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FACTORS AFFECTING DISSEMINATED INTRAVASCULAR COAGULATION (DIC) IN POST PARTUM WOMEN: A META ANALYSIS

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ABSTRACT

Disseminated intravascular coagulation (DIC) is one of the risk factors that can increase mortality with a prevalence of about 82% when bleeding occurs. Information on how influential maternal characteristics are to the incidence of DIC in postpartum mothers will be very useful in detecting and performing care, however. Indonesian researchers are still lacking in conducting studies on the impact and influence of maternal characteristics with the incidence of DIC on postpartum mothers. The purpose of this meta-analysis was to find out what factors influence the incidence of DIC in postpartum mothers. Primary data is obtained by searching several indexing including: PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. By using the search keywords "factor associated AND DIC", "characteristic AND DIC", " post partum AND DIC AND adjusted odds ratio", and "factors AND DIC AND adjusted odds ratio" . Inclusion criteria, including: Full paper article with observational study design from 2018-2023. Covid-19 infection and DIC gave Odds Ratio results (OR 2.32; 95% CI: 1.67 – 3.22; p value < 0.001). Hypertension and DIC Odds Ratio (OR 2.17; 95% CI: 0.84 – 5.58; p value < 0.11). and eclampsia and DIC give an Odds Ratio result (OR 24.64; 95% CI: 6.50– 93.39; p value < 0.001).

Keywords: disseminated intravascular coagulation, meta analysis, post partum

INTRODUCTION

Hemostasis is the body's mechanism to stop bleeding spontaneously. Some systems that play a role in hemostasis are the vascular system (vasoconstriction), platelets (platelet clot formation) and blood clotting (fibrin formation to stabilize platelet clots). Coagulation factors are synthesized independently, do not cross the placental barrier, influenced by gestational age and liver maturity (Umar & Sujud, 2020). At birth, contact factors (thromboplastin precursors (XI), Hageman (XII), kininogens) and vitamin K dependent factors, 50% lower than adult levels, thrombin generation 30-50% lower than adults. Prothrombin time (PT), partial thromboplastin time (PTTK) and thrombin time (TT) tests can be prolonged in neonates, but bleeding does not always occur because there is hemostasis compensation, namely the fibrinolytic system which has a decrease in plasminogen 50% from adults accompanied by an increase in plasminogen activator inhibitors (Umar &; Sujud 2020).

Disseminated intravascular coagulation (DIC) is one of the risk factors that can increase mortality with a prevalence of about 82% when bleeding occurs, a DIC condition characterized by activation of the systemic coagulation pathway. Initial DIC score assessment using the International Society on Thrombosis and Haemostasis (ISTH) score system can help diagnose and manage DIC and can predict mortality in pediatric patients with DSS. the first hour since DSS diagnosis and exclusion criteria are children with. The prevalence of this event continues to increase every year in line with the age of the patient, from 58.8%, to 76.0% with a median length of stay of 5 days (3-7) (Smith, 2021). Oxygen saturation 98% (97-99) and median GCS pediatric level of consciousness. Median laboratory profile of hematocrit 40.9% (32,944.9), platelets 20500 u/L (14000-32000), PT 17.8 sec (14.9-25.3), fibrinogen levels 123 mg/dL (106-184) and D-dimer levels 832.5 ng/mL (362-1119).

An initial DIC score of 5 of 25 (73.5%) with a mortality outcome of 9 (36.0%) had a survival of 92% within the first 6 hours. Survival in 6 hours each DIC component is platelets 50000 u/L (93.8%), fibrinogen <100 mg/dL (100%), D-dimer 1000 ng/mL (85.7%) (SUNBANU, 2021).

Some maternal conditions can disrupt this balance and increase the risk of bleeding or thrombus formation. In case of worsening due to eclampsia, the condition of Disseminated Intravascular Coagulation (DIC) can occur. In this condition there is an increased, persistent, and thorough activation of coagulation, and usually causes the formation of microthrombus in the microvascular. At the same time platelet ingestion and coagulation proteins can induce massive bleeding (Sohn, 2017). DIC always has an underlying disease such as a severe infection, hema ogic malignancy, trauma or obstetric disorder. Common symptoms of DIC are bleeding symptoms and organ symptoms. DIC is a serious condition and early treatment based on proper diagnosis is important to improve prognosis and save patients. Given that this diagnosis is the last diagnosis before the patient experiences mortality in the world of obstetrics and gynecology (Khan, 2021). Information on how influential maternal characteristics are to the incidence of DIC in postpartum mothers will be very useful in detecting and performing care, however. Indonesian researchers are still lacking in conducting studies on the impact and influence of maternal characteristics with the incidence of DIC on postpartum mothers. The purpose of this meta-analysis was to find out what factors influence the incidence of DIC in postpartum mothers.

