Maternal and perinatal outcome related to severity of chronic hypertension T in pregnancy

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Maternal and perinatal outcome related to severity of chronic hypertension in pregnancy

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ABSTRACT

Objectives: Chronic hypertension in pregnancy is an important cause of maternal and neonatal morbidity and mortality. The aim of this study was to determine the effect of severity of chronic hypertension in pregnancy on maternal and perinatal outcome in an Indonesian population.

Study design: This study was performed in Dr Soetomo General Hospital, a tertiary center in East – Java, Indonesia over the period of 2013–2017. Chronic hypertension (CH) was divided using JNC VII criteria, as stage 1 (Blood pressure ≥140/90 mmHg) and Stage 2 (BP > 160/110 mmHg) hypertension.

Main outcome measures: The primary outcomes were maternal and perinatal outcome. Data was statistically analyzed using Chi-square, Fischer exact test, and Mann-Whitney test (program: SPSS ®23).

Results: Over these 5 years, 352 patients were diagnosed with CH. The stage 2 of CH was associated with worse maternal outcome: maternal death (5.6% vs 0.8%; p = 0.016), laboratory values of urinary protein +3 (67% vs 21,5%, p = 0.001) and +4 (12.3% vs 0.4%, p = 0.001), LDH > 600 IU/L (11.3% vs 5.3%, p = 0.04), ALT > 70 IU/L (11.3% vs 4.1%, p = 0.01), AST > 70 IU/L (12.3% vs 5.3%, p = 0.02), BUN > 25 mg/dL (27.4% vs 8.1%, p = 0.001), SK > 1.1 mg/dL (29.2% vs 6.5%, p = 0.001) and Albumin < 3 g/dL (65.1% vs 10.2%, p = 0.001), need for ICU admission (76.4% vs 36.6%, p = 0.001), mechanical ventilation (48.1% vs 21.1%, p = 0.001), and occurrence of complications (72.6% vs 57.7%, p = 0.006). Stage 2 CH in pregnancy was associated with an increased risk of maternal death (OR: 7.22; 95% CI: 1.43–36.36; p = 0,016). Stage 2 CH was also associated with worse perinatal outcome, in terms of lower birth weight (1635 ± 863.27 vs 2063.74 ± 935.43, p = 0.001), lower Apgar score (p = 0.001), and number of intra uterine complications such as: IUGR, stillbirth, and placental abruption (27.4% vs 11.8%, p = 0.001).

Conclusions: Stage 2 CH in pregnancy is associated with worse maternal and perinatal outcomes compared with stage 1. Intervention to prevent disease progression to stage 2 before pregnancy may improve maternal and perinatal outcomes during pregnancy.

1. Introduction

Hypertension in pregnancy is one of the main causes of maternal-neonatal mortality and morbidity, with prevalence in the world ranges from 1 to 8%. Hypertension in pregnancy can be classified into 4 types: preeclampsia-eclampsia; chronic hypertension; chronic hypertension with superimposed preeclampsia; and gestational hypertension [1,2]. Chronic hypertension (CH) is an occurrence of hypertension (> 140/90 mmHg) before pregnancy or before 20 weeks of gestation, and persisting > 12 weeks after delivery [3]. According to the existing literature CH complicates between 1% and 5% of pregnancies [4–6]. The Seventh Joint National Committee (JNC 7) divided CH in two stages: stage 1 (systolic: 140–159; diastolic: 90–99) and stage 2 (systolic: ≥160; diastolic: ≥100) [7–9]. CH in pregnancy is associated with higher risk of poor maternal and neonatal outcome. The incidence of super imposed preeclampsia, cesarean section, preterm delivery, low birth weight, Neonatal Intensive Care Unit (NICU) admission, and perinatal death is higher in pregnancies in chronically hypertensive women [2,4,10]. Indonesia is the world's fourth most populous country, but so far no studies have addressed the important issue of CH in an

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Indonesian population. The aim of the current study was therefore to present a detailed analysis on a large cohort of pregnant Indonesian women presenting with CH.

