Long and short term complications of hypertensive disorders of pregnancy

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LONG AND SHORT TERM COMPLICATIONS OF HYPERTENSIVE DISORDERS
OF PREGNANCY

Masters in public health thesis

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Abstract

Introduction: Hypertensive disorders of pregnancy are a heterogenous group of disorders that affects 5-10% of pregnancies. These conditions are associated with increased maternal and neonatal morbidity and mortality. They have also been implicated in long term complications.

Objectives: To identify short and long term complications in women who had pregnancies complicated by hypertensive disorders in pregnancy and children who had prenatal exposure to the disorders.

Methods: The study is based on the generation XX1 birth cohort, 8647 women and their babies were recruited between 24 and 72 hours of delivery and were followed up over time. This study included 8184 women and their neonates. Data gotten at the 48 and 84 months follow up periods were analysed comparing women who had hypertensive disorders of pregnancy (HDP) and children who were exposed prenatally and their counterparts.

Results: The prevalence of HDP in the cohort is 5.8%, women with HDP were older, mostly primiparous, and were less educated than their counterparts. The risk of being admitted during pregnancy in women with HDP was 2.482 (95% CI; 2.102-2.931) times as high as the risk in normotensive women, they had 2.280 (95% CI; 0.976-5.321) times the risk of having babies with intrauterine growth restrictions and 1.531 (95% CI 1.403-1.671) times the risk of having a caesarean section compared to those normotensive. Neonates exposed to HDP are 3 (RR=3.005 95% CI 2.543-3.550) times as likely as being born premature, they had 2 times (RR;2.185, 95% CI;1.565-3.051) the risk of being born small for gestational age, 2.070 times (95% CI 1.675-2.558) the risk to be resuscitated, 2.689 (95% CI; 2.325-3.236) times the risk of being admitted to the neonatal ICU and 1.679 (95% CI;1.331-2.164) times the risk of receiving blood transfusion compared neonates unexposed. At 84 months children that had prenatal exposure had higher blood pressures than those unexposed, systolic blood pressure mean difference: 2.335(0.864-3.806), diastolic blood pressure mean difference 2.326(1.434-3.218). They also had 1.386 (95% CI;1.098-1.751) times the risk to develop behavioural problems compared to their unexposed counterparts. The exposed mothers had 6.511 (95% CI; 5.628-7.532) times the risk of developing new onset hypertension, 1.426 times (95% CI; 1.169-1.740) the risk of developing dyslipidaemia, 1.761 times (95% CI; 1.440-2.155) the risk of developing type 2 diabetes, 7.322 times the risk (95% CI;3.183-16.843) of developing a stroke and 1.633 times the risk (95% CI;1.161-2.297) the risk of

developing arrythmias compared to women who were normotensive at the 48 months follow up period. As at the 84 months follow up, the exposed mothers had 4.279 times the risk (95% CI; 2.951-6.204) of developing hypertension, 5.167 times the risk (95% CI; 2.222-12.015) of developing diabetes, 2.489 the risk (95% CI; 1.403-4.418) of developing dyslipidaemia and 5.525 times the risk (95% CI;2.885-10.581) of being obese compared to women who were not exposed to HDP.

Conclusion: Women who had HDP and children born from such pregnancies have increased risks of developing several health challenges, which translates in increase financial burden and increase DALYs.

Resumo

Introdução: Os distúrbios hipertensivos da gravidez são um grupo heterogêneo de distúrbios que afetam de 5 a 10% das gestações. Essas condições estão associadas ao aumento da morbidade e mortalidade materna e neonatal. Eles também foram implicados em complicações de longo prazo.

Objetivos: Identificar complicações de curto e longo prazo em mulheres que tiveram gestações complicadas por distúrbios hipertensivos na gravidez e crianças que tiveram exposição pré-natal aos distúrbios.

Métodos: O estudo é baseado na coorte de nascimentos da geração XX1, 8.647 mulheres e seus bebês foram recrutados entre 24 e 72 horas após o parto e acompanhados ao longo do tempo. Este estudo incluiu 8.184 mulheres e seus neonatos. Os dados obtidos nos períodos de seguimento de 48 e 84 meses foram analisados comparando mulheres que tiveram distúrbios hipertensivos da gravidez (HDP) e crianças expostas no período pré-natal e suas contrapartes.

Resultados: A prevalência de HDP na coorte é de 5,8%, as mulheres com HDP eram mais velhas, a maioria primíparas e tinham menos escolaridade do que suas contrapartes. O risco de internação durante a gravidez em mulheres com HDP foi 2,482 (IC 95%; 2,102-2,931) vezes maior do que o risco em mulheres normotensas, elas tinham 2,280 (IC 95%; 0,976-5,321) vezes o risco de ter bebês com restrição de crescimento intra-uterino e 1,531 (IC 95% 1,403-1,671) vezes o risco de cesariana em comparação às normotensas. Recém-nascidos expostos a HDP são 3 (RR = 3,005 IC 95% 2,543-3,550) vezes mais prováveis de nascerem prematuros, eles tiveram 2 vezes (RR; 2,185, IC 95%; 1,565-3,051) o risco de nascerem pequenos para gestacional idade, 2,070 vezes (IC 95% 1,675-2,558) o risco de ser ressuscitado, 2,689 (IC 95%; 2,325-3,236) vezes o risco de ser admitido na ICU neonatal e 1,679 (IC 95%; 1,331-2,164) vezes o risco de receber transfusão de sangue comparado a neonatos não expostos. Aos 84 meses, as crianças que tiveram exposição pré-natal tinham pressão arterial mais elevada do que as não expostas, diferença média da pressão arterial sistólica: 2,335 (0,864-3,806), diferença média da pressão arterial diastólica 2,326 (1,434-3,218). Eles também tinham 1,386 (IC de 95%; 1,098-1,751) vezes o risco de desenvolver problemas comportamentais em comparação com suas contrapartes não expostas. As mães expostas tiveram 6,511 (IC 95%; 5,628-7,532) vezes o risco de desenvolver novo início de hipertensão, 1,426 vezes (IC 95%; 1,169-1,740) o risco de desenvolver dislipidemia, 1,761 vezes (IC 95%; 1,440-2,155) o risco de desenvolver

diabetes tipo 2, 7,322 vezes o risco (IC 95%; 3,183-16,843) de desenvolver um acidente vascular cerebral e 1,633 vezes o risco (IC 95%; 1,161-2,297) o risco de desenvolver arritmias em comparação com mulheres que foram normotenso no seguimento de 48 meses. No seguimento de 84 meses, as mães expostas tinham 4,279 vezes o risco (IC 95%; 2,951-6,204) de desenvolver hipertensão, 5,167 vezes o risco (IC 95%; 2,222-12,015) de desenvolver diabetes, 2,489 o risco (IC 95%; 1,403-4,418) de desenvolver dislipidemia e 5,525 vezes o risco (IC 95%; 2,885-10,581) de ser obesa em comparação com mulheres que não foram expostas ao HDP.

Conclusão: Mulheres que tiveram HDP e crianças nascidas de tais gestações têm riscos aumentados de desenvolver vários problemas de saúde, o que se traduz em aumento da carga financeira e aumento de DALYs.

Chapter 1

Introduction

Pregnancy is a physiological condition that causes changes to all body organs, making them prone to developing complications. Pregnancy is characterized by significant metabolic, hemodynamic, hormonal and immunological changes which helps facilitates fetal growth. Major hemodynamic changes include increase in cardiac output during the first trimester, sodium and water retention leading to plasma volume expansion with a peak around week 30, and reductions in the systemic vascular resistance as well as systemic blood pressure [1]. The inability to adapt to these changes could result in the development of some hypertensive disorders of pregnancy (HDP).

Hypertension

Hypertension is defined as a sustained raise in systemic blood pressure, characterized by systolic blood pressure (SBP) of 140 mmHg or more and/or a diastolic blood pressure (DBP) of 90 mmHg or more.

Hypertension is a major global cause of morbidity and mortality, it increases the risks of developing cardiovascular, renal and cerebral diseases amongst others. Based on office BP measurements, the global prevalence of hypertension in 2015 was estimated to be 1.13 billion, 1 in 4 men and 1 in 5 women had hypertension. In all, its prevalence in adults is said to be around 30-45%, the age standardized prevalence in men is 24% while in women is 20%, this is consistent across the world irrespective of income status of countries.