METHOD

This study was conducted to analyze factors that influence the incidence of DIC in postpartum mothers using a meta-analysis research design and systematic review. Primary data is obtained by searching several indexing including: PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. By using the search keywords "factor associated AND DIC", "characteristic AND DIC", " post partum AND DIC AND adjusted odds ratio", and "factors AND DIC AND adjusted odds ratio" . Inclusioncriteria, including: Full paper article with observational study design from 2018-2023. Articles published in English and/or Indonesian. Include the results of research in the form of adjusted odds ratio as an indication of the most ideal analysis for multivariate research. outcome is a DIC event. Statistical analysis using RevMan (review manager).

RESULT AND DISCUSSION

Based on the results of literature review and data extraction, we found 3 risk factors that are most frequent and still very relevant to watch out for in the last 5 years. These factors are complications that are still the cause of most maternal deaths, namely high blood pressure (hypertension), eclampsia, and infectious diseases that still cannot be handled perfectly, namely Covid-19 infection.

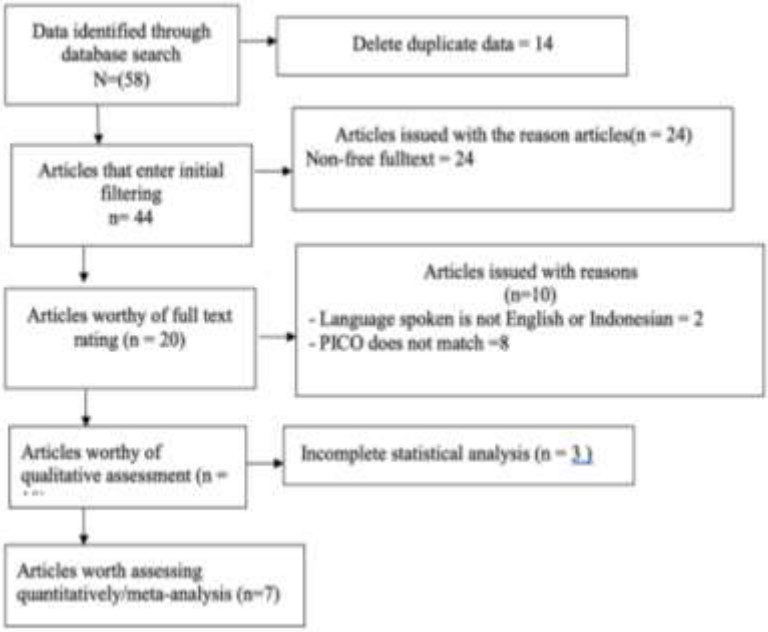

Figure 1. PRISMA flow diagram

Table 1
Summary table of study results / *summary source*

Author	Subjects	Country	Result
(Nowak, 2020)	169 patients	Polish	Covid-19 as a risk factor for DIC causes 27 (15.4%) patients to be admitted to the ICU. Overall mortality was 26.3% (n = 46) and was significantly higher in patients who came by referral (38 of 106; 35.8%), compared to patients admitted to hospital (8 of 63; 12.69%; P <0.001). Seventeen of the 29 patients admitted to the intensive care unit died (mortality, 58.6%), including 30 of the 41 patients with acute respiratory distress syndrome who had DIC had a mortality rate of 73.2%.
(Tang, 2020)	21 patients	China	The effect of Covid-19 on DIC disorder is an odds ratio of 0.8 for mortality (P <.05); 71.4% of non-survivors and 0.6% of survivors
(Lodigiani, 2020)	388 patients	Italian	The thromboembolic event occurred in 28 of the 388 Covid-19 patients (7.7% closed cases; 95% CI 5.4%-11.0%), corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward). Half of thromboembolic events are diagnosed within 24 hours of hospital admission. 44 patients underwent VTE imaging tests and VTE was confirmed at 16 (36%). Computed tomography pulmonary angiography (CTPA) was performed on 30 patients, corresponding to 7.7% of the total, and pulmonary embolism was confirmed on 10 (33% of CTPA). The rates of ischemic stroke and ACS/MI were 2.5% and 1.1%, respectively. Overt DIC was present in 8 (2.2%) patients.
(Helms, 2020)	150 patients	France	44 clinically relevant thrombotic complications were diagnosed, mainly pulmonary embolism (16.7%). 28/29 patients (96.6%) received dialysis therapy Three thrombotic occlusion (in 2 patients) centrifugal pumps occurred in 12 patients (8%) supported by ECMO. Most patients (> 95%) had elevated D-dimer and fibrinogen. 50/57 of the patients tested (87.7%) had positive lupus anticoagulants. Comparison with non-COVID-19

