety subjects (75.6%) had received ARV therapy, while 29 subjects (24.4%) had not received ARV. Unfortunately, data on the husbands' HIV status, maternal CD4 level and viral load were mostly not available (74.9%, 58% and 73%). Distribution of maternal HIV status can be seen on [Table 2](#).

Table 1. Distribution of maternal characteristic (2016-2020) (n=119)

Characteristic of subjects	n (%)
Age	
≤35 years	100 (84)
>35 years	19 (16)
Education	
Elementary	8 (6.7)
Junior high school	55 (46.2)
Senior high school	49 (41.2)
S1/Diploma	7 (5.9)
Employement	
Housewife	91 (76.5)
Employee	20 (16.8)
Self-employee	3 (2.5)
Others	5 (4.2)
Mode of delivery	
Vaginal delivery	15 (12.7)
Cesarean section	104 (87.3)
Contraception Method	
Implant	1 (0.8)
IUD	86 (72.4)
Tubectomy	32 (26.8)
Gravida	
1	24 (20.2)
≥ 2	95 (79.8)
Gestational age	
<32 weeks	3 (2.5)
32-36 weeks	23 (19.3)
>36 weeks	93 (78.2)
Neonatal outcome	
Live	118 (99.2)
IUFD	1 (0.8)

Table 2. Distribution of HIV status of the mothers

Characteristic of subjects	n (%)
ARV medication	
- On ARV	90 (75.6)
- Not yet therapy	29 (24.4)
Husband HIV status	
- Positive	11 (9.2)
- Negative	19 (15.9)
- No data	89 (74.9)
Mother's CD4 level	
- < 400 sel/uL	30 (25.2)
- ≥ 400 sel/uL	31 (26.1)
- N/A	58 (48.7)
Mother's viral load level	
<1000 copies/mL	36 (30.2)
>1000 copies/mL	10 (8.4)
N/A	73 (61.4)

From 100 subjects aged  $\leq 35$  years, 76 chose IUD, 23 used tubectomy and 1 subject used implant. Meanwhile, in subjects aged 35 years, 10 subjects chose to use IUD and 9 chose tubectomy. The relation between age of the subjects and the choice of family planning was statistically significant (P 0.04)

From 24 subjects with gravida one, 23 chose IUD and 1 used tubectomy, while in subjects with  $\geq 2$  gravida, 63 subjects chose IUD, 31 chose tubectomy and 1 used

implant. The relation between gravida and the choice of family planning was statistically significant (P 0.016).

From 104 patient with caesarian section delivery, 73 chose IUD and 31 used tubectomy. Meanwhile, in subjects with vaginal delivery, 13 subjects chose IUD, 1 chose tubectomy and 1 used implant. The relation between methods of delivery and the choice of family planning was statistically significant (P 0.049).

Table 3. The relationship between age, gravida and delivery methods with family planning choice

		Contraception methods			P Value
		IUD	Tubectomy	Implant	
Age	≤35	76	23	1	0.040
	>35	10	9	0	
Gravida	1	23	1	0	0.016
	≥2	63	31	1	
Methods of Delivery	SC	73	31	0	0.049
	PV	13	1	1	

Contraception use in women living with HIV plays a critical role in preventing mother to child transmission of HIV as it averts unintended births. Contraception plays a role in ending the epidemics of AIDS related to the Sustainable Development Goals 3.3.<sup>6</sup> Based on the WHO MEC for contraceptive use, women living with asymptomatic, mild, severe, or advanced HIV clinical disease may use COCs, CICs, contraceptive rings and patches, POPs, progesterone only-injections, and levonorgestrel and etonogestrel implants as those in MEC category 1. This means that there is no restrictions of its usage. In pregnant women with HIV, the contraceptive that must be used should be long-term family planning so that compliance is higher. Oral contraceptives are not suggested because they have the potential not to be routinely consumed. Meanwhile, levonorgestrel-IUD use in HIV positive women must be reconsidered as there is an increased risk of pelvic inflammation due to high rate of STI infection after the first 21 days of insertion (MEC category 2, category 3 in individuals with advanced HIV disease).<sup>5</sup> However, decision-making for contraceptive methods, moreover in women with HIV, is a complex process that require discussion on the trade-offs among the different methods, STI risk, and vary heavily on the biopsychosocial aspects of each individual and the environment they live in.