2. Material and methods

The inclusion criteria of this study involve all consecutive pregnant women with CH delivered in Dr. Soetomo Hospital, a tertiary center in East Java, Indonesia, from January 2013 - December 2017. After obtaining approval from the Ethics Committee of Dr Soetomo Hospital (No. 0135/KEPK/III/2018), data were collected from patients medical records. Patients with grossly incomplete medical records were excluded from this study. Many patients were referred from smaller primary or secondary regional health units and hospitals, so most of the data were collected after admission to Dr Soetomo hospital, often just in the last days prior to delivery. CH was diagnosed based on history of antihypertensive medication before pregnancy, and/or blood pressure data prior to 20 week's gestation recorded in patient's pregnancy book, which is mandatory regulated by government. The data was divided into two groups based on severity of hypertension prior to 20 weeks gestation: stage 1 or 2 (JNC VIII) [7]. Stage 1 hypertension was defined as a systolic blood pressure 140–159 mmHg or diastolic blood pressure 90–99 mmHg, while stage 2 had a systolic blood pressure ≥160 mmHg, and ≥100 mmHg, during two or more visits [7,8].

The general maternal characteristics, management, maternal and perinatal outcome were analyzed and compared between both groups. Primary outcome of this study include maternal outcomes (mode of delivery, ICU admission, length of stay in Intensive Care Unit (ICU), ventilator used, maternal complications [superimposed preeclampsia, placental abruption, and eclampsia], and maternal death) and perinatal outcome (sex, prematurity, baby birthweight, Apgar score, and antenatal complications: fetal distress, Intra Uterine Growth Restriction (IUGR), Intra Uterine Fetal Death (IUFD)).

Superimposed preeclampsia was diagnosed based on the new onset of proteinuria (dipstick test > +2), maternal organ dysfunction (renal insufficiency, liver involvement, neurological, hematological complication), or uteroplacental insufficiency in women with CH (ISSHP, 2014). Uteroplacental insufficiency was defined as an occurrence of fetal complication during pregnancy, such as IUGR, fetal distress, or IUFD. The IUGR was diagnosed during pregnancy based on serial ultrasound (abnormal growth, estimated fetal weight < 10th percentile), abnormal Doppler examination (middle cerebral artery, umbilical artery, cerebroplacental ratio < 1). After birth, the IUGR was confirmed using Ballard and Lubchenco score [11,12].

A Data were analyzed using SPSS ®23. Fischer test was used for categorical data, unpaired *t*-test was used to evaluate differences between two groups with normal distribution, and relation between two parameters. For variables with an abnormal distribution (e.g. blood pressure) the Mann-Whitney test was used to evaluate

3. Results

During the period January 2013 - December 2017, 352 pregnant patients were admitted with a diagnosis of CH out of a total of 6950 deliveries in our hospital (5.06%). Over these 5 years there was a significant increase in the number of CH patients (Table 1). Regarding maternal demographics, there were significant differences between the stage 1 and stage 2 groups in maternal age (p = 0.02), obesity class 2 (p = 0.001), education status (p = 0.001), and prior method of contraception use (p = 0.001) (Table 2). All laboratory values (prior to delivery) were significantly different between both groups, except for the platelet count. Stage 2 hypertensive patients had a higher rate of +3/+4 dipstick proteinuria, increased LDH, liver enzymes, creatinine and BUN levels, and hypo-albuminaemia (Table 3). But interestingly, patients with stage 2 CH had less anemia compared to stage 1 (OR: 0, 28, p = 0,001).

Table 1
Number of Chronic Hypertension in Pregnancy Cases 2013–2017.

Year	Total deliveries	Number of cases		
		Stage 1 n (%)	Stage 2 n (%)	Total n (%)
2013	1726	23 (57,5)	17 (42,5)	40 (2,31)
2014	1677	45 (65,2)	24 (34,8)	69 (4,11)
2015	1166	43 (70,5)	18 (29,5)	61 (5,23)
2016	1144	69 (71,1)	28 (28,9)	97 (8,47)
2017	1237	66 (77,6)	19 (22,4)	85 (6,87)
Total	6950	246 (69,9)	106 (30,1)	352 (5,06)

Table 2
Antenatal Care (ANC) Characteristics.