Globally, the prevalence of hypertension differs between sexes and ages, this difference is due to both biological and behavioral factors. Hypertension is more common in males before the age of 65, however at 65 the pattern reverses. The risk of being hypertensive increases with age such that it is said that the prevalence in people >60years is 60%[2-7]. Several studies have shown hypertension to be more common among middle-aged men than women, the risk of hypertension in women increases rapidly at menopause reaching that of men and exceeding it at the 6th decade of life[8-10]. Irrespective of gender however, the risk of hypertension increases with increasing age[2-7]. Data obtained during the Framingham Heart Study observed that SBP shows a continuous increase between the ages of 30 and 84 years or over[5].

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy (HDP) are a heterogeneous group of conditions which include chronic (preexisting) hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension[11]. These heterogenous group of

diseases have been defined, grouped and classified differently by various groups and association. Table 1 gives a summary of the various classes and definition.

Chronic hypertension is defined as high blood pressure that is present before the 20th week of gestation which does not resolve after delivery. Gestational hypertension is defined as having a blood pressure higher than 140/90 mmHg measured on two separate occasions, at least 4 hours apart in women who were normotensive before 20th week of gestation in the absence of proteinuria and without biochemical or hematological abnormalities.

Preeclampsia is defined as de novo hypertension at or after 20 weeks of gestation with proteinuria (> 300 mg of protein in a 24-hour urine sample or ≥ 30 mg/mmol urinary protein). However, proteinuria maybe absent in which case preeclampsia can be diagnosed by the presence of de novo hypertension after 20 weeks' gestation with evidence of maternal acute kidney injury (AKI), liver dysfunction, neurological features, hemolysis or thrombocytopenia, or fetal growth restriction. in some cases, it may develop or be recognized for the first time intrapartum or early postpartum [12].
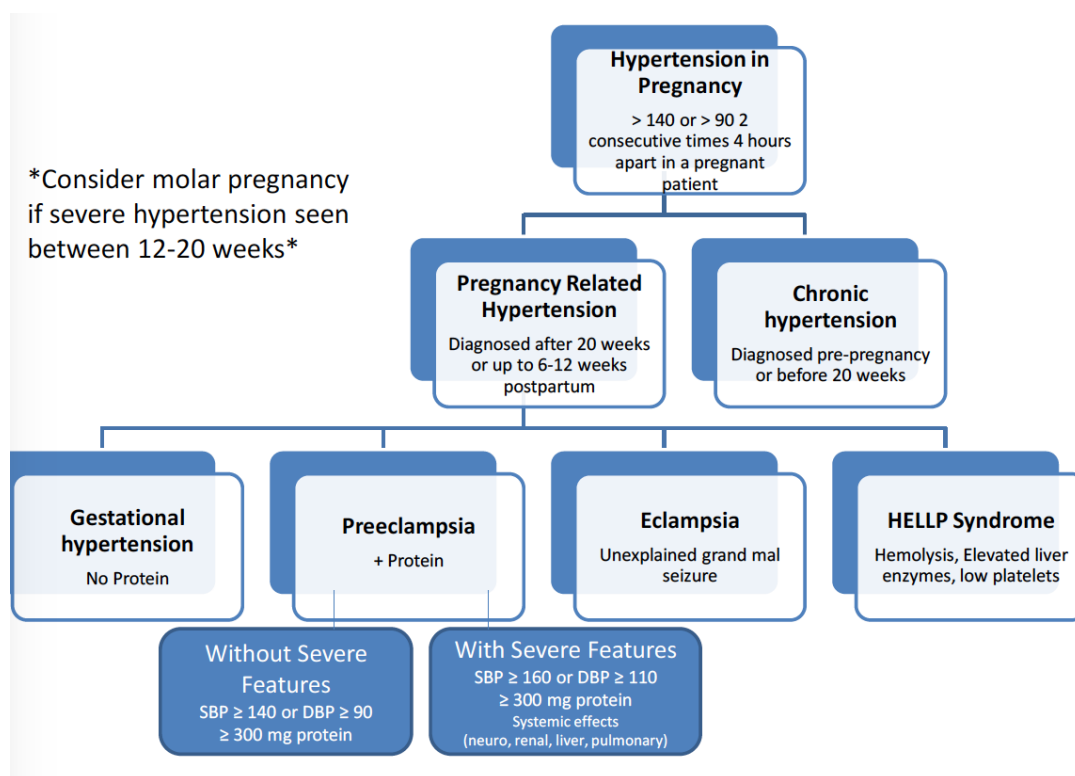
Figure 1; Classification of hypertensive disorders of pregnancy.

Source; https://d1yboe6750e2cu.cloudfront.net/i/ee9789e662e90aa1b30d5fda12c88474f1be767d

Preeclampsia superimposed on chronic hypertension is defined as chronic hypertension associated with further worsening of Blood Pressure and protein excretion ≥3 g/d in 24-hour urine collection after the 20th week of gestation[13].

Table 1; Definition and classification of HDP by various groups.

	Categories	Definitions
European Society of Cardiology (ESC)[14] 2018	Pre-existing hypertension Gestational hypertension Preeclampsia Pre-existing hypertension plus superimposed gestational hypertension with proteinuria Antenatally unclassifiable hypertension	Hypertension: SBP≥140 mmHg and/or DBP≥90 mmHg Mild: BP 140–159/90–109 mmHg Severe: SBP≥160 mmHg or DBP≥110 mmHg Emergent: SBP≥170 mmHg or DBP≥110 mmHg
American College of Obstetricians and Gynecologists (ACOG)[15] 2019	Chronic Hypertension Preeclampsia-eclampsia Chronic hypertension with superimposed preeclampsia Gestational hypertension	Hypertension: SBP≥140 mmHg and/ or DBP≥90 mmHg, measured at least 4h apart Severe: SBP≥160 mmHg and/ or DBP≥110 mmHg, measured at least 4h apart
Hypertension Canada[16] 2018	Chronic hypertension Gestational hypertension Preeclampsia (includes non-severe preeclampsia, severe preeclampsia, HELLP syndrome, eclampsia)	Hypertension: BP≥140/90 mmHg Severe: BP≥160/110 mmHg
Society of Obstetricians and Gynaecologists of Canada (SOGC)[17] 2014	Pre-existing (chronic) hypertension - With comorbid condition(s) - With evidence of preeclampsia Gestational hypertension - With comorbid condition(s) - With evidence of preeclampsia Preeclampsia Other hypertensive effects - Transient hypertensive effect - White-coat hypertensive effect - Masked hypertensive effect	Hypertension: SBP≥140 mmHg and/or DBP≥90 mmHg, measured at least 15min apart Severe: SBP≥160 mmHg and/or DBP≥110 mmHg
International Society for the Study of Hypertension in Pregnancy (ISSHP)[12] 2018	Chronic hypertension - Essential - Secondary White-coat hypertension Masked hypertension Gestational hypertension Transient gestational hypertension Preeclampsia – de novo or superimposed on chronic hypertension	Hypertension: SBP≥140 mmHg and/ or DBP≥90 mmHg, confirmed over a few hours Severe: SBP≥160 mmHg and/ or DBP≥110 mmHg, confirmed within 15min

Society of Obstetric Medicine of Australia and New Zealand (SOMANZ)[18] 2014	Preeclampsia - eclampsia Gestational hypertension Chronic hypertension - Essential - Secondary White Coat Preeclampsia superimposed on chronic hypertension	Hypertension: SBP⩾140 mmHg and/ or DBP⩾90 mmHg measured several hours apart Severe: SBP⩾160 mmHg or DBP⩾110 mmHg
Royal College of Obstetricians and Gynaecologists (RCOG)[19] 2011	Chronic hypertension Gestational hypertension Preeclampsia Severe preeclampsia Eclampsia HELLP	Hypertension: SBP⩾140 mmHg and/ or DBP⩾90 mmHg Mild: BP 140–149/90–99 mmHg Moderate: BP 150–159/100–109 mmHg Severe: SBP⩾160/110 mmHg

Pathophysiology

For a pregnancy to be successful (including optimal growth of the fetus), there has to be an intricate balance between immune suppression and immune tolerance. The immunology in pregnancy is such that the maternal immune system has to be suppressed to tolerate the fetus despite considering it a 'foreign body', the body has to do this in a way that it still works to prevent infections[20].