Author	Subjects	Country	Result
			ARDS patients (n = 145) confirmed that COVID-19 ARDS patients (n = 77) experienced significantly more thrombotic complications, especially pulmonary embolism (11.7 vs. 2.1%, p < 0.008). Coagulation parameters differed significantly between the two groups.
(Hitti, 2018)	7025 cases of delivery with DIC	Washington DC	284 (4%) had severe morbidity; 154 had transfusions, 27 had other procedures, and 103 women had 149 diagnoses of severe maternal morbidity (26 women had multiple diagnoses). Severe preeclampsia occurred in 438 deliveries (6.2%). Notably, hypertension was associated with severe maternal morbidity in a dose-dependent manner, with the strongest association observed for preeclampsia with a severe picture (odds ratio, 5.4; confidence interval 95%, 3.9–7.3). Severe maternal morbidity was also significantly associated with severe asymptomatic preeclampsia, chronic hypertension, preterm birth, pregestational diabetes, and multiple pregnancies.
(Erkılınç, 2018)	171 patients	Turkish	Clinical and laboratory parameters of 171 patients were analyzed. Influencing factors are as follows; aspartate amino transferase (AST) > 316 U/L, alanine aminotransferase (ALT) > 217 U/L, total bilirubin >2.0 mg/dL, lactate dehydrogenase (LDH) > 1290 U/L, blood urea nitrogen (BUN) > 44 mg/dL, and low platelets (<50,000/mm3). Eclampsia can increase the likelihood of DIC up to 4.1 times and 3.4 times in the presence of LDH >1290 U/L and headaches.
(Teefey, 2019)	152 patients	Philadelphia	The prevalence of the primary outcome was 15.8% with obese women less likely to have the combined outcome compared to non-obese women (7% vs 21.1%, p = 0.02). These remained after adjusting for confounders including maternal age, race, and chronic hypertension (adjusted odds ratio, 0.33 [0.12–0.89], p = 0.03). Obese women, however, were more likely to need peripartum intravenous antihypertensive drugs compared to nonobese women (49.1% vs. 28.4%, p=0.01).

Forest Plot of the Effect of Covid-19 Infection on the Incidence of DIC

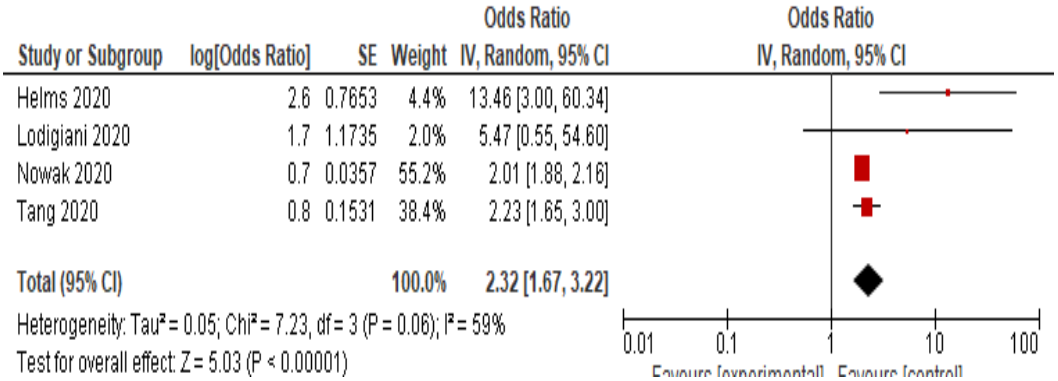

Figure 2. Forest plots the effect of Covid-19 infection on the incidence of DIC

Based on the results of the forest plot analysis above, it can be seen that pregnant women infected with Covid-19 have a worsening probability of experiencing DIC up to 2 times compared to pregnant women who do not experience or are infected with Covid-19 and statistically significant Odds Ratio (OR 2.32; 95% CI: 1.67 – 3.22; p value < 0.001).