	Chronic hypertension		*p value*
	Stage 1 (n = 246)	Stage 2 (n = 106)	
Antenatal Care Frequency			
0	6 (2,4%)	4 (3,8%)	0,03*
< 4	85 (34,6%)	51 (48,1%)	
≥ 4	155 (63%)	51 (48,1%)	
Health Care Provider			
Midwife/GP	131(54,6%)	42(41,2%)	0,03*
ObGYN Specialist	109(45,4%)	60(58,8%)	
ANC Location			
Surabaya	123(51,2%)	58(56,9%)	0,41
Outside Surabaya	117(48,8%)	44(43,1%)	
Referral Cases			
Yes	224(91,1%)	99(93,4%)	0,60
No	22(8,9%)	7(6,6%)	
Referral Origin			
Surabaya	125(55,8%)	57(57,6%)	0,86
Outside Surabaya	99(44,2%)	42(42,4%)	
Prior Contraception			
MPA Injection	54(22%)	2(1,9%)	0,001*
DMPA Injection	51(20,7%)	85(80,2%)	
OCC	63(25,6%)	5(4,7%)	
IUD	36(14,6%)	3(2,8%)	
No contraception	42(17,1%)	11(10,4%)	

*p < 0,05 indicate significant value. Abbreviations. GP: General Physician. MPA: Medroxyprogesterone Acetate. DMPA: Depomedroxyprogesterone Acetate. OCC: Oral Contraceptive Combination. IUD: Intra Uterine Device.

The results demonstrated a significant association between maternal education level and CH stage (p = 0,001) with stage 2 CH patients having lower education levels (primary and junior high school) compared with stage 1 (85.8% vs. 25.6%). The antenatal background (involving health care provider, ANC location and referral source) wasn't different between both groups, except the numbers of antenatal visits. Majority of patients with stage 2 CH used 3-monthly injection of Depomedroxyprogesterone Acetate (DMPA) before pregnancy; while majority stage 1 patients used Oral Combination Contraceptive (OCC) and Medroxyprogesterone Acetate (MPA) (p = 0,001) (Table 2).

The mean value of blood pressure in the overall cohort of CH patients at the first antenatal visit: systolic pressure 150 ± 9.91 mmHg (130–180 mmHg) and diastolic pressure 94.65 ± 6.05 mmHg (80–130 mmHg). Mean blood pressure in stage 1 group was 140/90 mmHg (systolic: 130–155 mmHg, diastolic: 80–98 mmHg), and in stage 2 160/100 mmHg (systolic: 140–240 mmHg, diastolic: 90–130 mmHg) (Table 3). Majority of first antenatal visits occurred before 12 weeks gestation (61.9%), the remainder between 12 and 20 weeks (38.1%). Patients with stage 2 CH were younger than the stage 1 patients as demonstrated by the significantly higher percentage of women being 20–35 year of age (60.4%) compared with the stage 2 group (46.7%; p = 0.02) (Table 3). Both groups had a relatively high percentage of comorbidities during pregnancy (including: renal disease,

Table 3
Maternal Characteristics of Patients with Chronic Hypertension in Pregnancy.