 Mor and colleagues[21] separated pregnancy into three immunological events characterized by specific biological processes. First immunological phase which occurs during early pregnancy (which includes implantation and placentation) is pro-inflammatory, the second immunological phase which occurs in mid-pregnancy (a period of rapid growth and development of the fetus) is anti-inflammatory, and the last immunological phase occurs near parturition and is proinflammatory. A dysfunction in the maternal immune response could lead to the development of preeclampsia. In preeclampsia, increased TNF-α and IL-6 (which are pro-inflammatory) and decrease levels of IL-4 and IL-10 (which are anti-inflammatory) are seen in the peripheral and placental circulation, which leads to chronic inflammation[22-25]. Multiple human studies have demonstrated a predominance of TH-1 cytokine profile which are proinflammatory in preeclampsia[26]. Figure 2 gives a summary of the pathophysiology of preeclampsia

In normal pregnancy, there is an increase in the circulating levels of renin, angiotensinogen and angiotensin II[27], although there is decreased vascular sensitivity to angiotensin II[28]. In preeclampsia however, plasma renin activity is supressed[29] and an increased vascular sensitivity to angiotensin II is seen[28]. Plasma renin concentrations and activity is reduced in women with PIH compared to women with normal pregnancy[29]. Figure 3 gives a summary of the pathogenesis and potential therapeutic markers for preeclampsia.
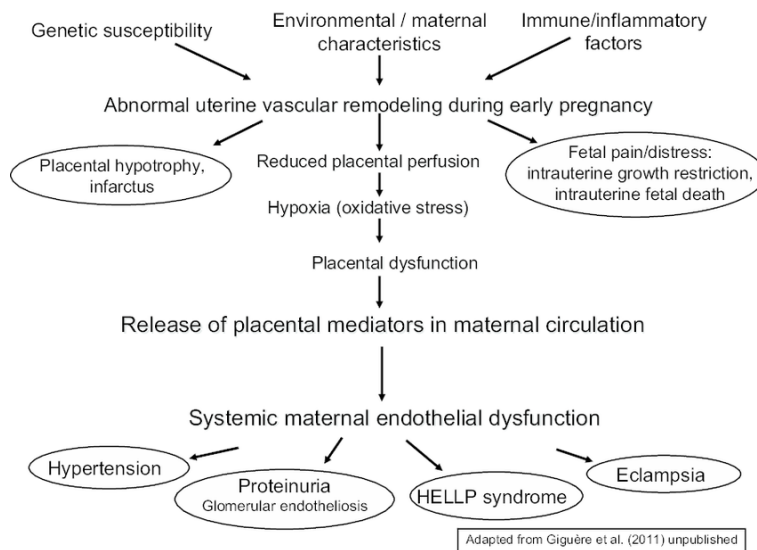
Figure 2; Pathophysiology of pre-eclampsia. Adapted from [30]

Risk factors

Modifiable risk factors

Many studies have documented positive associations between, low education, pre-pregnancy overweight/obesity, excessive weight gain during pregnancy, smoking, aneamia, alcohol intake and HDP[31-33]

Non modifiable risk factors

A number of studies have shown that advanced maternal age, primiparity, previous history of HDP, previous history of pregnancy complication, family history of cardiovascular disease, multiple gestation, gestational diabetes mellitus[31, 33-35] are risk factors for HDP.
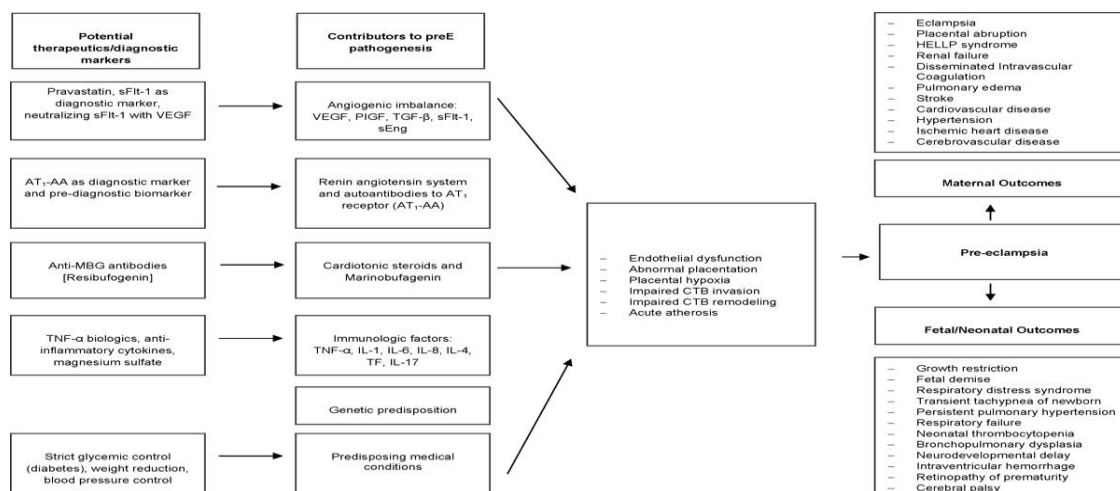
Figure 3; Pathogenesis and potential diagnostic markers and of Hypertensive disorders of pregnancy

Complication in children

A systematic review done by Kate et al.[36] observed that women with chronic hypertension had high pooled incidences of superimposed preeclampsia, caesarean section, preterm delivery (<37 weeks gestation), low birth weight (<2500 g), neonatal unit admission, and perinatal death. They also found that the incidences of adverse outcomes in women with chronic hypertension when compared with women from the US national population dataset showed higher risks.

A study done in Italy by Daniela Z et al.[37] on maternal complications in pregnancy and wheezing in early childhood found that the adjusted pooled RR for children who ever had wheezing and those with recurrent wheezing in children whose pregnancy was complicated by preeclampsia were; 1.09 (95% CI: 1.01–1.18) and 1.23 (95% CI: 1.07–1.43) respectively. Forgive et al.[38] reported that infants of women with HDP were more likely to be small for gestational age than the infants of women without HDP (31.7% vs. 10.6%, p<.002). Another study carried out by Jensen et al.[39] found that women with HDP were more likely to give birth to preterm infants who were SGA than to preterm infants who were not SGA.

A study done by Edwina et al.[40] on the developmental origins of cardiovascular disease shows that fetal adaptions during pregnancy, such as malnutrition caused by hypertension and/or placental ischemia during pregnancy, increases the offspring's risk of developing hypertension, stroke, diabetes, and Cardiovascular diseases later in life.

A population based sibling cohort showed that prenatal exposure to preeclampsia was associated with an increased risk of metabolic disorders (rate ratio, 1.6; 95% CI, 1.5–1.7) and respiratory disorders (rate ratio, 1.2; 95% CI, 1.1–1.2) among children born at term[41]. Another study done in Iceland by Sverrisson et al.[42] showed that children exposed to preeclampsia/eclampsia scored lower than those unexposed in mathematics across all grade levels, corresponding to a difference of 0.44 points (95% CI: 0.00, 0.89), 0.59 points (95% CI: 0.13, 1.06) and 0.59 points (95% CI: 0.08, 1.10), respectively.

Complications on mothers

A study carried out by Meriem et al.[43] on the short term outcome of patients with preeclampsia, found that preeclampsia was observed to be complicated in 13.5% of the patients by intrauterine growth restriction, in 14.8% by a HELLP syndrome, in 4.5% by IUFD, and in 1.3% by a retroplacental hematoma. It also showed that in the immediate postpartum period, 66% of patients had maintained elevated blood pressure levels, and 66% had proteinuria > 0.3 g/24 hours. At the 3-month postpartum assessment, persisting arterial hypertension was found in 16% of the patients, requiring continuation of antihypertensive therapy, and 22% of the patients had proteinuria over the accepted threshold (0.15 g/24 hours).

In a meta-analysis by Pensée Wu et al.[44] which included more than 6.4 million women with more than 258,000 women with preeclampsia and 39 years of follow-up, demonstrated that women with a history of preeclampsia have a 71% increased risk of CVD mortality, a 2.5-fold increase in risk of CAD, and a 4-fold increase in heart failure risk when compared to women without a history of preeclampsia.

In a study which assessed the association between gestational hypertension and risk of cardiovascular disease among 617 589 Norwegian women, which used data from the Medical Birth Registry of Norway and included all women with a first delivery from 1980 through 2009 they concluded that gestational hypertension was associated with increased risk of subsequent CVD, and observed the risk to be higher when gestational hypertension was combined with small for gestational age infants and/or preterm delivery[45].

Another study which included women aged 16 to 49 years who gave birth during 1980–2002 and registered in the Medical Birth Registry of Norway who were followed prospectively (1–29 years) they found that, the hazard ratio for major coronary event after preeclampsia alone compared with women without preeclampsia was 2.1 (95% CI 1.73–2.65), 3.3 (95% CI 2.37–4.57) after preeclampsia in combination with small for gestational age, and 5.4 (95% CI 3.74–7.74) after preeclampsia in combination with preterm delivery, hence the risk of major coronary events increases when preeclampsia is complicated by SGA or preterm delivery.

