PHYSICAL ACTIVITY,

UTEROPLACENTAL AND UMBILICAL CIRCULATION,

AND THE RISK OF GESTATIONAL HYPERTENSION/PREECLAMPSIA

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology

Chapel Hill
2009

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ABSTRACT

Nghia Cong Nguyen: Physical activity, uteroplacental and umbilical circulation, and the risk of gestational hypertension/preeclampsia
(Under the direction of Kelly R. Evenson, PhD)

Despite extensive research, etiology of hypertensive disorders during pregnancy and the roles of promising preventive factors remain unknown. The goal of this work was to investigate the association of physical activity and uterine and umbilical artery blood flow, thus making inference about maternal-fetal circulation and placental resistance. The work also investigated the association between physical activity before and during early pregnancy and the development of gestational hypertension and preeclampsia.

Data were collected through the third phase of the Pregnancy, Infection, and Nutrition Study. Information on exercise before pregnancy was collected through a self-administered questionnaire at 24-29 weeks' gestation. Self-reported physical activity was obtained through a telephone interview at 17-22 weeks' gestation. Uterine and umbilical artery Doppler flow velocimetry waveforms were recorded through ultrasound examinations at 15-20 weeks' and 24-29 weeks' gestation. Diagnoses of gestational hypertension and preeclampsia were made through information collected at prenatal care visits.

Our findings indicate that physical activity during pregnancy does not appear to be associated with meaningful changes of resistance in uterine and umbilical arteries that would be related to maternal-fetal haemodynamics and blood volume delivery. Thus, physical activity during pregnancy was not associated with major alterations of maternal-fetal circulation.

Exercise before pregnancy through the 2nd trimester was associated with a slightly reduced risk of gestational hypertension. A reduced risk of gestational hypertension was also found among women reporting total moderate to vigorous physical activity and recreational activity in the highest category during pregnancy, but no association was found with work activity.

Exercise before pregnancy through the 2nd trimester was associated with an increased risk of preeclampsia. Total, work, and recreational activity during pregnancy generally had no association with the risk of preeclampsia.

In conclusion, this study generally provides evidence that self-reported physical activity was not associated with maternal-fetal circulation and few associations were identified for the development of hypertensive disorders. These findings support the public health and American College of Obstetric and Gynecology physical activity guidelines for pregnant women.

ACKNOWLEDGEMENTS

I would like to express my sincere thanks to my doctoral committee, Julie Daniels, John Thorp, and Haitao Chu for their valuable inputs, comments and support over the past two years. I would like to thank my dissertation chair and advisor, Kelly Evenson, for her unlimited patience, guidance, technical and logistic assistance for the whole process of my doctoral dissertation. My special thanks to my previous advisor, David Savitz for all the things he has done for me for a long time, beginning with my master program at UNC. David showed me a real life of a researcher.

I will be forever grateful of uncountable support and assistance from many individuals. My family members include my parents – Mai Dang, Nhan Nguyen, and Chinh Dao; my graceful wife – Thuy Trinh, and my three lovely daughters. Nancy Colvin and Carmen Woody from UNC – Department of Epidemiology provided lots of logistic support. My colleagues and friends at New York State Department of Health, Mike Medvedsky, Trang Nguyen, and Melissa Lurie always encouraged me to continue my dream.

This study was funded by the following grants: NIH/NICHD #HD37584, NIH GCRC #RR00046, and NIH/NCI #CA109804-01. I am very proud to be a fellow of the Vietnam Education Foundation during my doctoral program. This foundation generously supported financial aid and legalized documents during my stay in the US.

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LIST OF ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ACSM	American College of Sports Medicine
AHA	American Heart Association
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control
CI	confidence interval
FITT	frequency, intensity, time, and type
FVW	flow velocity waveforms
GEE	generalized estimating equations
ICC	intra-class correlation coefficient
IOM	Institute of Medicine
IUGR	intra-uterine growth retardation
LTPA	leisure time physical activity
MET	metabolic equivalent
NHANES	National Health and Nutrition Examination Survey
NHBPEP	National High Blood Pressure Education Program
NHIS	National Health Interview Survey
NICU	neonatal intensive care unit
OR	odds ratio
PI	pulsatility index
PIN	Pregnancy, Infection, and Nutrition
RI	resistance index
RMR	resting metabolic rate
RR	risk ratio

S/D	systolic/diastolic
USDHHS	United States Department of Health and Human Services

I. INTRODUCTION

Hypertensive disorders during pregnancy are the second leading cause of maternal death, after embolism, responsible for approximately 15 - 18% of maternal mortality in the United States (Koonin et al. 1997; Walker 2000). Gestational hypertension and preeclampsia, characterized by the new development of hypertension after 20 weeks of pregnancy without and with proteinuria, respectively, are two subtypes of hypertensive disorders during pregnancy (NHBPEP 2000; Lyell et al. 2003). Hypertension during pregnancy represents many maternal complications including abruptio placentae, renal failure, hepatic failure, pulmonary edema, cerebral hemorrhage, stroke, and abnormalities of the coagulation system (NHBPEP 2000; Duley 2003; Weissgerber et al. 2004; ACSM 2006). Despite intensive research and advanced prevention and treatment, preeclampsia still affects 2-8% of all pregnancies and brings them to a 3- to 25-fold increased risk of severe obstetric complications (Duley 2003; Zhang et al. 2003; Bdolah et al. 2005).

Previous studies have shown substantial benefits from regular physical activity for health, particularly on cardiovascular and respiratory systems, with impact on cardiac output and blood flow. In adults, regular physical activity prevents or delays the development of high blood pressure, reduces blood pressure in people with hypertension, and is associated with reduced risk of cardiovascular-related death (USDHHS 1996, Warburton et al. 2006). There has been some evidence to support the association between recreational activity and decreased risk of gestational hypertension and preeclampsia among pregnant women in some epidemiological studies (Marcoux et al. 1989; Sorensen et al. 2003; Saftlas et al. 2004; ACSM 2006), but not all (Magnus et al. 2008; Rudra et al. 2008; Osterdal et al. 2009). In contrast, working during pregnancy was found to be associated with a decreased risk (Marcoux et al. 1989, Spinillo et al. 1995) or increased risk (Marbury et al. 1984, Klebanoff et al. 1990, Eskenazi et al. 1991, Walker et al. 2001, Higgins et al. 2002, Saftlas et al. 2004) of preeclampsia or gestational hypertension. However, findings from randomized clinical trials in pregnant women showed no significant effect of exercise on the development of preeclampsia (Avery et al. 1997; Yeo et al. 2000). In a systematic review, the authors (Meher & Duley 2006) concluded that the evidence of this association is lacking and both the biological pathways and mechanisms of the effect have not been clearly determined.