Maternal characteristics	Chronic hypertension		*p value*	*Odds ratio* (OR)
	Stage 1 (n = 246)	Stage 2 (n = 106)		
Ages (year old)				
20–35	115(46,7%)	64(60,4%)	0,02*	1,74(1,09–2,75)
> 35	131(53,3%)	42(39,6%)		
Blood Pressure (median, min–max)				
Systolic	140 (130–155)	160 (140–240)	0.000*	–
Diastolic	90 (80–98)	100 (90–130)	0.000*	–
Mean Arterial Pressure (MAP)	108.3 (96.6–117)	121.7 (113.3–146.7)	0.000*	–
Gravidity				
Primigravida	34(13,8%)	14(13,2%)	0,87	1,05(0,54–2,06)
Multigravida	212(86,2%)	92(86,8%)		
Education				
Primary School	15(6,1%)	65(61,3%)	0,001*	–
Junior High School	48(19,5%)	26(24,5%)		
Senior High School	166(67,5%)	14(13,2%)		
Bachelor	17(6,9%)	1(0,9%)		
Occupation				
House wife	151(61,4%)	74(69,8%)	0,12	–
Private Employees	79(32,1%)	30(28,3%)		
Government Officer	16(6,5%)	2(1,9%)		
Body Mass Index (kg/m^2)				
Normal	41(16,7%)	13(12,3%)	–	Ref
Overweight	86(35%)	24(22,6%)	0,74	0,8(0,41–1,90)
Obesity class 1	70(28,5%)	26(24,5%)	0,68	1,2(0,54–2,52)
Obesity class 2	24(9,8%)	30(28,3%)	0,001*	3,9(1,73–8,97)
Obesity class 3	25(10,2%)	13(12,3%)	0,29	1,6(0,65–4,09)
Gestational Age during first visit (week)				
< 12	151(61,4%)	67(63,2%)	–	Ref
12–20	95(38,6%)	39(36,8%)	0,75	0,9(0,57–1,48)
Gestational Age on delivery (week)				
< 23	5(2%)	6(5,7%)	0,04*	4,0(1,06–14,9)
23–34	148(60,2%)	65(61,3%)	0,25	1,4(0,76–2,79)
34–37	43(17,5%)	20(18,9%)	0,27	1,5(0,71–3,39)
37–42	50(20,3%)	15(14,2%)		Ref
Laboratory Protein urine				
Negatif	21(8,5%)	3(2,8%)	–	Ref
+1	83(33,7%)	3(2,8%)	0,11	0,25(0,05–1,35)
+2	88(35,8%)	16(15,1%)	0,11	1,23(0,33–4,77)
+3	53(21,5%)	71(67%)	0,72	9,37(8,54–33,1)
+4	1(0,4%)	13(12,3%)	0,001*	91,0(8,53–970)
Hb (g/dL)				
< 11	119(48,4%)	22(20,8%)	0,001*	0,28 (0,16–0,48)
≥11	127(51,6%)	84(79,2%)		
Platelet count (cell/mm^3)				
< 100.000	15(6,1%)	10(9,4%)	0,26	0,62(0,27–1,43)
> 100.000	231(93,9%)	96(90,6%)		
LDH (IU/L)				
< 600	233(94,7%)	94(88,7%)	0,04*	2,3(1,01–5,19)
> 600	13(5,3%)	12(11,3%)		
AST (IU/L)				
< 70	233(94,7%)	93(87,7%)	0,02*	2,5(1,12–5,61)
> 70	13(5,3%)	13(12,3%)		
ALT (IU/L)				
< 70	236(95,9%)	94(88,7%)	0,01*	3,0(1,26–7,21)
> 70	10(4,1%)	12(11,3%)		
BUN (mg/dL)				
< 25	226(91,9%)	77(72,6%)	0,001*	4,2(2,27–7,95)
> 25	20(8,1%)	29(27,4%)		
SK (mg/dL)				
< 1,1	230(93,5%)	75(70,8%)	0,001*	5,9(3,08–11,4)
> 1,1	16(6,5%)	31(29,2%)		
Albumin (g/dL)				
< 3,0	25(10,2%)	69(65,1%)	0,001*	16,4(9,3–29,3)
> 3,0	221(89,8%)	37(34,9%)		
Antihypertensive therapy prior to conceiving				

(*continued on next page*)

Table 3 (*continued*)

Maternal characteristics	Chronic hypertension		*p value*	*Odds ratio* (OR)
	Stage 1 (n = 246)	Stage 2 (n = 106)		
No therapy	44(17,9%)	18(17%)	0,001*	–
Mono Agent	192(78%)	44(41,5%)		
Multiple Agent	10(4,1%)	44(41,5%)		
Aspirin Used				
Yes	97(39,4%)	45(42,5%)	0,59	–
No	149(60,6%)	61(57,5%)		
Antihypertensive agent during pregnancy				
Nifedipine	98(39,8%)	16(15,1%)	0,001*	–
Methyldopa	147(59,8%)	2(1,9%)		
Methyldopa + Nifedipine	1(0,4%)	70(66%)		
Nicardipine pump	0(0%)	18(17%)		