Dr. Cipto Mangunkusumo Hospital is a tertiary, national referral hospital in Jakarta, Indonesia. The hospital's 5-year data showed 72.4% (n=86) of all patients chose IUD as the most common contraceptive method. Most patients chose the IUD because it has long-term but reversible characteristics, so there is still the possibility of getting pregnant in the future. Different results were found on a referral hospital in Ethiopia, that 28.4%

preferred IUD because most participants were well informed that hormonal methods were expected to have some reactions in ART medication.<sup>7</sup> Another study in three referral hospitals in Amhara, Ethiopia, found that the most commonly used contraceptive method was injections (42.8%) because all study participants were ART users that may increase pill burdens if they chose COCs.<sup>8</sup> In Thailand, participants preferred male condom (n:179, 79.9%) as a single contraception method among women living with HIV due to the risk of transmitting the virus. Many of the study participants (n:118, 34.3%) also used two or more contraception method. This might be because most of them had lived with HIV for more than a year and had received family planning education and referral services as part of their HIV service package. The most common practice of dual contraception were condom and sterilization (n:78, 66.1%).<sup>9</sup> Women living with HIV in India, based on the Integrated Counseling dan Testing Centers in their tertiary hospitals in Mumbai, relied on condom only method (71.7%) due to the transmission risk of HIV, while the other 25.3% did not use any contraception. Despite that number of condom use, only half of the study population believed that condom could give 100% protection from pregnancy and they did not use other methods due to the misconceptions that modern spacing methods of contraception are harmful because of their HIV status.<sup>10</sup>

Moving to a developed country, a large clinical trial in the US showed the most common contraceptive methods reported at baseline were permanent contraception (37%), which was because most of the respondents (80.9%) did not desire children in the future, despite the relatively young age of the population. The use of more effective contraception (permanent, injection, pills, patch, diaphragm) and dual methods was only associated with older age and parity. Use of effective contraception methods also did not change with ART initiation or CD4 T cell count.<sup>11</sup> Oral contraception pills were also commonly used in the U.S for they are often the first hormonal method used by young women for regulation and treatment of painful menstruation. As they become more sexually active, many women remain satisfied using OCs for decades.<sup>12</sup> IUDs popularity in the US has just only increased in the past decade, as they are long-acting and reversible with minimum effects on sexual activity.<sup>13</sup>

A prospective cohort study in St. Petersburg, Russia, conducted contraceptive counseling before participants chose their preferred contraceptive method. The participants did not use ART at enrollment, mostly chose COCs (n:183, 42.95%), followed by condom (n:123, 28.87%), while participants using ART at enrollment mostly chose condom (n:27, 35.06%)

followed by COCs (n:24, 31.16%).<sup>14</sup> Their initial study also found that condom alone was the most preferred method (43.9%), followed by its combination with COCs (33.5%). They stated that most women were most likely to choose a contraceptive method that was highly effective during typical usage and a female-controlled method, such as condom, was used inconsistently, affected by their partners.<sup>15</sup>

After comparing contraception use in women living with HIV in our center with those in other countries, we found that condom use was deemed essential in either developed or developing countries, suggesting the women with HIV generally understand the importance of preventing HIV transmission to their offspring. Condoms alone were more preferred compared to single modern contraceptive, as seen in studies in Thailand, Brazil, and India.<sup>7,8,9,10,16</sup> The right practice to use condoms may also pose as problem, especially in developing countries as most developing countries chose to use condom-only contraception.<sup>7-10</sup> It is presumed that their educational level contributes to their preferred method of contraception, as well as the government support to ensure more effective contraceptions that are widely available and promoted. Misconceptions about other more long-term contraception also needs to be corrected to prevent unintended pregnancy in HIV women more effectively, pushing the importance of good counseling before, during and after pregnancy in every health centers.