The etiology of gestational hypertension and preeclampsia is poorly understood, since many factors are believed to contribute to its development (Solomon & Seely 2004). Physical activity has been theoretically proposed to play a crucial role in preventing some key stages of the disease process such as enhanced placental growth and vascularity, reduction of oxidative stress, reversal of endothelial dysfunction (Weissgerber et al. 2004), reduced plasma triglycerides, and increased high-density lipoproteins (Dempsey et al. 2005).

A large amount of research has focused on seeking potential and effective biological markers in the early prediction of preeclampsia. Markers of impaired placentation, antigiogenic state, oxidative stress, endothelial dysfunction and vascular reactivity, and resistance have been investigated. However, at present, no marker has been proven to have a clinically useful predictive performance in the general population (Masse et al. 2002; Raijmakers et al. 2004). There is a broad agreement that the best predictive test, at present, involves assessment of the uterine artery Doppler flow velocity waveform (Raijmakers et al. 2004, Parra et al. 2005). Doppler ultrasound provides a non-invasive way to examine uteroplacental and umbilical blood flow as the sufficiency of uteroplacental function (Divon et al. 2001). Investigating uterine and umbilical artery blood flow allows inferences to be made about maternal-fetal circulation and placental resistance that are characterized by the development process of hypertensive disorders during pregnancy.

This study investigates the relationship between physical activity before and during pregnancy and maternal-fetal circulation measured by uterine and umbilical artery Doppler flow velocimetry waveforms in mid-pregnancy. With a comprehensive assessment of broad range of physical activities before and over the course of pregnancy and prospective design, together with evaluation of markers indicating uteroplacental and umbilical circulation, we can further clarify the role of physical activity and the risk for the development of gestational hypertension and preeclampsia. The results should be helpful for guidance in clinical practice and in future clinical trials.

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II. REVIEW OF THE LITERATURE

A. PART A: Gestational hypertension and preeclampsia

Hypertensive disorders during pregnancy are the second most frequent cause of maternal death, after embolism, responsible for approximately 15 - 18% of maternal mortality in the United States (Koonin et al. 1997; Walker 2000). Preeclampsia is a multi-system disorder that complicates an estimated 2–8% of pregnancies and is a major cause of maternal morbidity, perinatal death, premature delivery, and intrauterine growth retardation (Duley 2003). Severe obstetric complications can result from preeclampsia, including abruptio placentae, renal failure, hepatic failure, pulmonary edema, cerebral hemorrhage, and ischemia (NHBPEP 2000; Walker 2000; Duley 2003).

Definition and classification of hypertensive disorders during pregnancy

Many studies use inconsistent terminology, laboratory, and time criteria to define and classify hypertensive disorders during pregnancy. The classification scheme of these disorders was updated by the National High Blood Pressure Education Working Group on High Blood Pressure in Pregnancy (NHBPEP 2000). Four categories were classified as follows: 1) preeclampsia-eclampsia, 2) gestational hypertension, 3) chronic hypertension, and 4) preeclampsia superimposed upon chronic hypertension. Two first subgroups join together forming the term “pregnancy-induced hypertension” (Marcoux et al. 1999), although this term may not be universally agreed upon (Lyell et al. 2003).

(1) Preeclampsia-eclampsia is diagnosed in the presence of the following: 1) hypertension as blood pressure greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic after 20 weeks of gestation in a woman with previously normal blood pressure and 2)

proteinuria, defined as greater than or equal to 0.3 g of protein in a 24- hour urine collection. Preeclampsia that manifests with convulsion is defined as eclampsia.

(2) Gestational hypertension is diagnosed in the presence of hypertension as blood pressure greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic after 20 weeks of gestation in a woman with previously normal blood pressure, in the absence of proteinuria. Some authors also used the term “transient hypertension of pregnancy” for this hypertensive disorder (Lyell et al. 2003; Roberts & Gammill 2005).

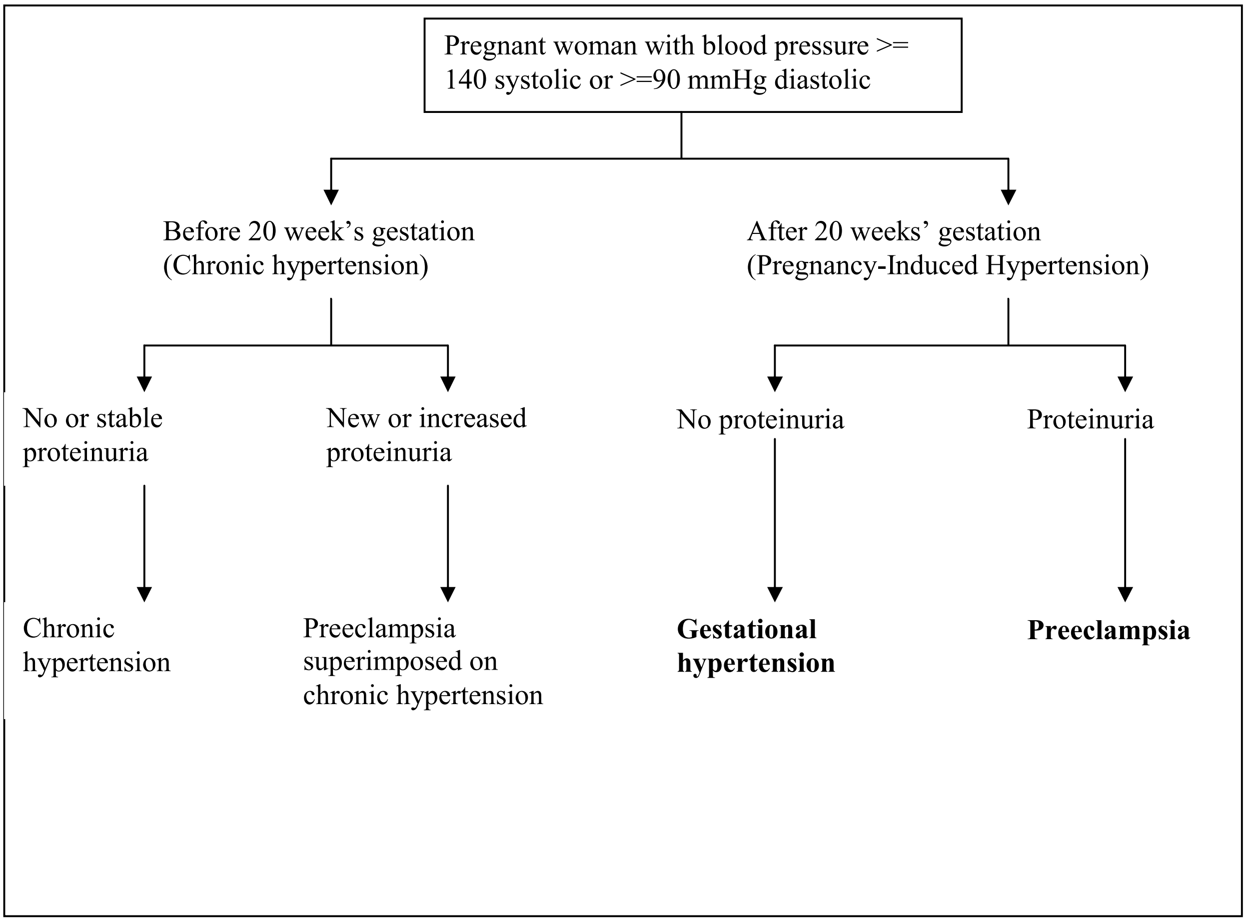
(3) Chronic hypertension refers to hypertension antedates pregnancy, which is a rise in blood pressure before pregnancy, or hypertension before 20 weeks’ gestation. If the woman with chronic hypertension also manifests evidence of preeclampsia, this is classified chronic hypertension with superimposed preeclampsia (4).