*p < 0,05 indicate significant value. Abbreviations: Hb: Hemoglobin. LDH: Lactate Dehydrogenase. AST: Aspartate Aminotransferase. ALT: Alanine Aminotransferse. SK: Serum Creatinine.

Table 4
Maternal Outcome in CH patients.

	Chronic hypertension		*p*
	Stage 1 (n = 246)	Stage 2 (n = 106)	
Mode of Delivery			
Vaginal Delivery	103(41,9%)	42(39,6%)	0,72
Cesarean Section	143(58,1%)	64(60,4%)	
Intensive Care			
Yes	90(36,6%)	81(76,4%)	0,001*
No	156(63,4%)	25(23,6%)	
Length of intensive care			
< 3 days	106(94,7%)	44(92,5%)	0,66
3–7 days	9(3,7%)	7(6,6%)	
> 7 days	4(1,6%)	1(0,9%)	
Ventilator used			
Yes	19(21,1%)	39(48,1%)	0,001*
No	71(78,9%)	42(51,9%)	
Coexisting disease			
Without disease	186(75,6%)	73(68,9%)	0,19
Renal Disease	14(5,7%)	7(6,6%)	
Diabetes Mellitus	20(8,1%)	16(15,1%)	
Heart Disease	9(3,7%)	2(1,9%)	
CVA	7(2,8%)	6(5,7%)	
Hypertiroid	9(3,7%)	1(0,9%)	
SLE	1(0,4%)	1(0,9%)	
Complication during pregnancy			
No complication	104(42,3%)	29(27,4%)	0,006*
Superimposed PE	139(56,5%)	71(67%)	
Placental abruption	1(0,4%)	4(3,8%)	
Eclampsia	2(0,8%)	2(1,9%)	
Maternal Death			
No	243 (99.2%)	101 (94.4%)	0.016*
Yes	2 (0.8%)	6 (5.6%)	
Cause of Maternal Death			
CVA	0(0%)	3(2,8%)	0,002*
Septic Shock	2(0,8%)	0(0%)	
Cardiogenic Shock	0(0%)	3(2,8%)	
Survive	243(99,2%)	101(94,4%)	
Contraceptive advice on discharge			
No contraception	128(52%)	44(41,5%)	0,17
IUD	57(23,2%)	27(25,5%)	
Sterilization	61(24,8%)	35(33%)	

*p < 0,05 indicate significant value. Abbreviations. CVA: Cerebrovascular accident. SLE: Systemic Lupus Erythematosus. PE: Preeclampsia. IUD: Intra Uterine Device.

diabetes mellitus, heart disease, CVA, hyperthyroidism and SLE) (24.4% and 31.1% NS) (Table 4).

The relative % of patient giving birth at pre-specified gestational ages 23–34 weeks, 34–37 weeks, and 37–42 weeks, was not different, but patients with stage 2 hypertension had a higher risk of delivering < 23 weeks (5.7% vs 2%; p = 0.04; OR 4.0 (CI 95% 1,1–14,9). Antihypertensive therapy was given to 82.5% cases (290/350 total cases), with different types of antihypertensive drugs in the 2 groups. Patients with stage 2 CH tended to have multiple antihypertensive agents (41.5%), while stage 1 CH patients mostly used monotherapy (methyldopa or nifedipine) throughout pregnancy (78%). Combination of antihypertensive drugs used in this study were nifedipine and methyldopa. Only stage 2 CH patients received intravenous antihypertensive agent as immediate treatment for hypertensive crisis (nicardipine (17%) (Table 3).