More effective and long-term contraception method usage were found in developed countries,<sup>12-16</sup> suggesting that higher educational level contributes to such decision, as well as sufficient governmental or health care support in giving counseling prior to choosing their contraception method. Women with better education also contributes to better compliance and are associated with using dual contraception method, as seen from studies in Brazil, Uganda and the US.<sup>16,17</sup> Our study presented IUD and tubectomy as preferred contraception, although our research subjects had low education, most of them wanted to use IUD because they have been educated on early arrival during antenatal care in obstetric clinic (bookcased) or during admission in emergency room (non-bookcased). Most of our participants had a relatively low educational status which translated to potential low compliance, as seen in other developing countries.<sup>7-10</sup> Most of our participants (75.6%) were also on ART therapy, which might increase pill burden if COCs were chosen. Those might be the reasons why longer-term contraception were more preferred in our study. Multigravida (79.8%) and delivery method of Cesarean section (87.3%) might also support the participants decision on choosing IUD and tubectomy. HIV positive women also had more

frequent contact with health care providers which allowed more frequent counseling and encouragement to select more effective and long-term method to minimize unintended pregnancy.

Our study had several limitations. Other baseline characteristics that may affect participant's decision such as health status, condom use and other available contraceptions, desired future pregnancy, family income, culture and ethnicity, relationship or marital status, sexual activity, et cetera were not available to be analyzed. More detailed factors affecting women with HIV in selecting contraception method should have been better obtained from large qualitative study. Population of our study were exclusive from patients registered in RSCM and could not be applied to larger population such as Jakarta or Indonesia in general.

## CONCLUSION

In this five-year cross-sectional study, we found that most women living with HIV chose to use IUDs as method of contraception. Most participants were on ART treatment, had low educational, history of multigravida, and delivery method of Cesarean section, which might explain their decisions to choose more long-term, practical and effective contraception. There was a statistically significant relationship between contra-ceptive method with age ( $p$  0.040), gravida ( $p$  0.016) and delivery method ( $p$  0.049). Frequent counseling is important in encouraging women with HIV to choose more effective and long-term contraception. Each visit of women with HIV that has desire to future pregnancy may be used as an opportunity to give or review information regarding the best contraception for the individual. Further studies are required to better explain factors involved in selecting contraception method in HIV-positive mothers.

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## CONFLICT OF INTEREST

All authors have no conflict of interest.