In a Canadian study including over 1 million women with 25 years of follow-up, it was found that recurrent preeclampsia was associated with a significantly greater risk of CVD. Relative to women without preeclampsia, women with recurrent preeclampsia had 4 times the risk of atherosclerosis when compared to women with more than 2 deliveries, and twice the risk of atherosclerosis when compared to women with nonrecurrent preeclampsia. This relationship held across all cardiovascular outcomes[46].

Scantlebury, D. C. et al.[47] conducted a nested case–control study within a cohort of 7566 women who had a live or stillbirth delivery in Olmsted County, Minnesota between 1976-1982 on the impact of a history of hypertension in pregnancy on later diagnosis of atrial fibrillation, they found that cases were more likely to have a history of HPDs, compared with controls: 28/105 (26.7%) cases versus 12/105 (11.4%) controls, odds ratio: 2.60 (95% confidence interval, 1.21–6.04).

Another study carried out on pregnant women resident in Avon, United Kingdom[48], found that gestational hypertension and preeclampsia were associated with greater BMI, waist circumference, systolic and diastolic blood pressure, insulin, proinsulin, and triglycerides and lower HDL cholesterol in both the basic and confounder-adjusted models. The calculated risk of a CVD event over 10 years was elevated in women with HDP compared with those without[48].

Even though there has been continuous tremendous improvement in healthcare services and delivery compared to previous decades, the global rise in the incidence of hypertension in recent times due to dietary and life style changes, frequent postponement of pregnancy until advanced maternal age (>35 years) for career purposes which is a risk factor for preeclampsia and gestational hypertension[49-52], this increased age itself is increases the risk of hypertension, all results in higher prevalence of HDP. However, the occurrence of HDP is not equally distributed as the prevalence is higher in underdeveloped and developing countries compared to the developed countries[13, 53-57].

Hypertension is the commonest medical complication encountered during pregnancy[58], it is associated with significant morbidity and mortality of the mother and fetus. HDP are ranked the second commonest cause of direct maternal death in the developed world[59]. They complicate 5–10 % of pregnancies globally[13], it is estimated that 192 people die every day because of hypertensive disorders in pregnancy[60].

The clinical symptoms of HDP usually gets resolved after delivery of the placenta, however women affected and their offspring have double the risk for subsequent cardiovascular complications such as heart diseases, stroke and diabetes mellitus over the subsequent 5–15 years after delivery and these women have greater risks of dying from cerebrovascular diseases after pregnancy compared to women who had a normotensivepregnancy[61, 62].

Chapter 2

Aim and objectives

Aim

This study is aimed at investigating long and short-term complications of hypertensive disorders of pregnancy in women and children.

Objectives

The aims shall be achieved through the following objectives:

1. To identify/assess short and long term complications in women who had pregnancies complicated by hypertensive disorders in pregnancy.
2. To evaluate short- and long-term complications in children with prenatal exposure to maternal hypertensive disorders during gestation.

Chapter 2

Chapter 3

Methods

Study design

This study is based on information obtained from a population-based birth cohort, Generation XX1. A total of 8495 mothers who gave birth to 8647 live infants were enrolled. Recruitment took place between April 2005 and September 2006, at all five public maternity units covering the metropolitan area of Porto, Portugal, during the post-delivery admission (between 24 and 72 hours after delivery), more information about the cohort is given in [63]. Data regarding their demographics, socioeconomic status, habits, family history, gynecological and obstetric history were collected via face-to-face interview by trained interviewers. Hospital and pregnancy records were reviewed for associated medical conditions, pregnancy and delivery data and complications. At 48 and 84 months follow up periods data on diseases, medications, physical activities, habits, anthropology and biochemistry were collected from mothers and children.

Exposure variable

We considered women to have HDP if they had pre-pregnancy (chronic) hypertension, gestational hypertension, preeclampsia, eclampsia or HELLP syndrome. The outcome variable was computed by adding up the aforementioned variables. To deal with missing values due to participants not responding to these questions on the questionnaire, we also used data extracted from their hospital records (clinical process).

Outcome variables

The outcome variables in both mothers and children were broadly divided into short term and long term. Short term outcomes variables in children included prematurity, small for gestational age (SGA), admission into neonatal intensive care unit (ICU), being resuscitated, developing neonatal jaundice, receiving blood transfusion, and neonatal death. Long term outcome variables were asthma, wheezing, rhinitis, pneumonia, obesity, hypertension, growth, language and behavioural disorders, social problems, renal and liver disorders, and delayed development. Data on these variables were collected at the 48 and 84 months follow up periods as indicated.

Short term outcome variables in mothers included intrauterine growth restriction (IUGR), caesarean section, infections, hospital admission, and having multiple health problems. Long term outcome variables in mothers included new onset hypertension, diabetes, dyslipidaemia, depression, obesity, stroke, arrythmias, having other heart diseases, having multiple medical problems and being on chronic medication. The data was collected during

the 48 and 84 months follow up period, the outcome variables were computed by subtracting the participants who had the conditions before being enrolled in the cohort from all individuals with the conditions.

Statistical analysis

Categorical variables are presented as frequencies and percentages while continuous variables are reported as mean and standard deviation (SD). Categorical variables were compared using Pearson's χ2 test, associations were determined using rate ratios, while comparisons between categorical and continuous variable were done using student's t test. For all the statistical tests, a *p*-value < 0.050 was considered significant. All data analysis was carried out using Statistical Package for Social Sciences software (SPSS 25.0 for Macintosh, SPSS Inc., Chicago, Illinois).

Ethical consideration

The Ethical Committee of hospital Sao Joao approved the study. Written informed consent was obtained from all participants.

Chapter 4

Results

Table 2; Baseline characteristics of participants.

Characteristics	HDP	No HDP	p
Continuous	Mean (SD)	Mean (SD)	
Maternal age at birth(years)	30.10(5.61)	28.93(5.56)	<0.0001
Gestational age(weeks)	37.20(2.84)	38.58(1.84)	<0.0001
Educational status(years)	9.76(4.32)	10.54(4.26)	<0.0001
BMI (kg/m^2)			
Start of pregnancy	26.41(5.47)	23.72(4.13)	<0.0001
Gain in pregnancy	5.36(2.79)	5.26(2.28)	0.455
Categorical	N (%)	N (%)	
Parity			
Primipara	290(62.5)	4308(56.5)	0.012
Multipara	174(37.5)	3311(43.5)	
Marital status			
Married/cohabitting	454(95.4)	7241(93.9)	0.186
Single/Divorced /Widow	22(4.6)	471(6.1)	
Maternal age (years)			0.004
<30	218(45.8)	4023(52.1)	
31-35	182(38.2)	2802(36.3)	
>35	76(16.0)	898(11.6)	
Educational status(years)			
<9	197(41.4)	2529(32.7)	<0.0001
9-12	185(38.9)	3298(42.7)	
>12	94(19.7)	1896(24.6)	
Family income(€)			
<500	21(5.6)	370(6.2)	0.051
500-1500	221(59.2)	3143(52.8)	
>1500	131(35.1)	2443(41.0)	
Gestational diabetes			<0.0001
Yes	74(15.6)	4776.2)	
No	401(84.4)	7246(93.8)	
Smoking during pregnancy			
No	324(68.1)	4770(61.8)	0.006
Yes	152(31.9)	2950(38.2)	
Mode of delivery			
Vaginal	216(45.4)	4949(64.1)	<0.0001
Eutocic	159(3.9)	3874(96.1)	

	51(4.9)	3874(96.1)	
Vacuum	51(4.9)	3874(96.1)	
Forceps	6(6.2)	91(93.8)	
Caesarian	260(54.6)	2773(35.9)	<0.0001
Gestational age (weeks)			<0.0001
<32	29(6.1)	105(1.4)	
32-36	96(20.2)	570(7.4)	
>36	351(73.7)	7048(91.3)	
Singleton birth			<0.0001
Yes	442(92.9)	7477(96.8)	
No	34(7.1)	246(3.2)	
Infant sex			0.198
Male	257(54.0)	3935(51.0)	
Female	219(46.0)	3788(49.0)	
Birth weight(grams)			
<1500	34(7.1)	81(1.0)	<0.0001
1500-2499	85(17.9)	561(7.3)	
2500-4000	345(72.5)	6807(88.1)	
>4000	12(2.5)	274(3.5)	
5 minutes APGAR score			
<7	6(1.3)	93(1.2)	0.913
≥7	470(98.7)	7630(98.8)	

Baseline characteristics

The total number of women included in this study is 8184, 476 women (5.8% of all women included) had HDP, of these 224 women had gestational hypertension, 165 had preeclampsia and 150 women had chronic hypertension (of which 11 had superimposed preeclampsia). The distribution of HDP is summarized by the Venn diagram in Figure 4.