In the overall cohort, 58.8% of patients were delivered by cesarean section, stage 1 58.1%, versus stage 2 60.4%. Followed by sterilization and IUD as the main choices of contraception. Stage 2 CH patients had significantly higher percentage of intensive care admission (76.4% vs 36.6%, p = 0.001), while the duration of care in ICU was not different, mostly < 3 days. The number of patients requiring ventilator assisted breathing was also significantly higher in stage 2 CH (48.1% vs 21.1%, p = 0.001) (Table 4).

The rate of antenatal complications was significantly higher in the stage 2 CH group compared with the stage 1 group, in particular superimposed preeclampsia, placental abruption, and eclampsia. There were 8 maternal deaths in the overall cohort of CH patients (2.27%), with cardiogenic shock, septic shock and stroke (CVA) as the most important causes of death; 6 maternal deaths occurred in the stage 2 group, versus 2 in the stage 1 group (OR:7.22; 95% CI: 1.43–36.36) (p = 0,016) (Table 4). Patients with stage 2 CH give birth to smaller babies compared to stage 1 patients (1635 ± 863 vs 2063 ± 935, p = 0.001). This birthweight difference was primarily explained by the difference in gestational age; only 14.2% patients with stage 2 CH were delivered at > 37 week's gestation, compared to 20.3% with stage 1 (Table 5), and 46% of baby born from mother with stage 2 CH had birthweight < 1500 g, versus only 28.9% in stage 1 CH mothers. Low Apgar scores were very common in the stage 2 CH group compared to stage 1 (Table 5).

4. Discussion

As far as we know this is first paper presenting pregnancy outcome in patients with CH in Indonesia. The incidence of CH in pregnancy in these series was 5.06%, but this does not reflect the incidence in our population, since Dr. Soetomo Hospital is a tertiary referral hospital with high risk cases only. The number of pregnant CH patients

Table 5
Perinatal Outcome in CH patients.

	Chronic hypertension		*p* value
	Stage 1 (n = 246)	Stage 2 (n = 106)	
Gender			
Male	121(49,2%)	46(43,4%)	–
Female	125(50,8%)	60(56,6%)	
Delivery status			
Preterm	196 (79,7%)	91 (85,8%)	0.17
Term	50 (20,3%)	15 (14,2%)	
Gestational age at delivery			
< 34 weeks	153 (62,2%)	71 (67%)	0.39
> 34 week	93 (37,8%)	35 (33%)	
Birthweight (Mean ± SD gram)	2063,74 ± 935.43	1635 ± 863.27	0.001*
Birthweight (gram)			
< 1500	71(28,9%)	49(46,2%)	0,001*
1500–1999	31(12,6%)	29(27,4%)	
2000–2499	71(28,8%)	13(12,3%)	
2500–2999	38(15,4%)	8(7,5%)	
> 3000	35(14,2%)	7(6,6%)	
Apgar Score			
0–3	49(19,9%)	36(34%)	0,001*
4–6	69(28%)	41(38,7%)	
7–10	128(52%)	29(27,4%)	
Complication			
Fetal Distress	13(5,3%)	5(4,7%)	0,001*
IUGR	11(4,5%)	15(14,2%)	
IUFD	5(2%)	9(8,5%)	
No complication	217(88,2%)	77(72,6%)	

*p < 0,05 indicate significant value. Abbreviations. IUGR: Intra Uterine Growth Restriction. IUFD: Intra Uterine Fetal Death.

Table 6
Logistic Regression of Model Risk Factor for Stage 2 CH.

Risk factor	P Value	OR	95% C.I	
			Lower	Upper
Maternal Ages	0,557	0,837	0,440	1,592
Education Level				
Primary School	0,000*	ref	ref	ref
Junior High School	0,000*	0,186	0,079	0,439
Senior High School	0,000*	0,052	0,022	0,123
Bachelor Degree	0,001*	0,021	0,002	0,187
BMI				
Normal	0,684	ref	ref	ref
Overweight	0,490	1,481	0,485	4,522
Obesity class 1	0,545	1,407	0,466	4,243
Obesity class 2	0,197	2,185	0,667	7,158
Obesity class 3	0,932	1,059	0,289	3,883
Contraception				
No contraception	0,000*	ref	ref	ref
MPA	0,027*	0,218	0,057	0,838
DMPA	0,044*	2,377	1,025	5,510
OCC	0,091	0,390	0,131	1,163
IUD	0,089	0,276	0,063	1,215