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## REFERENCES

1. Respon terhadap HIV & AIDS. Ringkasan kajian [Internet]. UNICEF, Indonesia [Response to HIV & AIDS. Summary of investigation]. 2012 [cited 12 December 2018]. Available from: [https://www.unicef.org/indonesia/id/A4\\_-\\_B\\_Ringkasan\\_Kajian\\_HIV.pdf](https://www.unicef.org/indonesia/id/A4_-_B_Ringkasan_Kajian_HIV.pdf)
2. Indonesian National AIDS Commission, Republic of Indonesia. Country Report on the Follow up to the Declaration of Commitment on HIV/AIDS (UNGASS) Reporting Period 2010–2011/2012.
3. Indarti J, Christiawan L, Suhartomo D, et al. Postpartum contraceptive use among pregnant women who delivered at Cipto Mangunkusumo General Hospital: A descriptive study. *Majalah Obstetri & Ginekologi*. 2021;29(3); 124-8. doi: 10.20473/mog.V29I32021.124-128
4. Wilcher R, Petruney T, Cates W. The role of family planning in elimination of new pediatric HIV infection. *Curr Opin HIV AIDS*. 2013 Sep;8(5):490-97. doi: 10.1097/COH.0b013e3283632bd7. PMID: 23743790; PMCID: PMC4052828.
5. World Health Organization. Medical eligibility criteria for contraceptive use 5th ed Executive summary. Geneva, Switzerland: World Health Organization; 2015. [citedL 2020 Dec 21]. Available from: [www.who.int/reproductivehealth/publications/family\\_planning/Ex-Summ-MEC-5/en/](http://www.who.int/reproductivehealth/publications/family_planning/Ex-Summ-MEC-5/en/).
6. Lim SS, Allen K, Bhutta ZA, et al. Measuring the health-related Sustainable Development Goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. *The Lancet*. 2016;388(10053):1813–50. doi: 10.1016/S0140-6736(16)31467-2
7. Mersha AG, Erku DA, Belachew SA, et al. Contraceptive use among HIV-positive and negative women: implication to end unintended pregnancy. *Contracept Reprod Med*. 2019;4:3. doi:10.1186/s40834-019-0084-2
8. Alene KA, Atalell KA. Contraceptive use and method preference among HIV-positive women in Amhara region, Ethiopia. *BMC Womens Health*. 2018;18:97. doi: 10.1155/2020/6465242
9. Munsakul W, Lolekha R, Kowadisaurana B, et al. Dual contraceptive method use and pregnancy intention among people living with HIV receiving HIV care at six hospitals in Thailand. *Reprod Health*. 2016; 13:8. doi: 10.1186/s12978-016-0123-2
10. Joshi B, Velhal G, Chauhan S, et al. Contraceptive use and unintended pregnancies among HIV-infected women in Mumbai. *Indian J Community Med*. 2015;40(3):168-73. doi: 10.4103/0970-



- 0218.158855. PMID: 26170540; PMCID: PMC4478657.
11. Sheth AN, Angert CD, Haddad LB, et al. Contraception methods used among women with HIV starting antiretroviral therapy in a large United States clinical trial, 2009–2011. *Contraception*. 2020;0:0. DOI 10.1016/j.contraception.2020.11.004
  12. Daniels K, Daugherty J, Jones J. Current contraceptive status among women aged 15-44: United States, 2011-2013. *NCHS Data Brief*. 2014 Dec;(173):1-8. PMID: 25500343.
  13. Higgins JA, Smith NK. The sexual acceptability of contraception: Reviewing the literature and building a new concept. *J Sex Res*. 2016;53(4-5): 417-56. doi: 10.1080/00224499.2015.1134425. Epub 2016 Mar 8. PMID: 26954608; PMCID: PMC4868075.
  14. Whiteman MK, Jeng G, Samarina A, et al. Associations of hormonal contraceptive use with measures of HIV disease progression and antiretroviral therapy effectiveness. *Contraception*. 2016;93(1):17-24. doi:10.1016/j.contraception.2015.07.003
  15. Whiteman MK, Kissin DM, Samarina A, et al. Determinants of contraceptive choice among women with HIV. *AIDS*. 2009;23 Suppl 1:S47-54. doi: 10.1097/01.aids.0000363777.76129.b4. PMID: 20081388.
  16. Tsuyuki K, Barbosa RM, Pinho Ade A. Dual protection and dual methods in women living with HIV: The Brazilian context. *J Sex Transm Dis*. 2013;2013:540789. doi: 10.1155/2013/540789
  17. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med*. 2016;375(9):830-9. doi: 10.1056/NEJMoal600693. Epub 2016 Jul 18. PMID: 27424812; PMCID: PMC5049503.