Forest plot of the Effect of Hypertension on the Incidence of DIC

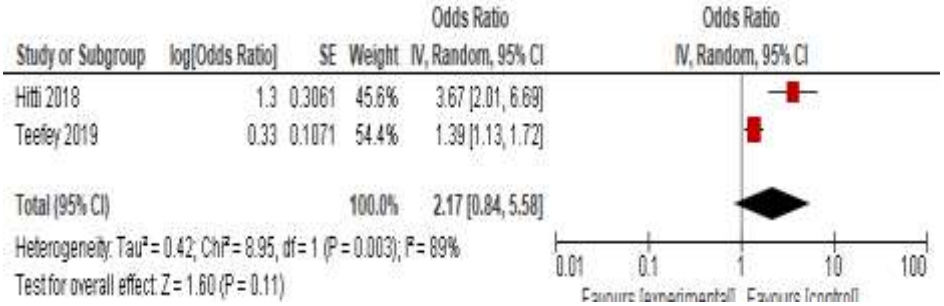

Figure 3. Forest plots hypertension against the incidence of DIC

Based on the results of the forest plot analysis above, it can be seen that pregnant women who experience high blood pressure during pregnancy and childbirth have a worsening likelihood of experiencing DIC up to 2 times compared to pregnant women who have normal blood pressure during pregnancy to postpartum but statistically not significant Odds Ratio (OR 2.17; 95% CI: 0.84 – 5.58; p value < 0.11).

Forest Plot of the Effect of Eclampsia on DIC Incidence

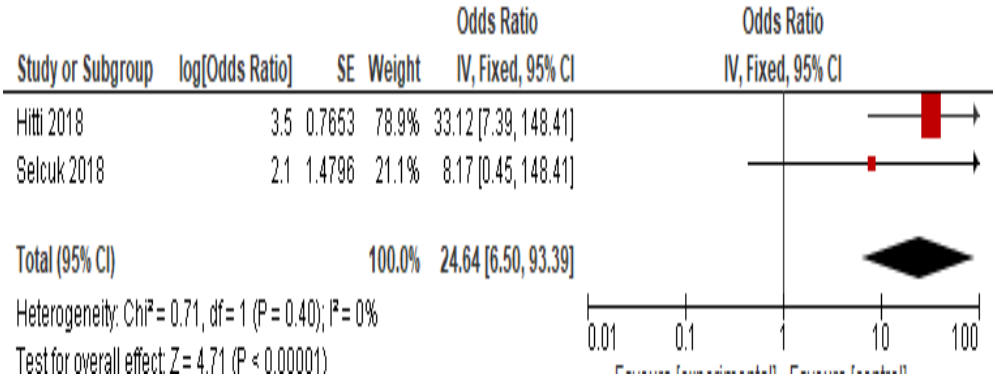

Figure 4. Forest plots the relationship between eclampsia and DIC

Based on the results of the forest plot analysis above, it can be seen that pregnant women who experience eclampsia at the end of their pregnancy or before delivery have a worsening likelihood of experiencing postpartum DIC up to 24 times compared to pregnant women who do not experience eclampsia until labor is complete and statistically significant Odds Ratio (OR 24.64; 95% CI: 6.50 – 93.39; p value < 0.001).

The relationship between Covid-19 and DIC

Studies have provided evidence that COVID-19 is generally accompanied by severe inflammatory symptoms, in clinical practice, several thrombotic complications are described in patients with increased frequency, including stroke, deep vein thrombosis, myocardial infarction, pulmonary embolism, as well as disseminated intravascular coagulation (DIC) (Jing Lu, 2020). Currently, many clinical studies have analyzed COVID-19 patients with coagulation disorders and it is found

that patients with COVID-19 show marked coagulation system changes, therefore, the relationship between coagulation dysfunction and prognosis in patients infected with COVID-19 is very complex but the strongest reason is coagulopathy system changes due to acute inflammation (D. Paparella, 2020).