Baseline characteristics of participants are summarized in Table 2. Compared with women who were normotensive, those with HDP were older (mean age 30.10 ± 5.61years versus 28.93 ± 5.56 years p;<0.0001), most of them were primipara (62.5% vs 56.5% p=0.012) and married (95.4% vs 93.9% p =0.186), they tend to be less educated (19.7% has more than 12 years of education vs 24.6% p<0.0001).

Women with HDP were more likely to develop gestational diabetes compared with those without (15.6% vs 6.2% p<0.0001), more likely to have multiple gestation (7.1% vs 3.2%, p<0.0001), they were also more likely to have a caesarean delivery (54.6% vs 35.9%, p<0.0001). However, there was no significant difference in the family income.

Compared to neonates of mothers without HDP, those born by women who had HDP were more likely to be of low birth weight (LBW) or very low birth weight (VLBW) (7.1% vs 1.0% and 17.9 vs 7.3 respectively, p<0.0001), and were more likely to be born late preterm or very

preterm (6.1% vs 1.4% and 20.2% vs7.4% respectively, p <0.0001). However, there was no significant difference in the gender and their APGAR scores. BMI
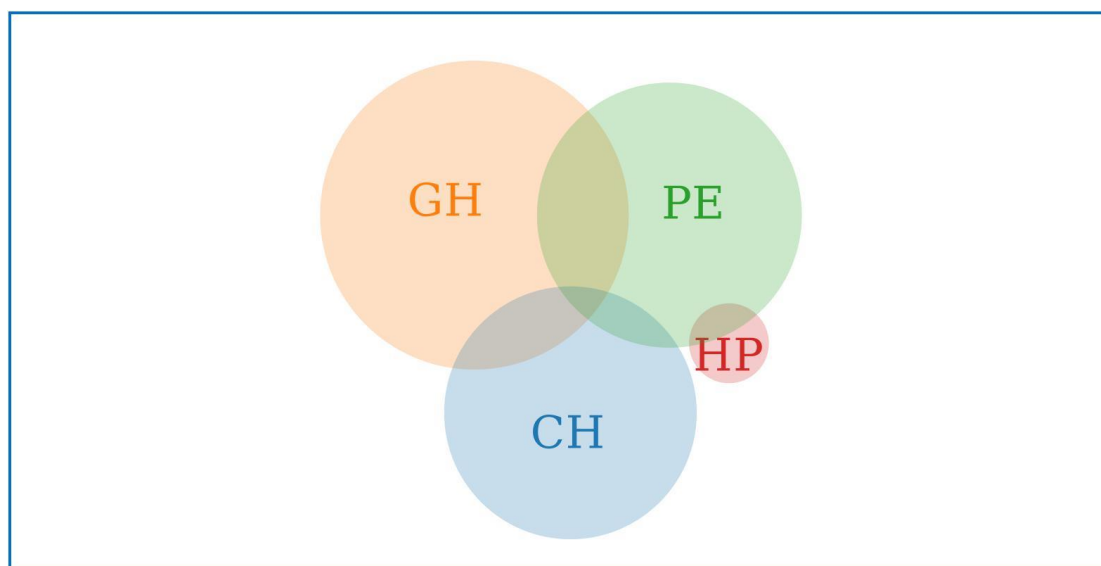
Figure 4; Diagram showing the distribution of HDP

CH; Chronic hypertension, GH; Gestational hypertension, PE; Preeclampsia, HE; Hemolysis, elevated liver enzymes, low platelet count (HELLP syndrome)

Short term Complications
Child

Neonates of women with HDP had 3 times (RR=3.005 95% CI 2.543-3.550) the risk of being born prematurely than those born by women who did not have HDP (Table 3), they were also more likely to be born SGA (8.1% vs 3.7% p <0.0001) having about 2 times(RR;2.185, 95% CI;1.565-3.051) the risk to be born SGA than the their contemporaries. These group of neonates were more likely to have been resuscitated (17.2% vs 8.3% p <0.0001), the risk of being resuscitated was 2.070 times (95% CI 1.675-2.558) as high as neonates born by mothers who did not have HDP.

The risk of being admitted into the neonatal intensive care unit (ICU), developing neonatal jaundice and having blood transfusions in neonates exposed to HDP was 2.689 (95% CI; 2.325-3.236) ,1.694 (95% CI; 1.432-2.004) and 1.679 (95% CI;1.331-2.164) times as high as those born by mothers unexposed respectively.

Mothers

The risk of being admitted during pregnancy in women with HDP was 2.482 (95% CI; 2.102-2.931) times as high as the risk in women who were not exposed. Women exposed to HDP

had 2.280 (95% CI; 0.976-5.321) times the risk of having babies with intrauterine growth restrictions compared to those who were not exposed (Table 4).

Although the rate of caesarean section in the entire sample was high (36.8%), the risk of having a caesarean section in women who had HDP was 1.531 (95% CI 1.403-1.671) as high as those who did not have HDP.

Table 3; Short term complications in child.

Complication	HDP	No HDP	RR	95% CI	p
Prematurity eco	125(26.3)	675(8.7)	3.005	2.543-3.550	<0.001
Small for gestational age	36(8.1)	278(3.7)	2.185	(1.565-3.051)	<0.001
Admission into ICU	104(22.5)	632(8.4)	2.689	2.235-3.236	<0.001
Resuscitation	81(17.2)	637(8.3)	2.070	(1.675-2.558)	<0.001
Other problems	89(19.2)	892(11.8)	1.633	1.342-1.988	<0.001
Jaundice	114(24.9)	1112(14.7)	1.694	1.432-2.004	<0.001
Blood transfusion	16(15.1)	628(8.9)	1.697	1.331-2.164	<0.001
Neonatal death	2(50)	2(0.0)	18.470	2.608-130.795	<0.001

ICU; intensive care unit

Table 4: Short complications in mothers

Complication	HDP	No HDP	RR	95% CI	p
Infections	42(8.8)	654(8.4)	1.059	0.786-1.426	0.708
Others	196(42.4)	1578(20.4)	2.076	1.851-2.329	<0.001
IUGR	6(1.3)	44(0.6)	2.280	0.976-5.321	0.051
Cesarean section	256(54.9)	2744(35.9)	1.531	1.403-1.671	<0.001
admission	121(26.3)	814(10.6)	2.482	2.102-2.931	<0.001
UTI	28(6.1)	681(8.8)	0.687	0.477-0.991	0.041

IUGR; intrauterine growth restriction, UTI; urinary tract infection.

Table 5: Complications in child 48months

Complication	HDP	No HDP	RR	95% CI	p
Asthma	22(5.7)	268(4.3)	1.327	0.870-2.024	0.191
Rhinitis	22(5.8)	260(4.2)	1.380	0.904-2.106	0.137
Pneumonia	15(3.7)	151(2.3)	1.619	0.961-2.726	0.069
Hospital admission	185(45.3)	2599(39.2)	1.158	1.036-1.293	0.013
Growth disorder	21(5.2)	241(3.6)	1.421	0.920-2.195	0.113
Language disorder	87(21.3)	1209(18.3)	1.168	0.914-1.014	0.121
Hypertension	50(17.5)	562(13.4)	1.306	1.004-1.699	0.051
Child complication	141(51.1)	2178(54.3)	0.940	0.835-1.059	0.294

Table 6: Complications in mothers 48months

Complication	HDP	No HDP	RR	95% CI	p	missing
Hypertension	161(44.7)	446(6.9)	6.511	5.628-7.532	<0.0001	80.1
Dyslipidemia	83(21.7)	982(15.2)	1.426	1.169-1.740	0.001	80.1
Diabetes	83(21.4)	790(12.2)	1.761	1.440-2.155	<0.0001	80.1
Depression	130(32.7)	2045(31.5)	1.036	0.896-1.198	0.637	80.0
Angina	1(0.3)	7(0.1)	2.218	0.274-17.978	0.444	64.4
Arrythmia	33(9.9)	313(6.0)	1.633	1.161-2.297	0.005	64.2
Rheumatic fever	5(1.5)	71(1.4)	1.092	0.444-2.686	0.848	64.3
Other Heart diseases	12(3.0)	204(3.1)	0.958	0.540-1.699	0.882	79.9
Stroke	8(2.4)	17(0.3)	7.322	3.183-16.843	<0.0001	64.3
Medical conditions	183(54.6)	2244(43.2)	1.264	1.141-1.401	<0.0001	80.1
Chronic medication	204(50.9)	2230(33.9)	1.499	1.354-1.660	<0.0001	80.1
Mothers complication	287(87.2)	2908(56.4)	1.547	1.475-1.623	<0.0001	