increased over the study period, due to increased prevalence of women with high risk of hypertension, such as obesity, maternal age > 35 years, hormonal therapy, pre-gestational diabetes, systemic lupus erythematosus, and kidney disease [4,10]. In this Indonesian cohort, patients with stage 2 CH had less antenatal care (< 4 times throughout pregnancy) and lower education status. These data indicate that the quality of ANC in these patients was still poor, which might relate to the lower educational and social-economic status. Educational level and socio-economic conditions are risk factors for the occurrence of hypertension in pregnancy [13–15]. Patients with a low education level are more likely to have unhealthy life styles, unhealthy diet, more obesity, and low compliance to medication [16–18]. These factors might be contribute to the high incidence of severe CH and superimposed preeclampsia in this series.

The current study clearly demonstrates that stage 2 CH is associated with a dramatic and significantly worse maternal and perinatal outcome compared with stage 1. The stage 2 CH patients had a significantly higher risk of maternal death (5.6% vs 0.8%); the risk was increased 7.2 fold compared to stage 1. The literature affirms that uncontrolled severe CH in pregnancy increased the risk of CVA and maternal death [19,20]. The main issue in Indonesia is the late referral to tertiary care hospital at a stage when serious complications have already developed, resulting in the very high maternal death rate. In this cohort of 352 CH patients, 8 died (2,27%), 2 in stage 1 CH and 6 in stage 2 CH. All these cases suffered multiple organ involvement, 5 of these 8 cases had developed superimposed preeclampsia, other complications involved (number cases): acute pulmonary edema (2), eclampsia (3), HELLP syndrome (1), acute renal failure (ARF) (3), peripartum cardiomyopathy (PPCM) (2), sepsis (3), pneumonia (3), pulmonary hypertension (1), thyroid crisis (1), and CVA (3). Late referral by the primary or secondary hospital, poor antenatal care, and low compliance were the main contributors to these maternal deaths. All of these patients already had multiple organ complication with poor prognosis when admitted to the tertiary unit.

Maternal complications such as: superimposed preeclampsia, eclampsia, placental abruption, need for ICU admission, and ventilator use were significantly higher in stage 2 CH. Both stage 1 and stage 2 CH patients had a very high rate of superimposed preeclampsia (respectively 56.5% and 67%). A large *meta*-analysis (795.221 pregnancies) confirmed that CH increases the relative risk of superimposed preeclampsia 7.7 fold (95% CI: 5.7 to 10.1) [4]. The very high incidence in our stage 1 CH group is however noteworthy. The factors that could explain this high rate included: high number of women aged > 35 years, women with overweight and obesity (only 16.7% patient had normal BMI), and/or the presence of coexisting disease (24.4% patients had preexisting disorders like renal disease, diabetes mellitus, hyperthyroidism, SLE). All these factors could further increase the risk of developing superimposed preeclampsia in the stage 1 CH group [21].

In the stage 2 CH group 76.4% patient were admitted to ICU, 48.1% required mechanical ventilation. Conditions necessitating intensive care and mechanical ventilation included: pulmonary edema, hypertensive crisis, PPCM, eclampsia, and CVA. These data make it clear that patients with stage 2 CH need to have their care in tertiary units with access to ICU, in anticipation of the high rate of complications like stroke and hypertensive crisis [19,20].

In this large Indonesian series, 58–60% of patients were delivered by cesarean section, this percentage is markedly higher than in the recent large *meta*-analysis study by Braham K et al (41.4%) [4]. The indications for cesarean in our study were mostly the occurrence of one or more severe complication of CH followed by fetal distress (55.3%), or obstetrical indications such as malpresentation, placenta previa, history of cesarean ≥2, and multiple pregnancy (44.7%).