Currently, four categories of hypertensive disorders are widely accepted (Lyell et al. 2003; Wagner 2004; Levine et al. 2005; Meher & Duley 2006). Most research agrees on the definition of preeclampsia (Aquilina et al. 2000; Higgins et al. 2002; Duley 2003; Conde-Agudelo et al. 2004; Weissgerber et al. 2004). In few studies, however, other terms have been applied (e.g., pregnancy hypertension) with more detailed criteria for diagnosis of high blood pressure, or the definition of preeclampsia was modified, taking account for other symptoms such as generalized edema (Jacobs et al. 2003). Some confusion still exists with terminology. For example, the term “pregnancy-induced hypertension” is used interchangeably with “gestational hypertension”(Perry & Beevers 1994; Duley 2003).

In this study, gestational hypertension and preeclampsia is strictly defined following the NHBPEP 2000 recommendation (described in Figure 2-1), only taking into account the new development of hypertension after 20 weeks of pregnancy, and excluding any chronic hypertension or hypertension before 20 weeks of pregnancy.

Classification scheme for hypertensive disorders used in this study is summarized in Figure 2-1:

Figure 2-1. Classification scheme for hypertensive disorders in this study (based on NHBPEP 2000).



Normal maternal-fetal circulation and blood pressure in normal pregnancy

Pregnancy introduces important alterations in maternal haemodynamics. The most fundamental changes include an increase in blood volume, cardiac output, heart rate, and stroke volume (Clark et al. 1989; Artal & O'Toole 2003). Cardiac output is the total volume of blood pumped by the left ventricle of the heart per minute. By mid-pregnancy, cardiac outputs are 30–50% greater than before pregnancy (Morton 1991).

Pregnancy also results in a decrease in systemic vascular resistance (Artal & O'Toole 2003). Mean arterial pressure is proportional to cardiac output and total peripheral resistance. Hypertension results from increased vasoconstriction and failure to reduce peripheral vascular resistance during pregnancy. In normal pregnancy, maternal adaptations increase placental bed blood flow through hormonally mediated vascular growth and remodeling, changes in vascular tone and distensibility, trophoblastic invasion, decreased adrenergic responsiveness, and plasma volume expansion (Clapp 2006). These physiological alterations result in low vascular impedance in the placenta and lead to a decrease in placental vascular resistance. When placental impedance increases, the umbilical arterial diastolic flow decreases, which is associated with either low, absent, or even reversed end-diastolic blood flow in uteroplacental circulation (Divon 1996). At mid-second trimester, mean arterial pressure decreases 5 to 10 mm Hg and then gradually increases back to pre-pregnancy levels in normal pregnancy at third trimester (Artal & O'Toole 2003). This decreased pressure results from the decrease in vascular resistance of predominantly the skin and kidney, and the increase in uterine vasculature and uteroplacental circulation (ACOG 1996).

Etiology and pathogenesis of preeclampsia – Theoretical mechanisms

Preeclampsia has been called a "disease of theories" since its etiology and pathogenesis is poorly understood, despite extensive study (Dekker & Sibai 1998; Weissgerber et al. 2004). A large number of etiologic mechanisms for the development of this disease during pregnancy have been implicated as possible etiologic factors, but none of them has been proven with unarguable evidence

(Sibai 2005). Most findings agree that the disease development is caused by a set of biological alterations in accordance with other predisposing factors, rather than a change in one solely dominated factor.

More recently, a 2-stage model of preeclampsia was proposed for the conceptual disease development. Stage 1 is considered the “root cause”, and is indicated by reduced placental perfusion. For some women, stage 1 moves into stage 2: the multi-systemic maternal syndrome of preeclampsia (Roberts 2000; Roberts & Gammill 2005).

In a 1998 review, Dekker and Sibai focused on 4 etiologic mechanisms: 1) placental ischemia with increased trophoblast deportation that can cause endothelial cell dysfunction, 2) very low-density lipoprotein versus toxicity-preventing activity, 3) immune maladaptation that may cause shallow invasion of spiral arteries by endovascular cytotrophoblast cells and endothelial cell dysfunction, and 4) genetic imprinting with an abnormal or incomplete penetrance gene (Dekker & Sibai 1998). In another review, Weissgerber (Weissgerber et al. 2004) summarized 5 main factors that contributed to the development of preeclampsia. These included: 1) abnormal placental development caused by abnormal trophoblast invasion, 2) predisposing maternal constitutional factors, 3) oxidative stress, 4) maternal immune maladaptation, and 5) genetic susceptibility. Each of these factors contributes to systemic maternal endothelial dysfunction, which leads to vasoconstriction and reduced perfusion of critical organs and tissues. Other suggested factors or pathways include: proangiogenic and anti-angiogenic factors (Bdolah et al. 2005), prostacyclin and thromboxane (Chien et al. 2000), and many other metabolic disorders such as hypertriglyceridemia, insulin resistance, elevated plasma homocysteine (Sorensen et al. 2003).

These mechanisms have plausible biological pathways for the disease development but no markers have been firmly confirmed, and there has been unclear about the role of each factor upon individuals as well as the cause-effect relationship between manifestation symptoms and pathophysiological changes and among these factors themselves. In addition, not all women exposed with these factors develop preeclampsia. This obviously comes to the concept of potential interaction with maternal factors to result in clinical preeclampsia. These factors may be behavioral or environmental. In the following parts, we will briefly review these mechanisms.