Table 7: Complications in child 84months

Complication	HDP	No HDP	RR	95% CI	p
Asthma	22(5.8)	389(6.4)	0.905	0.597-1.373	0.638
Wheezing	162(50.6)	2577(49.6)	1.021	0.913-1.142	0.713
Rhinitis	27(7.1)	476(7.8)	0.908	0.625-1.319	0.610
parcer	3(0.9)	9(0.2)	5.400	1.469-19.848	0.004
Hypertension	188(59.9)	2264(45.6)	1.315	1.194-1.448	<0.0001
GI problem	13(4.0)	279(5.4)	0.756	0.438-1.303	0.309
Cardiac problem	14(4.4)	269(5.2)	0.843	0.499-1.426	0.523
Renal problem	8(2.5)	208(4.0)	0.629	0.313-1.262	0.185
Liver problem	2(0.6)	15(0.3)	2.159	0.496-9.401	0.294
Obesity	6(1.9)	105(2.0)	0.930	0.412-2.100	0.861
Language problem	73(19.0)	973(15.9)	1.198	0.967-1.484	0.104
Social problem	27(7.0)	375(6.1)	1.145	0.786-1.669	0.481
Behavioral problem	64(16.7)	737(12.1)	1.386	1.098-1.751	0.007
Admissions	25(6.5)	368(6.0)	1.084	0.732-1.603	0.689
Delayed development	13(3.4)	154(2.5)	1.344	0.770-2.344	0.298
More than 3 problems	5(1.7)	27(0.5)	3.069	1.190-7.913	0.015
Child complication	98(32.1)	1586(31.9)	1.008	0.852-1.192	0.927

Table 8: Complications in mothers 84 months

complications	HDP	No HDP	RR	95% CI	p
Stroke	1(0.3)	9(0.2)	1.739	0.221-13.693	0.595
Asthma	14(3.7)	241(4.1)	0.909	0.536-1.543	0.724
Diabetes	7(1.9)	22(0.4)	5.167	2.222-12.015	<0.0001
Dyslipidemia	13(3.7)	85(1.5)	2.489	1.403-4.418	0.001
Hypertension	31(10.2)	140(2.4)	4.279	2.951-6.204	<0.0001
Obesity	12(3.2)	34(0.6)	5.525	2.885-10.581	<0.001
Depression	40(10.7)	555(9.5)	1.128	0.833-1.528	0.438
Mother complication	149(39.8)	1059(18.1)	2.203	1.923-2.523	<0.001

Table 9; Mean differences in blood pressure measurements in children.

	Mean difference	95% CI	p	SE
Systolic BP 48months	1.005	-0.001-2.010	0.050	0.513
Diastolic BP 48 months	0.958	-0.020-1.937	0.055	0.499
Systolic BP 84 months	2.335	0.864-3.806	0.002	0.750
Diastolic BP 84 months	2.326	1.434-3.218	<0.0001	0.455

long term complications

Child

At 48 months follow up, children whose pregnancy was complicated by HDP were more likely to develop asthma, rhinitis, pneumonia, hypertension, growth and language problems than children whose pregnancy was not exposed, however these differences are not statistically significant (Table 5). Nevertheless, the risk of being admitted into the hospital in these children was 1.158 times (95% CI;1.036-1.293) as high as the risk in those children who were not exposed.

At 84 months of follow up, children whose pregnancy was exposed to HDP had more tendency of having language problems (19.0% vs 15.9%), social problems (7.0% vs 6.1%), delayed development (3.4% vs 2.5%) however these differences are not statistically significant (Table 7). However, the risk of becoming hypertensive was 1.315 (95% CI; 1.194-1.448) as children whose pregnancy was not complicated with HDP, Table 9 shows the mean differences in the systolic and diastolic blood pressure measurements, the risk of having behavioural problems in these children was 1.386 (95% CI;1.098-1.751) times as high as the risk in children whose pregnancy was not exposed to HDP. Also, these children

had 3.069 (95% CI;1.390-7.913) times the risk of having 3 or more medical problems compared to children whose pregnancy was not exposed.

Mother

At 48 months follow up we found that, women who were exposed to HDP had 6.511 (95% CI; 5.628-7.532) times the risk of developing new onset hypertension compared to those not exposed (Table 6), the risk of developing new onset dyslipidaemia in these women was 1.426 times (95% CI; 1.169-1.740) as high as the risk in women not exposed to HDP. These women also had 1.761 times (95% CI; 1.440-2.155) the risk of developing new onset diabetes compared to women unexposed, they had 7.322 times the risk (95% CI;3.183-16.843) of having a stroke, 1.264 times the risk (95% CI;1.141-1.401) of suffering from other medical conditions, 1.499 times the risk (95% CI;1.354-1.660) of taking chronic medications and 1.633 times the risk (95% CI;1.161-2.297) of developing arrythmias compared to women who didn't have HDP. Even though these women had an increased tendency of developing depression (32.7% vs 31.5%) and rheumatic fever (1.5% vs 1.4%), these differences were not significant.

At 84 months follow up, women who were exposed to HDP had 4.279 times the risk (95% CI; 2.951-6.204) of developing hypertension (Table 8), 5.167 times the risk (95% CI; 2.222-12.015) of developing diabetes, 2.489 times the risk (95% CI; 1.403-4.418) of developing dyslipidaemia and 5.525 times the risk (95% CI; 2.885-10.581) of being obese compared to women who are not exposed to HDP. Although these women have a slightly higher tendency of being depressed (10.7% vs 9.5%), it was however not statistically significant.

Table 10; Mean differences between mothers with and without HDP 8yrs

	Mean difference	95% CI	p
Total cholesterol	4.590	0.988-8.193	0.013
HDL	1.851	0.482-3.220	0.008
LDL	2.678	-0.395-5.752	0.088
Triglycerides	-0.489	-5.045-4.068	0.834
Glucose	-0.415	0-1.399-0.570	0.409
Glycated heamoglobin	0.147	-0.441-0.736	0.624

Table 11; Mean differences between mothers with and without HDP 4yrs

	Mean difference	95% CI	p
Total cholesterol	8.779	2.393-15.166	0.007
LDL	7.908	2.591-13.225	0.004

| HDL | -0.805 | -2.996-1.386 | 0.471 |
| Triglycerides | 9.682 | 1.309-18.069 | 0.023 |

CHAPTER 5

Discussion

Prevalence

The prevalence of HDP in our study was found to be 5.8%. This is similar to what was obtained in Haiti (5.8%) by Bridwell M. et al.[64], and to what A. M. Povoa et al.[65] found (6%) in their study which measured the prevalence of HDP in Portugal, a little higher that what Chun Ye et al.[55] obtained from China (5.2%), and much higher than what was obtained in the study based on WHOMCS database where found that 2.73% of their of women in their database had HDP[66], which is similar to the study done in Western Saudi Arabia by Subki AH et al[67] where they found the prevalence to be 2.4%. However, the prevalence is much higher in underdeveloped and developing countries[53, 57, 68, 69], this could be due to poor health systems and other underlying issues like malnutrition, poverty, etc.

Risk factors

We found a positive association between higher maternal age and the risk of HDP (16% versus 11.6% in participants older than 35years), this is similar to the findings in China, where the risk of HDP was 1.8 times higher in those aged 35-39 years and 2.4 times higher in women aged 40 years and above compared to those aged 20-24 years[55], the WHOMCS database study[66] has shown that the risk of women aged >35 years to develop PE was 1.78 the risk of those aged 20-35 years, more studies have found similar findings[31, 67, 70-72].

Primiparity is said to be a risk factor for developing HDP, in our study 62% of women who had HDP were primipara as opposed to 56.7% of women without HDP, this finding is similar to what was obtained by Alves, Elisabete et al.[56] where 5% of primiparae and 4% of multiparae had HDP, a study based on WHOMCS database[66] also found that 61.6% of women with eclampsia and 42.0% of women with preeclampsia were primigravid as opposed to the group of those without eclampsia/preeclampsia where only 36.3% were primigravid. Similar findings were also obtained in China and Saudi Arabia [55, 67].

We found HDP to be associated with multiple gestation, the rates of multiple gestation was 9.6% in women with HDP versus 3.2% in women who didn't develop HDP. This is similar to the findings of the WHOMCS database which showed a 2.55-fold higher risk of preeclampsia

in multiple gestation compared with those with singleton. This is also similar to the findings of a Chinese study where 16.29% of women with twin pregnancy developed HDP compared to 5.02% of those with singleton pregnancy[73].