Based on this evidence, monitoring of coagulation and anticoagulant biomarkers, such as D-dimers, fibrin degradation product (FDP) levels, and prothrombin time, is as early as possible. But how to properly apply this indicator is still unknown because the explanation of the pathophysiology of COVID-19 from the perspective of laboratory hematology has not found agreement (T. Iba, 2018). Researchers assume that although there is a relationship between the increase in DIC cases in pregnant women infected with Covid-19, various studies still cannot produce high enough evidence and the number of studies is still limited, this is of course because the selection of patients for DIC diagnosis is quite rare and difficult, related comorbidities and pharmacological treatments are also still not able to be carried out in all hospitals.

The relationship between hypertension and DIC

Research reported by states that hypertension in pregnancy (Preeclampsia and Eclampsia) is one of the three leading causes of maternal death besides bleeding and infection. Hypertension in pregnancy has a greater risk of preterm labor, IUGR (intrauterine growth retardation), illness and death, acute renal failure, acute liver failure, bleeding during and after delivery, HELLP ((Hidayat, 2022)*hemolysis elevated liver enzymes and low platelet count*), and DIC (*disseminated intravascular coagulation*).The association of hypertension with the incidence of DIC has been described as a triad relationship between hypertension, eclampsia, and HELLP *syndrome.* The most likely explanation for the incidence of chronic hypertension related to DIC is due to abnormal implantation of the placenta, increased placental vascular lesions and abruption. Abnormal implantation of the placenta will cause blood flow between the mother and fetus to be obstructed. Increased amount of blood produced by the body but inhibited placental absorption will cause disruption and excessive work in the heart muscles so that blood pressure will increase, the body will swell due to excess fluid and blood, besides that the kidneys will also experience an increase in the amount of blood filtered by the glomerulus and eventually sugar and protein can come out through the urine.(Gomez-Tolub, 2022)(Hidayat, 2022)

There is a triad of symptoms of preeclampsy, namely, proteinuria, edema, and hypertension. This occurrence is still unknown etiology and pathophysiology but there is agreement that there are three important conditions that can be found such as placental ischemia, hypertension, and DIC (*Disseminated Intravascular Coagulation*). Although the cause of preeclampsy is still unknown, stage 1 pathogenesis begins with an abnormal placenta due to nutrition. One of the nutrients that play a role is folic acid which functions for the biosynthesis of DNA and RNA, homocysteine metabolism, enzymatic functions, as well as differentiation processes.(Lestari, 2019)

The relationship of eclampsia with DIC

Theories have explained the very relationship between the incidence of eclampsia and DIC. Eclampsia caused by abnormal implantation of the placenta is a definite precursor to the prognosis and worsening of DIC. Preeclampsy is a syndrome typical of pregnancy with signs of hypertension in which there is an increase in systolic blood pressure ≥ 140 mmHg or an increase in ≥ 30 mmHg from before pregnancy or a diastolic increase ≥ 90 mmHg or an increase in ≥ 15 mmHg from before

pregnancy. In addition to hypertension, proteinuria was also found with urine protein levels of 300 mg per 24 hours or 30 mg / dk (1+ on the dipstick) in random urine samples and edema (Lestari, 2019). Under normal circumstances, placentation requires complete invasion of the extravillous trophoblast into the spiral artery of the mother's uterus. Changes in the spiral arteries occur that allow easy delivery of large amounts of blood to the intervilus space. When 8-12 weeks gestation, trophoblastic blockage accumulates in the spiral arteries resulting in endothelial cell damage, invasion and modification of the tunica muscular media layer. This results in oxidative stress. To reduce oxidative stress, folic acid plays an important role in capturing free radicals and increasing nitric oxide bioavilability (Nowak, 2020). But in pregnant women who experience preeclampsy, folic acid levels are very low and homocysteine is very high. This causes people with preeclampsy to experience maternal hypertension, proteinuria, kidney damage, and DIC (Lestari, 2019).

CONCLUSION

Covid-19 infection, Hypertension, and eclampsia can affecting disseminated intravascular coagulation in post partum phase and statistically significant

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