Role of trophoblast invasion

Preeclampsia has been long characterized as failure of the second wave trophoblastic invasion of the endometrio- myometrial vasculature (Chien et al. 2000). The placenta is classified as hemochorial, and the process of trophoblastic invasion contributes to the establishment of the maternal placental circulation. The uteroplacental blood flow increases ten-fold during pregnancy (van Asselt et al. 1998), therefore, in uncomplicated pregnancies, the spiral arteries undergo a series of changes (Papageorghiou et al. 2004). During normal pregnancy, trophoblast invasion is observed from implantation up to the twentieth week (El-Hamedi et al. 2005). Extravillous trophoblastic, a subset of the trophoblast cells, transforms the low-caliber, high-resistance spiral arteries into high-caliber, low-resistance, and high-capacity uteroplacental arteries (Bdolah et al. 2005; Gupta et al. 2005). In normal pregnancy, impedance to flow in the uterine arteries decreases with gestation, and abnormal trophoblast invasion of the spiral arteries of the decidua and myometrium leads to a failure to establish an adequate uteroplacental blood flow (Myatt 2002).

Placental bed biopsies in preeclamptic and intra-uterine growth retardation pregnancies have shown the failure of trophoblastic invasion of the myometrial segments of the spiral arteries resulting in high impedance in the uteroplacental circulation and a subsequent reduction in the flow volume (van Asselt et al. 1998; Antsaklis et al. 2000). In these pregnancies, the uteroplacental circulation remains in a state of high resistance (Papageorghiou et al. 2004). In the study by Guzin (Guzin et al. 2005), all the cases in the control (normotensive) group demonstrated trophoblast invasion in decidual spiral arteries, and trophoblast invasion into decidual spiral arteries was observed in 75% of mild (9/12) and 55% of severe (11/20) preeclampsia cases.

Placental growth and vascularity resistance

Under normal pregnancy, the placenta is an area of low vascular impedance, thus allowing continuous forward blood flow throughout the cardiac cycle (Divon 1996). Failure of the trophoblast to invade the maternal spiral arteries in the first half of pregnancy can cause reduced placental perfusion in preeclampsia (Chappell & Bewley 1998). It may also alter the implantation of the placenta (Merviel et al. 2004). Reduced placental blood supply then may cause persistent placental hypoxia or repeated episodes of hypoxia and reperfusion. Many toxic products such as cytokines, lipid peroxides, or placental villous tissue fragments may result from the underperfused placenta (Weissgerber et al. 2004).

There is evidence for both abnormal placental vascular structure and abnormal vascular reactivity in the placenta in preeclampsia (Myatt 2002). Poor placentation can play an important role, by producing inflammatory signals; however, poor placentation may need to interact with the maternal response to those signals from placentation (Roberts 2000; Sibai et al. 2005).

Oxidative stress, lipid peroxidation and preeclampsia

Placental oxidative stress is a state of placental damage caused by reactive oxygen species. Prooxidants include free radicals and other reactive oxygen species. Antioxidants are compounds and reactions that dispose and suppress actions of reactive oxygen species (Yeo & Davidge 2001). Oxidative stress level is determined by the imbalance between increased prooxidants and decreased antioxidants resulting in an increased released of prooxidants (Yeo & Davidge 2001). In many vascular diseases, such as atherosclerosis, diabetes, and preeclampsia, oxidative stress has been postulated as the initiator of endothelial cell dysfunction (Roberts 2000; Yeo & Davidge 2001).

Pregnancy itself potentially increases susceptibility to oxidative stress, leading to tissue damage (Rodrigo et al. 2005). Reduced placental perfusion as a result of abnormal placentation and failure of the trophoblast to invade the maternal spiral arteries leads to ischemia reperfusion injury resulting in the release of oxidative molecules (Lyell et al. 2003). This condition promotes lipid peroxidation and the endothelial cell dysfunction that may play important roles in pathophysiology of preeclampsia or intra-uterine growth retardation (Gupta et al. 2005). Also the hypoxia/oxidative stress condition may then further enhance abnormal trophoblast invasion as well as alter placental villous angiogenesis leading to a poorly developed fetoplacental vasculature with abnormal reactivity (Myatt 2002). However, it has been unclear whether oxidative stress is a stage in the disease process or a cause of preeclampsia (Weissgerber et al. 2004). Several multi-center randomized clinical trials using antioxidants for prevention of preeclampsia are currently underway and the findings have been mixed (Raijmakers et al. 2004).

Endothelial dysfunction

Endothelial cell dysfunction, which possibly results from abnormal placentation and placental development, oxidative stress, and the potential interaction between these factors with maternal response, could be responsible for all the clinical aspects of the maternal syndrome of preeclampsia including hypertension, proteinuria, and edema (Lyell et al. 2003; Davison et al. 2004; Weissgerber et al. 2004). Evidence of endothelial cell dysfunction were observed in preeclamptic patients including increased production of vasoconstrictors and coagulants, decreased production of vasodilators, and reduced endothelium-dependent dilation (Weissgerber et al. 2004; Rodrigo et al. 2005). These changes result in increased peripheral vascular resistance, changing in the modulation of vascular tone, excessive vasoconstriction in the small arterioles in the uteroplacental compartment as well as other systemic vascular beds (Papageorghiou et al. 2004; Weissgerber et al. 2004; Rodrigo et al. 2005). Endothelial dysfunction was a potential contributory factor in the hypothetical pathway for the development of preeclampsia (Savvidou et al. 2003).

Other hypothetical mechanisms and biological changes

Some other mechanisms (immune maladaptation, genetic susceptibility, and lipid metabolism) and factors (pro-angiogenic and anti-angiogenic, and predisposing maternal factors) may play a role in the development of preeclampsia. We describe here these more recent findings.

Immune maladaptation

Foreign paternal antigens of the fetoplacental unit, or foreign genetic material in the developing embryo has been suggested as a cause of preeclampsia (Lyell et al. 2003; Weissgerber et al. 2004) by activating the maternal immune system and triggering a widespread nonspecific inflammatory response, and in turn, impairing endothelial cell function (Redman et al. 1999). In addition, immune maladaptation may cause abnormal trophoblast invasion in spiral arteries and endothelial cell dysfunction mediated by an increased decidual release of cytokines, proteolytic enzymes, and free radical species (Dekker & Sibai 1998).

Genetic susceptibility

Predisposing genetic factors are believed to be strongly related with the development of preeclampsia, and the investigation for those genes intensively continues (Bdolah et al. 2005). There is a hypothesis that development of preeclampsia/eclampsia may be based on a single recessive gene or a dominant gene with incomplete penetrance from contributions of maternal and fetal genes, or an interaction between maternal and fetal genotypes (Dekker & Sibai 1998; Weissgerber et al. 2004). In addition, inheritance of preeclampsia may be mediated by multiple genes that increase maternal susceptibility to conditions strongly suggested to contribute to the development of preeclampsia (Weissgerber et al. 2004).

Proangiogenic and anti-angiogenic factors

Preeclampsia has recently been described as a state of imbalance between pro-angiogenic and anti-angiogenic factors. The roles and contributions of angiogenic factors to the development of preeclampsia are ongoing studied. Some angiogenic factors has been investigated including high serum levels of soluble fms-like tyrosine kinase 1 (sFlt1), an anti-angiogenic protein, and low levels of placental growth factor (PlGF), a pro-angiogenic protein (Bdolah et al. 2005; Levine et al. 2005).