We observed a positive association between women with less education and HDP, 40.8% of women with HDP had less than 9 completed years of education compared to 32.9% among women without HDP (p =0.002). A study from china weakly supports this where they showed that women with low education had 1.06 (95% CI;1.03-1.10) the risk of developing HDP compared to those with higher education[55], this is in keeping with the observations made by the WHOMCS database study[66] where they found that women who went to school for 0 years and 5-8 years has 1.20 and 1.21 times respectively the risk of preeclampsia compared to women who had higher than 11 or more years of education, however they did not find a significant difference in the risk of preeclampsia between subjects that went to school for 1-4 years, 9-11 years and > 11 years, which is similar to the findings of some cross-sectional studies carried out in Latin America and Taiwan, which shows no association between educational status and the risk of preeclampsia[74, 75].

Short term complications
Child

We found the risk of having SGA babies in women with HDP to be 2.185 (95% CI;1.565-3.051) times as high as the risk in women without HDP. This can be explained by inadequate growth of the fetus in utero due to altered placental bed perfusion hence decreased availability of nutrients and other substances necessary for adequate growth and development. Same findings have been reported by some studies[26, 38, 76, 77].

The risk of being born premature in neonates exposed to HDP was 3.005 (95% CI 2.543-3.550) times the risk in neonates not exposed, this is in keeping to a Chinese study (29.36% vs 6.78% p;0.001)[55] where they found the prevalence of preterm birth to be significantly higher in women with HDP compared to women without, many studies have shown similar findings[36, 55, 64, 77, 78]. This is mainly because when HDP gets severe and expectant management cannot be continued, the baby has to be delivered to save the lives of both mother and child. However, these preterm babies face complications which are proportionate to how early they were delivered, mainly due to immature organ systems that are not yet prepared for extrauterine environment, these complications can also be explained by underdevelopment caused by altered placental perfusion. These complications include, respiratory distress syndrome (respiratory difficulties due to immaturity of the lung and lack of surfactant) which is sometimes followed by bronchopulmonary dysplasia and chronic lung disease, feeding problems, necrotizing enterocolitis (injury to intestines due to immaturity),

hearing and visual problems, cardiovascular disorders (ranging from morphological defects to dysfunctional autoregulation), e.t.c [79].

The risk of getting admitted into the neonatal ICU in babies exposed to HDP was found to be 2.689 (95% CI;2.235-3.236) times as high as the risk in babies unexposed. This is because these neonates are faced with numerous challenges and complications as aforementioned. For example, the risk for the need to be resuscitated in babies exposed to HDP was 2.070 times (95% CI;1.675-2.558) as high as the risk in babies unexposed, the risk of developing neonatal jaundice in neonates exposed to HDP was 1.694 times (95% CI 1.432-2.004) the risk of unexposed neonates, the risk of receiving blood transfusion in exposed babies was 1.697 times (95% CI 1.331-2.164) the risk in the unexposed, also the risk to have other problems was 1.633 times (95% CI;1.342-1.988) the risk in babies unexposed, this can be explained by the fact that their bodies are not mature enough to adapt to the extrauterine environment, hence, their need for special support and continuous close monitoring to thrive. Of the 4 neonates that died in the cohort, 50% of them were exposed to HDP, despite only 5.8% of the neonates were exposed to HDP. Table 12 shows the similar findings by other studies.

Table 12; Findings of different studies on immediate complications of HDP in offspring

Author		prematurity	SGA	NICU	LBW
Our study	HDP	3.005(2.543-3.550)	2.185(1.565-3.051)	2.689(2.235-3.236)	
Kate et al [36] 2014	Chronic hypertension	Yes		Yes	yes
Forgive et al.[38] 2019	HDP	-	31.7% vs. 10.6%, p<.002)	-	-
Jensen et al.[39]2019	Pre/eclampsia, GH	-	Yes (p <0.001)	-	-
Adu-Bonsaffoh et al. [76] 2017		-	2.693 (1.659–4.373)	-	3.918 (2.385–6.438)
Allen et al.[80] 2004	HDP	-	1.6(1.5-1.6)	-	-
Zhu et al. [77] 2016	HDP	22.2% vs 5.1%	11.4% vs 4.7%	-	-
Ye C. et al [55] 2014	HDP	29.36% vs 6.78%	-	-	27.39% vs 5.70%
Kwame et al. [76] 2017	HDP	-	-	1.745(1.007-3.024)	2.496(1.272-4.897)
Wang et al. [78] 2011	HDP	1.41(1.22-1.63)	-	-	-
Mathew et al. [64] 2019	Haiti	27.9% vs 9.9% (<0.0001)	-	-	4.17, 95% CI 3.19–5.45)

Table 13; Findings of different studies on long term complications of HDP in offspring

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Author/year		Wheezing	Hypertension	Asthma
Our study 4 years 7 years	HDP	- 1.021(0.913-1.142)	1.168(0.914-1.014) 1.315(1.194-1.448)	1.327(0.870-2.024) 0.905(0.597-1.373)
Daniela Z et al[37] 2015	HDP	1.09 (1.01–1.18)	-	-
Edwina et al.[40]	HDP	-	Yes	-
Shaheen et al. [81] 2016	Preeclampsia	1.31 (0.94–1.82)	-	-
Xiaoqin Liu et al. [82] 2015	Preeclampsia	-	-	1.19 (1.15, 1.24).
Magnus M. et al. [83] 2016	Preeclampsia	-	-	1.19 (0.99–1.44)
Jakob S. et al. [84] 2017	Preeclampsia	-	-	1.09 (1.05–1.12)
Freke et al. [85] 2018	GH PE/HELLP	0.95 (0.63–1.42) 0.70 (0.36–1.39)	-	0.99 (0.57–1.73) 0.80 (0.32–2.01)
Mariana et al. [86] 2019	CH/GH	OR4.7 (1.29- 17.56).	-	-
Meng et al. [87]2019	PIH THP PE/eclampsia PE Eclampsia	-	-	1.45(1.29–1.63) 2.00(1.52–2.63) 1.28(1.25–1.32) 1.43(1.31–1.57) 1.56(1.13–2.15)
Palmstein et al. [88]	HDP	-	1.73 (1.06, 2.83)	-

PIH; pregnancy-induced hypertension, THP; transient hypertension of pregnancy

Table 14; Blood pressure findings of HDP exposed children in different studies.

	Age	Disorder	SBP(mmHg)	DBP(mmHg)
Our study	4 years 7 years	HDP	1.005 (-0.001-2.010) 2.335 (0.864-3.806)	0.958 (-0.020-1.937) 2.326 (1.434-3.218)
Lawlor et al.[89]	9-12 years	PE GH	2.04 (1.33-2.76) 1.82 (0.03-3.62)	1.10 (0.47-1.73) 1.26 (−0.32-2.85)
Fraser et al.[90]	9 years	GH PE	2.06 (1.28–2.84) 1.12 (−0.89–3.12)	1.11 (0.54–1.69) 1.71 (0.23–3.17)
Geelhoed et al.[91]	9 years	PE GH	2.05 (0.72-3.38) 2.04 (1.42-2.67)	1.00 (0.01-2.10) 1.07 (0.60-1.54)
Staley et al.[92]	7 years	CH GH PE	1.67 (0.48-2.86) 1.98 (1.32, 2.65) 1.22 (-0.52-2.97)	1.32 (0.41-2.23) 0.97 (0.46-1.48) 0.80 (-0.53-2.13)
Miettola et al.[93]	16 years	GH	2.7 (1.6-3.8)	3.4 (2.1-4.6)

PE; preeclampsia, GH; gestational hypertension, CH; chronic hypertension.