**REVIEW ARTICLE****Potential of trichloroacetic acid (TCA) for cervical precancerous lesions treatment in Indonesia****I Gde Sastra Winata, <sup>ID</sup>\* Musa Taufiq**

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**ABSTRACT**

Cervical cancer becomes one of the most prevalent disease in female worldwide. Human papillomavirus (HPV) is main etiology of cervical cancer, thus this disease is preventable. Before progressed into invasive cervical cancer, cervical precancerous lesions developed and classified into 3 stages: CIN1 (LSIL), CIN2, and CIN3 (CIN2+ also referred as HSIL). World Health Organization (WHO) arranged 'screen-and-treat' programme to treat cervical precancerous lesions immediately before it progressed to cancer. However, a simple and safe modality with high efficacy is necessary to accommodate this strategy. Trichloroacetic acid (TCA) has those advantages and some research suggested high efficacy to treat cervical precancerous lesions with simple, safe, and cost-effective. TCA has potential to become effective treatment for cervical precancerous lesions in the future.

**Keywords:** Cervical cancer; cervical precancerous lesions; trichloroacetic acid

**ABSTRAK**

Kanker serviks merupakan salah satu penyakit dengan prevalensi tinggi pada wanita di seluruh dunia. Human papillomavirus (HPV) adalah penyebab utama kanker serviks. Oleh karena itu sebenarnya penyakit ini dapat dicegah. Sebelum menjadi kanker serviks invasif, terjadi perkembangan lesi prakanker serviks yang diklasifikasikan menjadi 3 stadium: CIN1 (LSIL), CIN2, dan CIN3 (CIN2+ juga disebut sebagai HSIL). Organisasi Kesehatan Dunia (WHO) mengatur program 'screen-and-treat' untuk mengobati lesi prakanker serviks segera sebelum berkembang menjadi kanker. Diperlukan modalitas sederhana dan aman dengan kemanjuran tinggi untuk mengakomodasi strategi ini. Asam trikloroasetat (TCA) memiliki keunggulan tersebut dan beberapa penelitian mengungkap efikasi tinggi pengobatan lesi prakanker serviks dengan sederhana, aman, dan hemat biaya. TCA berpotensi menjadi pengobatan yang efektif untuk lesi prakanker serviks di masa depan.

**Kata kunci:** Kanker serviks; lesi prakanker serviks; asam trikloroasetat

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## INTRODUCTION

Cervical cancer is one of the most common cancer in women worldwide, yet preventable. The incidence of cervical cancer worldwide is more than 528 000 cases with estimated mortality rate of 266 000 death. In Indonesia, prevalence of cervical cancer is 98 692 cases with incidence rate of 90-100 cases in 100 000 population each year.<sup>1</sup> Those numbers are estimated to rise in the next 10 years by 25% and become a significant health problem if appropriate preventive and treatment programs are not taken.<sup>2</sup>

Human papillomavirus (HPV) contributes to 99.7% of all cervical cancer.<sup>3</sup> HPV16 and 18 are the most virulent high-risk types which contribute to 70% among invasive cervical cancer and only 10% of cervical precancerous lesions may develop to invasive cervical cancer.<sup>4,5</sup> Cervical intraepithelial neoplasia (CIN) is precancerous lesions which classified into 3 stages: CIN1, CIN2, and CIN 3. There is higher risk of CIN2+ (CIN2 or above) to develop into cervical cancer if the treatment is inadequate.<sup>6</sup>

World Health Organization (WHO) recommends 'screen-and-treat' strategy to cope with cervical precancerous lesions, especially in developing countries where health care resources and costs are limited. Screen-and treat approach is a method which treatment decision provided immediately after a positive screening test result. The screening tests for cervical cancer vary from visual inspection with acetic acid (VIA), cytology (Pap smear), to a genetic-based test such as HPV test.<sup>6,7</sup> The treatments for positive screening test include ablative and excision procedure. Ablative procedures for precancerous lesions include cryosurgery, monopolar diathermy, CO2 laser vaporization, or topical application of chemical substances.<sup>7</sup> However, there is no clear evidence that any of surgical procedures are more preferable to treat cervical precancerous lesions.<sup>8</sup>