Lipid metabolism

During pregnancy, maternal plasma lipids are significantly elevated. Increased triglycerides, cholesterol, low-density lipoprotein and decreased high-density lipoprotein concentrations were observed among women who developed preeclampsia compared to a control group (Enquobahrie et al. 2004). Women with high triglycerides levels had a 4-fold increase in the risk of preeclampsia in this study.

Role of predisposing maternal factors

Several maternal constitutional factors may increase the risk of preeclampsia or increase maternal susceptibility to preeclampsia. These include diabetes, hypertension, obesity, and hyperlipidemia (Weissgerber et al. 2004).

Risk factors for preeclampsia/hypertensive disorders during pregnancy

Many studies have focused on identifying risk factors for preeclampsia as well as hypertensive disorders during pregnancy in general, and several risk factors have been recognized. The following list in Table 2-1 briefly summarizes demographic, behavioral and medical risk factors (Stone et al. 1994; Jacobs et al. 2003; Lyell et al. 2003; O'Brien et al. 2003; Wagner 2004; Roberts & Gammill 2005; Sibai et al. 2005) for preeclampsia/hypertensive disorders during pregnancy.

Table 2-1. Risk factors for preeclampsia/hypertensive disorders during pregnancy:

Maternal demographic risk factors:
- Extremes of age: greater than 35 years or less than 20 years
- African American

Maternal pregnancy history:
- Nulliparity
- Family history of preeclampsia
- Previous history of preeclampsia

Maternal medical conditions during pregnancy:
- Pre-gestational diabetes mellitus or gestational diabetes
- Obesity and insulin resistance
- Chronic hypertension
- Renal disease
- Thrombophillias

Maternal pregnancy-related factors:
- Chromosomal abnormalities
- Hydatidiform mole
- Hydrops fetalis
- Multiple gestations
- Assisted reproduction: Oocyte donation, donor insemination, or embryo donation
- Structural congenital anomalies
- Urinary tract infection

Paternal factors:
- First time father

Maternal behavioral factors:
- Not smoking

Biomarkers for prediction of preeclampsia

Many biochemical markers have been proposed to predict which women are likely to develop preeclampsia. Following hypothesized etiology of the disease, markers of maternal predisposition, placental implantation, oxidative stress, vasomotor regulation, and endothelial dysfunction are investigated as candidate markers in the early prediction of preeclampsia. In 2004, Conde-Agudelo et al. conducted a systematic review of screening tests for preeclampsia with the list of 48 screening tests identified in the literature and concluded that as of 2004, there is no clinically useful screening test to predict the development of preeclampsia (Conde-Agudelo et al. 2004). Several others authors shared the agreement that no single marker is currently adequate to predict the development of preeclampsia, therefore, a combination of indices would be most effective (Masse et al. 2002; Raijmakers et al. 2004; Weissgerber et al. 2004; Sibai et al. 2005). The rationale for using a combination of markers is that data for the reliability of single markers in indicating preeclampsia have been inconsistent, and many screening markers had low specificity and positive predictive value for routine use in clinical practice.

Many biomarkers and screening tests have been studied separately and in the combination. The study by Parra et al. (Parra et al. 2005) in 2002-2003 among Chilean normal pregnancy women assessed a broad range of biomarkers of impaired placentation, antiangiogenic state, oxidative stress, and endothelial dysfunction and concluded that these biomarkers predated the development of preeclampsia by several weeks.

Potential biomarkers and screening tests are listed as below:

. Assessment of oxidative stress: ferric iron (FRAP, ferric reducing ability of plasma), plasma uric acid levels, Peroxynitrite, Malondialdehyde, F2-isoprostanes, Carbonyls.

. Lipid peroxidation and protein carbonylation: FreeF2-isoprostane.

. Antioxidant enzymes: Catalase (CAT), superoxide dismutase (SOD), and gluthatione peroxidase (GSH-Px).

. Assessment of endothelial dysfunction: Plasma von Willebrand factor (vWF), plasminogen activator inhibitor type-1 (PAI-1), PAI-2 and thrombomodulin (TM), fibronectin, Nitric oxide, Asymmetric dimethylarginine, Peroxynitrite, Endothelin and F2-isoprostanes, Homocysteine, Dyslipidemia.

. Assessment of angiogenesis-related and placental function factors: serum levels of soluble fms-like tyrosine kinase 1 (sFlt1), human PlGF, and human VEGF.

. Uterine artery Doppler waveforms.

Some markers have been suggested to be promising such as fibronectin and the three combination indices recently identified by Chappell (Chappell et al. 2002)(Log_ePIGF - 3.0(PAI-1/PAI-2 ratio), PAI-2-PIGF, and leptin/PlGF ratio). This combination enhances the specificity and improves predictive value for the prediction, especially when combined with the sensitive abnormal uterine artery Doppler waveforms.

Some single biomarkers showed strong association with the development of preeclampsia such as urinary PlGF at mid gestation, or activin A (Levine et al. 2005; Madazli et al. 2005). However, no one single marker is specific enough to be representative for the prediction of preeclampsia. There is a broad agreement that uterine artery Doppler waveform during the second trimester is currently the best predictor for preeclampsia by introducing high sensitivity (Raijmakers et al. 2004; Parra et al. 2005), especially among high risk population, and the combination of this test with other biomarkers will increase its predictive power.

Challenges with diagnosis of gestational hypertension/preeclampsia.

Diagnosis of gestational hypertension/preeclampsia in clinical practice might be simplified with the requested data from blood pressure, proteinuria, and gestational age. Although the criteria for diagnosis of hypertension is not always standardized for all studies, it mainly requires measurement of systolic or diastolic blood pressure or both on at least two occasions, at least 4-6 hour apart. Blood pressure must be measured at rest, without using medication. Accurate measurement of blood pressure depends on equipment (cuff size, position of arm at heart level, calibration of equipment) and on the accuracy of the recorder. Blood pressure may be hard to accurately measure among obese women. Blood pressure fluctuates throughout the day and can be influenced by external stimulus.

Proteinuria is measured by 24-hour urine samples. In some case, if 24-h urine sample is not available, concentration of protein in at least two random urine samples taken at least 4-6 hour apart may substitute. Like blood pressure, proteinuria does not remain constant throughout the day, therefore, the definitive test for proteinuria should be a quantitative protein excretion over 24 hours.

Gestation can be measured by either the women's last menstrual period (LMP) or by an early pregnancy ultrasound. Accurate measurement of gestational age is not very important, since we only need to know the time for the cut-point of 20 week's gestation for the diagnosis of hypertension.