During pregnancy, the 2 groups were managed with different antihypertensive agents. Stage 1 patients mostly used a single agent, with methyldopa as the drug of choice followed by the calcium channel blocker (nifedipine), while patients with stage 2 CH often received multiple agents, mostly a combination of methyldopa and nifedipine in line with the recommendations of combination therapy for pregnant women with severe CH [22,23]. Some of the patients in stage 2 who had hypertensive emergencies (blood pressure > 180/120 mmHg), received intravenous nicardipine as a first treatment. In our hospital protocol, we tend to decrease blood pressure gradually with a maximum decrease of 25% MAP/days to avoid sudden reduced uteroplacental blood flow [24]. The aim was to adapt treatment until target blood pressures ≤ 140/90 mmHg were achieved. Over the study period

Indonesian specialists tended to follow the less tight control of hypertension in pregnancy as used in the CHIPS [Control of Hypertension in Pregnancy Study] trial (target diastolic blood pressure < 100 mmHg) rather than tight control (target diastolic blood pressure < 85 mmHg) [5,20].

Stage 2 CH had a significantly lower birthweights, lower Apgar scores, and high incidence of antenatal complication (fetal distress, IUGR, and IUFD). In this study, we did encounter a much higher number of low birthweight neonates (birth weight < 2500 g) (Stage 1: 70.4%, stage 2: 85.9%), compared with the large multicenter *meta*-analysis study by Bramham, with only 22.2% [4]. The low birth weights in this cohort appears to be primarily due to the high rate of iatrogenic preterm birth (stage 1:79.7%, and stage 2: 85.8%), due to the high number of maternal complications (stage 1: 57.5% and stage 2: 72.6%), and the existence of co-existing disease. According to Sibai et al pregnant women with CH have a 4 times increased risk of poor neonatal outcome compared with normal pregnancies, and this risk is further associated with the presence of other comorbid disease [10]. High blood pressure in early pregnancy increase the risk of IUGR, preterm delivery, newborn asphyxia, because of the lack of remodeling of the spiral arteries in many patients with longstanding CH, interfering with uteroplacental blood flow, and eventually affecting fetal growth [25–27]. Superimposed preeclampsia-eclampsia was – not surprisingly - the major contributor to the high incidence of prematurity, IUGR, low birthweight, and asphyxia in this study [28]. Rates of superimposed preeclampsia, eclampsia, and placental abruption were much higher in stage 2 CH, leading to an even higher rate of newborn complications [4,25,27,28].

Another interesting finding in this study is the difference in mode of pre-conceptional contraception between both groups, with over-represented DMPA use in stage 2 CH women (80,2% vs 20,7%). This could be explained by the relatively younger age in stage 2 CH group, which eventually determined the preference of contraceptive methods choice. In Indonesian women aged > 35 years old usually prefer long term contraceptive methods such as IUD, or directly into sterilization, and this was also a soft recommendation from Indonesian government. Women in the reproductive age group (20–34 years old) tend to choose DMPA injection as it also compatible with breastfeeding. While DMPA injection is contraindicated in hypertensive women, there is no actual good quality evidence demonstrating that this method increases the risk of hypertension. But long term used of DMPA could increase weight gain and the rate of obesity, which eventually will increase the risk of hypertension [17,29,30]. Further logistic regression on our data indicated that DMPA was the only contraceptive methods increasing the risk of stage 2 hypertension (OR 2.37, 95% CI: 1.025–5.510), while the other contraceptive methods contrarily were associated with a lower risk (Table 6). Based on this finding and low compliance of majority Indonesian women, we proposed that long term non hormonal contraception (IUD or even sterilization) is the best suitable methods for our population.

5. Conclusions

Chronic hypertension in pregnancy in Indonesia is a major risk factor of poor maternal and perinatal outcome, and in particular stage 2 CH is associated with increased risk of maternal death, maternal complications, and poor perinatal outcome. Patients with stage 2 CH need early referral to a tertiary hospital with ICU facilities, in order to allow a multidisciplinary team approach.

Conflict of interest

The authors declare no conflict of interest in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.04.007.

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