Trichloroacetic acid (TCA) is widely used as treatment for condylomata acuminata and seems to be a promising option for cervical precancerous lesions treatment because it is simple, cost-effective, can be easily tolerated, zero side effects in systemic, and pregnancy safe.<sup>9-11</sup> TCA using caustic agents to destruct precancerous tissues, preventing it to progress into cancer. It can be used as therapy immediately to patient with positive IVA test. A research stated that after 8 weeks there is high HPV clearance rate and regression of 85% TCA treatment in high-grade CIN.<sup>12</sup>

## CERVICAL PRECANCEROUS LESIONS

### Cervical lesions associated with HPV infection

HPV infection is the main cause and critical precursor in cervical cancer progress. HPV is one of the most well known sexually transmitted infection which affects basal layer of cervical epithelium in the transformation zone containing HPV-specific receptors. The activation and duplication of HPV in converting epithelium cells affect changes cellularly which commonly in the lower third of the epithelium, distinguished by perinuclear cytoplasmic clearing koilocytotic, nuclear enlargement, hyperchromasia, and atypia. About 90% of the HPV infections eliminated by natural immunity within 12-24 months along with CIN1 (low-grade squamous intraepithelial lesions) changes.<sup>13,14</sup> Lots of studies concluded that steady infection with high-risk HPV (oncogenic type) is the predominant riskfactor for CIN that may ranges from CIN-1 to CIN-3 and invasive cervical cancer.<sup>15-17</sup> A study named VIVIANE study confirmed that HPV-33 and HPV-16 were related with the highest risk of the development of CIN, followed by HPV-18, HPV-31, and HPV-45.<sup>16</sup>

### Natural history and classification of cervical precancerous lesions

Each grade of CIN lesions has different natural history. About 70-80% of low-grade squamous intraepithelial lesion (LSIL/CIN1) regress spontaneously without intervention and become undetectable.<sup>18,19</sup> This data suggests that CIN1 is more about a state of infection than a stage of disease development. Successful CIN1 detection does not represent disease progression and inability to detect might be correlated with viral clearance.<sup>16</sup>

There are well-known high-grade dysplasia which are CIN2 and CIN3 or high-grade squamous intraepithelial lesion (HSIL). Although classified as HSIL, CIN2 has better prognosis which less possibility to progress into cancer. CIN2 has two different ways either regression or progression. The annual regression rate of CIN2 is approximately from 15% to 23%, with up to 55% regressing by 4-6 years. Otherwise, about 2% of CIN2 lesions progress to CIN3 within the same period.<sup>19,20</sup> On the other hand, CIN3 is seen as potential true precancer which able to progress to invasive cervical cancer at rate of 0.2-4% within 12 months. Furthermore, it has 30% of probability to progress to invasive cervical cancer in over 30 years if left untreated. Treated CIN3 can become invasive in about 1% cases.<sup>15,19,21,22</sup>

## TRICHLOROACETIC ACID 80-90% SOLUTION FOR CERVICAL PRECANCEROUS LESIONS

### Mechanism of action

Trichloroacetic acid is classified as keratolytic agents and widely used for treatment of condylomata acuminata.<sup>10,23</sup> A research showed general mechanism of TCA which involved negative-charged trichloroacetate ions. Those ions disrupt electrostatic interactions that stabilize native conformation of proteins which resulting in protein unfolding and denaturation.<sup>24</sup> This mechanism leads to skin and mucosa disintegration which characterized by white-changing color of ecto-cervix.<sup>12</sup>