However, diagnosis of gestational hypertension and preeclampsia in clinical practice is not so simple. Fluctuation of blood pressure during the day, and from one day to the next, is influenced by many factors and may lead to errors in the medical record. Proteinuria is also not a stable indicator throughout a long period of time. Therefore, the controversy of diagnosis still remains in the case of appearance and disappearance of symptoms in the short time.

B. PART B: Physical activity during pregnancy and the development of gestational hypertension/preeclampsia

This section provides overview of physical activity during pregnancy and the proposed mechanisms of the benefits of physical activity on the development of gestational hypertension/preeclampsia. We briefly summarize the literature on the associations of work physical activity, recreational physical activity, and exercise and the development of gestational hypertension/preeclampsia. In addition, we present limitations of previous studies and recommendations for future research.

Definition of physical activity and benefits of physical activity in general health

In general, physical activity is defined as any bodily movement produced by the contraction of skeletal muscles that increase energy expenditure above the basal level (USDHHS 1996). Strong evidence indicates that regular physical activity provides benefits for both mental health and physical health among humans. Voluntary physical activity is associated with a reduced risk of premature mortality in general, and the risk of many specific diseases, such as coronary heart disease, hypertension, colon cancer, and diabetes mellitus (USDHHS 1996). Despite the well-documented benefits of a physically active lifestyle, more than 60% of American adults are not regularly physically active. Data from NHIS, Behavioral Risk Factor Surveillance System (BRFSS) and National Health and Nutrition Examination Survey (NHANES) III consistently found that about 25 % of adults did not engage in any leisure time physical activity (USDHHS 1996). On the basis of this substantial body of scientific evidence, the U.S. Centers for Disease Control and Prevention and the American College of Sports Medicine (CDC/ACSM) have recommended that adults of all ages to include a minimum of 30 minutes of physical activity of moderate intensity (such as brisk walking) on most, and preferably all, days of the week (Pate et all. 1995). These recommendations have been endorsed and updated with clarifications by the American College of Sports Medicine and the American Heart Association (ACSM/AHA) (Haskell et al. 2007).

Measurement of physical activity

It has been challenging over years to develop accurate, valid, and cost-effective techniques to measure human daily physical activity (Zhang et al. 2003). More than 12 methods for measuring physical activity are currently available and they can be categorized in to two main groups: direct (objective methods) or indirect (subjective methods) (Dishman et al. 2001). Objective methods include measures with direct observation, doubly labeled water, calorimetry, heart rate, pedometers, accelerometers, physiologic surrogates, and biomarkers (USDHHS 1996; Dishman et al. 2001; Sirad & Pate 2001). Subjective methods include self-reports with instruments such as surveys, diaries or logs, proxy reports, and interviews.

Self-reported questionnaires are the most common method to measure physical activity in epidemiological studies. Self-reported questionnaires offer researchers an inexpensive tool to estimate physical activity levels in a large population while maintaining low investigator and respondent burden (Sirad & Pate 2001). However, its accuracy varies according to the length of time being recalled, respondent's ability to provide good information about behaviors, complexity of questionnaires, or regularity of respondent's habits (Dishman et al. 2001).

Physical activity is multidimensional behavior with its inherently complex nature that leads to have no single method able to assess all of its dimensions (Dishman et al. 2001). Dimensions of physical activity measurement include the frequency, intensity, time or duration, and type or mode of each activity (FITT). Frequency is used to indicate how often physical activity is performed. Intensity can be categorized as mild, moderate, vigorous, or very vigorous. Measurement of intensity can be relative (perceived intensity) or absolute (based on MET values). Time shows the length of time a person engages with an activity, and type indicates the mode of activity, such as running, walking, or swimming.

Absolute intensity measures of physical activity are measured in metabolic equivalents (MET), a unit to estimate the metabolic cost or oxygen consumption. One MET represents the body's energy requirements while at rest, referred to as the resting metabolic rate (RMR). One MET equals

3.5 milliliters of oxygen per kilogram of body weight per minute (3.5 ml O_2*kg^{-1}*min^{-1}) or 1 kilocalorie per kilogram of body weight per hour (1 Kcal*kg^{-1}*$hour^{-1}$) for adults. Activities can be classified according to their "MET level", or the intensity of an activity, as a multiple of the resting metabolic rate.

MET values for specific physical activities have been widely used in many epidemiologic studies. In the general adult population, light intensity is estimated at less than 3 METs. Moderate activity is estimated at 3 to 6 METs, and vigorous activity is more than 6 METs (USDHHS 1996). Classification of a large variety of physical activities according to previously published MET levels was presented by Ainsworth et al. (Ainsworth et al. 1993, Ainsworth et al. 2000) in the compendium of physical activities. For example, brisk walking at 3-4 mph for a typical adult is categorized as moderate intensity with an energy requirement of 3-5 METs (Dempsey et al. 2005).

Validity of physical activity questionnaires

Because of the potential recall bias in self-report measures, the validity of this indirect method is of concern. In addition, one of the principal difficulties in establishing the validity of a self-report measure is the lack of a suitable "gold-standard" criterion measure for comparison. Using physiological measures as a criterion measure to compare against physical activity questionnaires, the correlation coefficients usually vary from 0.10 to 0.59, and the overall central tendency suggests only moderate external validity (USDHHS 1996). For example, in the Black Women's Health Study, Carter-Nolan et al. (Carter-Nolan et al. 2006) reported significant correlation coefficients ($r = 0.26$ to 0.42) between physical activity questionnaires (7-day physical activity recall) and criterion measures of exercise. In the Shanghai Women's Health Study, an intra-class correlation coefficient of 0.70 for adult exercise energy expenditure and significant Spearman correlations ($r = 0.62$ to 0.80) between physical activity questionnaires (7-day physical activity recall) and criterion measures of exercise was reported (Matthews et al. 2003). Results from Shanghai Men's Health Study (Jurj et al. 2007) showed

Spearman correlations (r = 0.45 to 0.62) between physical activity questionnaires (PAQ) (7-day physical activity recall) and criterion measures of exercise.

Some limitations of using physical activity questionnaire measures have been noted. There is inherent subjectivity when individuals are asked to respond to questions about their behavior. The issue of recall error, especially in questionnaires with long time of recall, can lead to misclassification. If physical activity is evaluated before the ascertainment of outcome, the misclassification is more likely to be non-differential and this may bias the relationship between physical activity and the outcome toward a null association. If physical activity is evaluated after the outcome happens (e.g., in case-control studies), the misclassification is more likely to be differential with the existence of recall bias. Second, the lack of standardization and validation in the types of self-report activity questionnaires or categorization of physical activity makes it difficult to compare with other activity measurement methods. Third, physical activity patterns may change over the period of pregnancy, depending on many other factors; therefore, measurement of physical activity at certain points in time may not adequately capture activity throughout pregnancy.