Table 15; Findings of different studies on complications of HDP

Author/year		C/S	IUGR	Placental abrupti
Our study	HDP	1.531 (1.403-1.671)	2.280(0.976-5.321)	-
Meriem et al.[43]	HDP	-	Yes	-
Ye C. et al. [55] 2014	HDP	2.92 (2.74-3.10)	-	-

Zhu et al. [77] 2016	HDP	64.9% vs 41.8%	-	-
Ye C. et al [55] 2014	HDP	76.95% vs53.365	-	3.20% vs 0.42%
Wang et al. [78] 2011	HDP	-	-	2.27 (1.32–3.91)
Mathew et al. [64] 2019	HDP	36.1% vs 30.1% (0.04)	-	1.8% vs 0.3% (0.04)

Table 16; Findings of different studies on complications of HDP

Author/year		Hypertension	Heart failure	CAD	CVD	Stroke	DM	Dyslipidemia
Our study 4 years 7 years	HDP	6.511(5.628-7.532) 4.279(2.951-6.204)	-	-	-	7.322(3.183-16.843) 1.739(0.221-13.693)	1.761(1.440-2.155) 5.167(2.222-12.015)	1.426(1.169-1.740) 2.489(1.403-4.418)
Pensée Wu et al[44]	Preeclampsia	-	4.19; (2.09–8.38)	2.50; (1.43–4.37)		1.81; (1.29–2.55)	4.19; (2.0–8.38)	-
Auger et al.[46]	Preeclampsia	-	-	-	yes	-	-	-
Fraser A. et al.[48] 2012	Preeclampsia	-	-	-	Yes	-	-	-
Berks et al. [94] 2013	Preeclampsia	-	-	1.89 (IQR 1.76–1.98)		1.55 (IQR 1.40–1.71)	-	-
Oliver-Williams et al.[95] 2019	GH	-	1.70(1.43–2.02)	1.40(1.26–1.54)	1.53(1.25–1.88)	1.35(1.14–1.60)	-	-
Bellamy et al.[96] 2007	Preeclampsia	3.70 (2.70-5.05)	-	2.16 (1.86-2.52)		1.81 (1.45-2.27)	-	-
Tooher et al.[54] 2017	Australia HDP	2.78(2.47–3.13)		2.16(1.98–3.84)		1.94(1.39–2.69)	-	1.07(1.01–1.14)XX
Behrans et al. [97]	HDP	12-25-fold higher	-	-	-	-	-	-
Jennifer et al [98]. 2018	GH Preeclampsia	HR 2.8(2.6-3.0) 2.2(2.1-2.3)	-		-	-	1.7(1.4-1.9) 1.3(1.3-1.4)	-
Thais C et al.[99] 2018	HDP	3.7(2.7-5.1)	4.19(2.09-8.38)	2.50(1.43-4.37)		1.81(1.29-2.55)		-

Wang et al. [78] 2011	HDP	-	-	0.96 (0.60–1.53)	-	2.04 (95% CI, 1.18-3.51)	2.74 (1.67–4.50)	-
Katrien et al[100]	HDP	Yes <0.0001	-	-	-	-	Yes 0.001	-

GH; gestational hypertension

Mothers

We found the risk of IUGR in mothers with HDP to be 2.280 times (95% CI; 1.080-5.881) as high as the risk in mothers not exposed, these could be due to the under perfusion of the placental bed hence inadequate growth and development of the fetus as stated earlier.

In recent years more women tend to opt for caesarian section due to different reasons[73, 101-104]. Despite the overall high prevalence of CS, we found the prevalence in women with HDP to be significantly higher than in those without (54.9% versus 35.9%, p<0.001. RR=1.531, 95% CI; 1.403-1.671), this is in keeping with what was obtained China where 76.95% of women with HDP had CS as compared to 53.36% of women who did not have HDP (OR=2.92, 95% CI; 2.74-3.10)[55], which is similar to the findings of the WHOMCS dataset study, where the rate of CS was significantly higher in women with preeclampsia and eclampsia, 60.8% and 58.0% respectively versus 27.7% in unaffected women. This can be explained by the fact that when HDP becomes severe and women starts to develop life threatening symptoms, expectant management cannot be continued, the baby has to be delivered immediately usually through CS even in women who ordinarily would opt for vaginal delivery to save the lives of both mother and child. The risk of being admitted in women with HDP was 2.482 times (95% CI; 2.102-2.931) that of women without. Women with HDP tend to have other problems compared to women without; 42.4% versus 20.4% (RR: 2.076, 95% CI: 1.851-2.329). Table 15 shows findings of other studies.

Long term complications
Child

At around 4years of age there was no significant difference in respiratory problems between children exposed and unexposed to HDP, Asthma 1.327 (95% CI 0.870-2.024), Rhinitis 1.380 (95% CI 0.904-2.106) and pneumonia 1.719 (95% CI 0.961-2.726). These findings are comparable to what was observed at 7 years of age, asthma 0.905 (95% CI 0.597-1.373), wheezing 1.021 (95% 0.913-1.142), rhinits 0.908 (95% CI 0.625-1.319). Which is similar to a number of studies Shaheen et al. [81], Freke et al. [85], Magnus M. et al. [83]. However, some studies have contrasting findings, Daniela Z et al[37] found the risk of wheezing in children exposed to HDP to be 1.09 (1.01–1.18) times the risk of those

unexposed, Mariana et al. [86] found chronic and gestational hypertension to be associated with high risk of recurrent wheezing OR 4.7 (1.29-17.56), Xiaoqin Liu et al. [82] found the risk of Asthma in exposed children to be 1.19 (1.15, 1.24) times that of unexposed, Jakob S. et al. [84] found the odds of asthma in exposed to be 1.09 (1.05–1.12) times the odds in unexposed, Meng et al. [87] also had similar findings. Table 13 gives a summary of different findings of studies on these subject.

Exposure to HDP was associated with an increased risk of hypertension during both 4 years 1.306 (95% CI 1.004-1.699) and 7 years follow up periods 1.315 (95% CI 1.194-1.448), with the risk at the latter period higher than the former. A number of studies have shown HDP to be associated with an increase in blood pressure of the offspring [88-90, 105-107]. Table 14 gives a summary of various findings of studies on blood pressure measurements at different ages.

At about 4 years, children had a higher risk of having growth and developmental problems, although they were not significant, these problems persisted even at 7 years, however, they also have a higher risk of behavioural problems, than their counterparts, RR 1.386 (95% CI; 1.098-1.751), this is similar to the findings of a meta-analysis by Maher et al.[108].

However, these children tend to have frequent hospital admissions compared to children unexposed, they generally had more health problems, they had 3.069 (95% CI; 1.190-7.913) times the risk of having 3 or more medical problems than those unexposed.

Mothers

With increasing age, the risk of developing hypertension increases, however many factors and conditions increase these risks. Women in our study who had HDP had 6.51 and 4.279 times the risk of developing hypertension 4 and 7 years after the index pregnancy respectively than women who were exposed. This is similar to the findings of Tooher et al.[54] where they found women with HDP had 2.78(2.47–3.13) times the risk of developing hypertension later in life than women without HDP. This is also similar to finding of Bellamy et al.[96] where women with preeclampsia had 3.7(2.7-5.1) times the risk of developing hypertension than women without. Similar findings have been reported by [98-100]. They also had 1.633 times the risk of developing arrythmias and 7.322 times the risk of having a stroke compared to normotensive women.

These women had 1.761 and 5.167 times the risk of developing diabetes compared to women unexposed 4 and 7 years postpartum respectively. This is similar to the findings of Jennifer et al. [98] where they found mothers who had gestational hypertension and preeclampsia had hazard ratio of 1.7(1.4-1.9) and 1.3(1.3-1.4) respectively of developing diabetes compared to women who were normotensive. Similar findings have been reported by [44, 78, 100]

The risk of developing dyslipidaemia in the exposed women was 1.426 and 2.489 times as high as women not exposed to HDP 4 and 7 years postpartum respectively. This is in keeping with findings of Tooher et al.[54] where they found women who had HDP to have 1.07(1.01–1.14) times the risk of developing dyslipidemia as normotensive women. They had 5.525 times the risk of being obese compared to normotensive women. In general, these women have higher risk (1.264) of suffering from other medical conditions, higher risk (1.499) of being on chronic medications. They have 1.547 and 2.203 times the risk of having complications at 48 and 84 months respectively. Table 16 gives a summary of findings of different studies on these complications.

Women who had HDP had higher risks of developing cardiometabolic diseases compared to their counterparts. This translates in spending time away from work at the hospital, purchase of drugs, equipment and gadgets necessary for management of these disorders. Which translates in reduction in quality of life and increase in disability adjusted life years (DALY). This also translates in increase in financial burden on the patient, decreased productivity for the employer due to loss of time spent in hospital visits and sick leaves, and for the State loss of productivity and economic burden of cost of drugs, services and payment of salaries during sick leave.

CHAPTER 5

Conclusion

Women who had HDP and children born from those pregnancies have increased risks of developing complications later in life, affecting their health and productivity, translating in reduced quality of life and DALYs, this reduced productivity would in the long run affect their employers and the State at large. Routine follow up checks should be scheduled at required time intervals for early diagnosis and management of these disorders

Limitations

We had some loses to follow up, especially at the 84 months follow up period which must have invariably affected our analysis. Even in participants who continued with the study, there were many instances where they didn't fill out some questions on the questionnaires.

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