### Short-term efficacy of TCA for cervical precancerous lesions

A study conducted in Austria, involved 241 patients with cervical precancerous lesions were treated with a single 85% TCA treatment as first-line therapy and observed after 8 weeks. Out of those 241 patients, there were 179 patients with HSIL (CIN2+) and 62 patients with LSIL (CIN1). The histologic regression rate of patients with HSIL after 8 weeks was 87.7% (95% confidence interval [CI] 82.0-92.1) and the remission rate was 80.3% (95% CI 73.3-85.5). Meanwhile the remission rate of LSIL patients was 82.3% (95% CI 70.5-90.8). Clearance rate of HPV16 and HPV18 were 73.5% (95% CI 62.5-81.3) and 75.0% (95% CI 46.2-95.0), respectively. There were no reported side effects during management and monitoring. This study concluded that high regression, high remission, and high HPV clearance rate after 8 weeks of follow-up were obtained.<sup>12</sup>

### TCA vs. Spray monopolar diathermy

A study conducted by Darwish and Zahran (2013), compared the efficacy, tolerability, and safety of 70% TCA versus monopolar spray coagulation for persistent benign cervical lesions treatment. The results were both of 70% TCA that applied topically and monopolar spray coagulation obtained remarkable efficacy, high accomplishment rates, and very little complications. However, 70% TCA has higher tolerability and safety. Moreover, 70% TCA is simple and can be used widely by gynecologists with limited experience. It is recommended for ectopic cervical lesions or cervicitis that are nonspecific, but not for hypertrophic lesion, such as polyps.<sup>7</sup>

### TCA vs. Cryotherapy

Cryotherapy becomes treatment of choice to destruct cervical precancerous lesions. However, this procedure has limited access and instrument. TCA has potential to become alternative treatment for precancerous lesions. A research conducted to measure the effectiveness of 85% TCA versus cryotherapy to treat patient with positive IVA result. The conclusion of this study was there is not statistically difference between 85% TCA and cryotherapy.

### CONCLUSION

Some studies suggested 70-85% TCA has potential to support 'screen-and-treat' program of the WHO to eradicate cervical precancerous lesions, thus mortality and morbidity risk of cervical cancer could be decreased in the future. Moreover, TCA is simple, well-tolerated, minimal complications, and side effects with high efficacy as available treatment for precancerous lesions.

### REFERENCES

1. International Agency for Research on Cancer. Cervical cancer estimated incidence, mortality and prevalence worldwide in 2012. Ministry of Health, Republic of Indonesia. 2017.
2. Andrijono. Sinopsis kanker ginekologi [Synopsis of gynecological cancer]. 4th ed. Jakarta: Balai Penerbit FK UI; 2013. p. 59–129.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3): 209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.
4. Centers for Disease Control and Prevention. Basic information about HPV and cancer [Internet]. CDC. 2020 [cited 2021 Sep 27]. Available from: [https://www.cdc.gov/cancer/hpv/basic\\_info/index.htm](https://www.cdc.gov/cancer/hpv/basic_info/index.htm)
5. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem and its associated goals and targets for the period 2020 – 2030. Vol. 2, United Nations General Assembly. 2021. Available from: <http://apps.who.int/bookorders>.
6. World Health Organization. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. World Health Organization; 2013.
7. Darwish AM, Zahran KM. Trichloroacetic acid application versus spray monopolar diathermy for