Physical activity during pregnancy

During pregnancy, physical activity is considered to be any leisure, occupational work, child/adult care, exercise, or household activities completed by the pregnant women during the day outside of their sleep or rest hours (Lindseth & Vari 2005). A large body of research has focused on the biological effects and pregnancy outcomes among women who engaged in physical activity during pregnancy. Among many biological changes, some most important effects include increased resting maternal plasma volume, intervillous space blood volume, cardiac output, enhanced fetoplacental growth, and placental function (Clapp et al. 2002; Clapp 2003). Some potential risks may be observed including increased uterine blood flow, fetal hyperthermia, changes in carbohydrate metabolism, and increased uterine contractions (Jaski & Trippett 1990; Sternfeld 1997). An acute reduction of oxygen and nutrition delivery to the placenta site may happen as an immediate effect of exercise, however, the blood flow rapidly returns to normal. The chronic effects on increased plasma volume and enhanced placental function increase overall oxygen and substrate delivery (Clapp 2003). There has been evidence that physical activity reduces the occurrence of gestational diabetes mellitus and preeclampsia (Dempsey et al. 2005). Other positive associations on pregnancy delivery include shorter delivery time or reduced need for obstetric interventions (Wang & Apgar 1998). Currently, no significant adverse effects on pregnancy outcomes for both the mother and fetus were reported (Artal & O'Toole 2003; Paisley et al. 2003) among women who continued with a regular exercise regimen or with high volume intensity, such as swimming, biking, and aerobic walking (Jaski & Trippett 1990). In several clinical trials, regular aerobic exercise during pregnancy appears to improve physical fitness, but the evidence is insufficient to infer important risks or benefits for the mother or the baby (Kramer 2006). However, it is noted that the sample size for these clinical trials was relatively small.

The Centers for Disease Control and Prevention and the American College of Sports Medicine recommend 30 minutes or more of moderate physical activity on most, if not all, days of the week to improve general health and well being (Pate et all. 1995). The American College of Obstetricians and Gynecologists (ACOG) guideline for physical activity during pregnancy (ACOG 2002) states that pregnancy is no longer considered a condition requiring the endorsement of a sedentary lifestyle. Engaging in moderate leisure activity on most days of the week is recommended for pregnant women with no medical or obstetric complications (Artal & O'Toole 2003; Paisley et al. 2003; Dempsey et al. 2005). The most updated USDHHS 2008 guidelines for Americans (USDHHS 2008) recommend at least 150 minutes of moderate intensity aerobic activity a week for pregnant women who are not already doing vigorous intensity physical activity.

Pattern of physical activity among pregnant women

Little is known about the physical activity pattern of leisure activity among pregnant women and only few population-based data are available. Data from the 1994-2000 Behavioral Risk Factor

Surveillance System (BRFSS) showed that 33-36% of pregnant women reported not engaging in any leisure activity in the past month and 16-20% of pregnant women reported engaging to either moderate (meeting guidelines) or vigorous (meeting guidelines) physical activity during the past month (Evenson et al. 2004, Petersen et al. 2005). In the National Maternal and Infant Health Survey in 1988 among almost 10,000 pregnant women, Zhang & Savitz (Zhang & Savitz, 1996) reported that approximately 45% of women in the US did not exercise at least 3 times per week before or during pregnancy, 13% exercised before pregnancy but stopped after recognition of pregnancy, 7% did not exercise before pregnancy but exercised during pregnancy, and 35% exercised before and during pregnancy. Walking was the most popular activity, followed by swimming and aerobics.

Physical activity and cardiovascular system and blood pressure

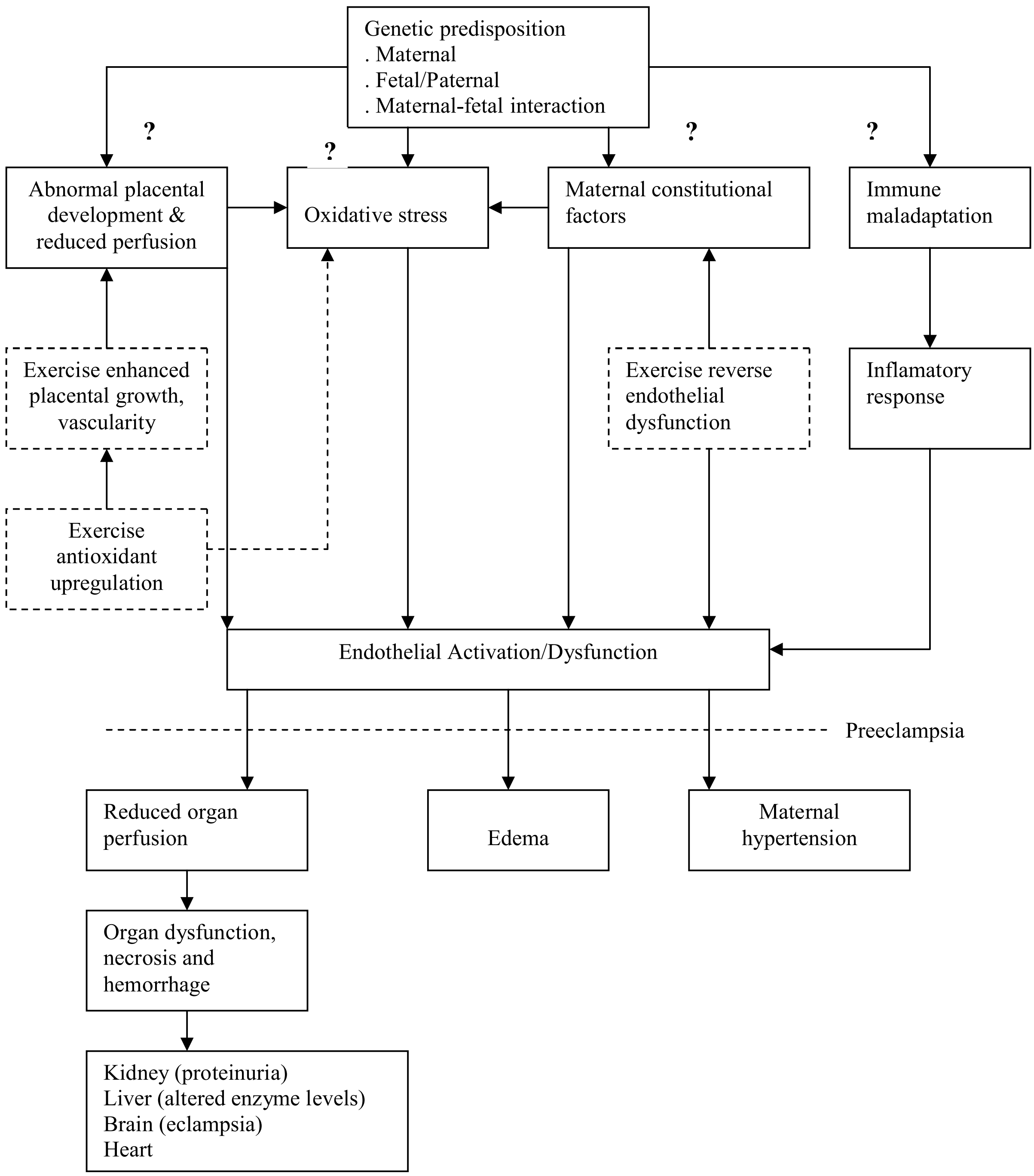
Physical activity produces important positive effects on many body systems such as musculoskeletal, cardiovascular, respiratory, endocrine systems, functioning of metabolic, and immune systems (USDHHS 1996). It has been well documented that regular physical activity prevents or delays the development of high blood pressure, and can reduce blood pressure in people with hypertension. Physical activity produces both immediate and temporary effects on blood pressure. Physical activity increases the cardiac output and blood flow capacity in the active muscle (Terjung 1995), together with a reduction in total peripheral resistance through dilating the peripheral blood vessels. Also, physical activity impacts the sympathetic nervous system that may lead to reduce renin-angiotensin system activity, reset baroreceptors, and promote arterial vasodilation. These adaptations help control blood pressure(Tipton 1984; Tipton 1991). In addition, exercise may help to reduce blood pressure among hypertensive persons through various indirect mechanisms, such as improving plasma lipoprotein-lipid profiles (reduction in plasma low density lipoprotein cholesterol levels, increase in plasma high density lipoprotein cholesterol levels), improving insulin sensitivity, or resulting in regression of pathological left ventricular hypertrophy (Hagberg et al. 2000).