- treating benign cervical lesions: a randomized controlled clinical trial. *J Low Genit Tract Dis.* 2013(3):248-54. doi: 10.1097/LGT.0b013e31827527e3. PMID: 23733165.
8. Fader AN. Surgery in cervical cancer. *N Engl J Med.* 2018;379(20):1955-7. doi: 10.1056/NEJMe1814034. Epub 2018 Oct 31. PMID: 30379600; PMCID: PMC6989030.
  9. Wakeham K, Kavanagh K. The burden of HPV-associated anogenital cancers. *Curr Oncol Rep.* 2014;16(9):402. doi: 10.1007/s11912-014-0402-4. PMID: 25118645.
  10. Ratnasari DT. Kondiloma akuminata. *J Ilm Kedokt Wijaya Kusuma.* 2018;5(2). doi: 10.30742/jikw.v5i2.336
  11. Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health.* 2021;9(2):e161-e169. doi: 10.1016/S2214-109X(20)30459-9. Epub 2020 Nov 16. Erratum in: *Lancet Glob Health.* 2021 Feb;9(2):e119. PMID: 33212031; PMCID: PMC7815633.
  12. Geisler S, Speiser S, Speiser L, et al. Short-term efficacy of trichloroacetic acid in the treatment of cervical intraepithelial neoplasia. *Obstet Gynecol.* 2016;127(2):353-9. doi: 10.1097/AOG.0000000000001244. PMID: 26942365.
  13. Basu P, Taghavi K, Hu S-Y, et al. Management of cervical premalignant lesions. *Curr Probl Cancer* 2018;42(2):129–36. doi: 10.1016/j.currproblcancer.2018.01.010
  14. Liu Y, Sigel K, Gaisa MM. Human papillomavirus genotypes predict progression of anal low-grade squamous intraepithelial lesions. *J Infect Dis.* 2018;218(11):1746-52. doi: 10.1093/infdis/jiy463. PMID: 30053247; PMCID: PMC6195660.
  15. Kombe Kombe AJ, Li B, Zahid A, et al. Epidemiology and burden of human papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation. *Front Public Health.* 2021 ;8:552028. doi: 10.3389/fpubh.2020.552028. PMID: 3355 3082; PMCID: PMC7855977.
  16. Skinner SR, Wheeler CM, Romanowski B, et al. Progression of HPV infection to detectable cervical lesions or clearance in adult women: Analysis of the control arm of the VIVIANE study. *Int J Cancer.* 2016;138(10):2428-38. doi: 10.1002/ijc.29971. PMID: 26685704; PMCID: PMC4787275.
  17. Mirabello L, Clarke MA, Nelson CW, et al. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. *Viruses.* 2018 Feb 13;10(2):80. doi: 10.3390/v10020080. PMID: 29438321; PMCID: PMC5850387.
  18. Bowden SJ, Kalliala I, Veroniki AA, et al. The use of human papillomavirus DNA methylation in cervical intraepithelial neoplasia: A systematic review and meta-analysis. *EBioMedicine.* 2019;50:246-259. doi: 10.1016/j.ebiom.2019.10.053. Epub 2019 Nov 12. PMID: 31732479; PMCID: PMC6921230.
  19. Koeneman MM, van Lint FHM, van Kuijk SMJ, et al. A prediction model for spontaneous regression of cervical intraepithelial neoplasia grade 2, based on simple clinical parameters. *Hum Pathol.* 2017;59:62-69. doi: 10.1016/j.humpath.2016.09.012. Epub 2016 Sep 30. PMID: 27697590.
  20. Rositch AF, Burke AE, Viscidi RP, et al. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: acquisition and reactivation in older women. *Cancer Res.* 2012;72(23):6183-90. doi: 10.1158/0008-5472.CAN-12-2635. Epub 2012 Sep 27. PMID: 23019223; PMCID: PMC3513486.
  21. Gravitt PE, Rositch AF, et al. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. *J Infect Dis.* 2013;207(2):272–80. doi: 10.1093/infdis/jis660
  22. Demarco M, Lorey TS, Fetterman B, et al. Risks of CIN 2+, CIN 3+, and cancer by cytology and human papillomavirus status: The foundation of risk-based cervical screening guidelines. *J Low Genit Tract Dis.* 2017;21(4):261-267. doi: 10.1097/LGT.0000000000000343. PMID: 28953 116; PMCID: PMC5625966.
  23. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. *J Clin Aesthet Dermatol.* 2012;5(6):25-36. PMID: 22768354; PMCID: PMC3390234.
  24. Fein LA, Marbin SJ. Condylomata acuminata of the neovagina in a transgender woman treated with trichloroacetic acid. *Int J STD AIDS.* 2020;31(10):1011–3. doi: 10.1177/0956462420937161

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