Hypothetical mechanisms of the benefits of physical exercise on the development of preeclampsia

Hypothetical pathways of the benefits of physical activity on the prevention of preeclampsia remain unclear. Many hypotheses have been proposed, and experiments exploring these hypotheses are currently underway. In normal pregnancy, maternal adaptations increase placental bed flow with changes in vascular tone, plasma volume expansion, and increased intervillous space blood volume. These changes increase the basal rate of regional perfusion in a low resistance vascular bed, like the intervillous space (Clapp 2006).

In a 2004 review, Weissberger et al. proposed three mechanisms of protective effects of physical activity on the development of preeclampsia: 1) stimulation of placental growth and vascularity, 2) reduction of oxidative stress, and 3) exercise-induced reversal of maternal endothelial dysfunction (Weissgerber et al. 2004). The evidence for these effects is discussed next and summarized in Figure 2-2.

Figure 2-2. Hypothetical mechanisms of the effect of physical activity on the development of preeclampsia (adapted from Weissberger et al. 2004): Postulated etiology of preeclampsia and proposed benefits of exercise; solid-line boxes, effects of preeclampsia; dash-line boxes, effects of exercise.



Increased placental growth and development

Maternal exercise during pregnancy is associated with increased placental volumes and growth rates. Enhanced placental growth and vascularity may be an adaptive response to intermittent reductions in placental blood flow during exercise (Clapp 2003). This observation is supported by findings by Jackson et al. (Jackson et al. 1995) in 60 women who delivered. The authors used stereological techniques to estimate placental volumetric composition, surface areas, and villous and vascular configurations of the placenta in the three groups: 1) control – no exercise, 2) exercised in early pregnancy only, and 3) exercise continued throughout pregnancy. Compared to control group, the villi in the placenta from the early exercise group had a significantly greater total vascular volume and total capillary volume. Details in the biopsy showed that the villi of the placenta in the exercise continued group had a significantly greater stromal volumes at most levels and a greater capillary volume at the level of peripheral villi with diameters >80 pm, and total villous surface area was significantly increased, compared to two other groups. Exercise in early pregnancy increased the parenchymal component of the placenta and site-specific capillary volume and surface area. Exercise throughout pregnancy appeared to increase these and multiple other histomorphometric parameters associated with the rate of placental perfusion and transfer function. The fraction of nonfunctional tissue (fibrin, damaged villi, septa, basal plate and decidua) was reduced in both exercising groups. Another study (Bergmann et al. 2004) examined the effects of running throughout pregnancy on villous vascular development and cell proliferation. The findings showed that the placenta of the runners had greater villous vascular volumes in both absolute (measured by the volume in cm^3) and relative (measured by percentage of total villous volume per total placental volume) index. The proliferation index (number of mitoses per 1000 nuclei) was also greater among runners as compared to non-runners.

Prevention/reduction of oxidative stress

Oxidative stress is proposed as a pathway between reduced placental perfusion and preeclampsia (Roberts & Gammill 2005). Reduced perfusion as a result of abnormal placentation leads to ischemia reperfusion injury to the placenta (Gupta et al. 2005). In a 1999 review, Powers et al.(Powers et al. 1999) proposed that regular exercise training reduces oxidative stress by enhancing antioxidant defense systems. Although acute exercise episode increases production of pro-oxidants, regularly repeated exercise re-establishes the balance between prooxidants and antioxidants through activated antioxidant defense system.

Correction of vascular endothelial dysfunction

Endothelial cell dysfunction is proposed as a result of all abnormal placentation and placental development, oxidative stress, and the potential interaction between these factors with maternal response (Lyell et al. 2003; Davison et al. 2004; Weissgerber et al. 2004). Large muscle mass exercise has been proposed to be associated with elevated vascular shear stress. Aerobic training produces short-term improvements in endothelial function to compensate for high levels of shear stress during exercise, and repeated shear stress exposure leads to structural remodeling of the vascular system (Laughlin 1995). Exercise training may not alter endothelial function in adults with normal endothelial responses, but may attenuate or correct disease-related endothelial dysfunction.

Other mechanisms

Several other mechanisms have been proposed and extensively studied for the impact of physical activity on other biological changes that may relate to the development of hypertensive disorders during pregnancy. Physical activity is associated with improvements in lipid concentrations, specifically, reduced plasma triglycerides and increased high-density lipoproteins (Dempsey et al. 2005). Blood glucose and insulin levels are decreased among pregnant women with sustained exercise (Clapp 2006).

There are two notable points about hypothetical mechanisms of physical activity on preeclampsia. First, there has been not any confirmed biomarker of preeclampsia with strong supported evidence for a plausible mechanism that links physical activity to preeclampsia. Also, the potential biomarkers may not be specific only for the hypothetical pathway between physical activity and development of preeclampsia. Second, the cause-effect relationship between preeclampsia and potential factors remains undetermined. There is reason to suggest prospective or randomized trials to assess the role of physical activity on the development of hypertensive disorders during pregnancy.

Previous studies on effects of leisure time physical activity on the development of gestational hypertension/preeclampsia

We are aware of six published studies that assessed the occurrence of preeclampsia in relation to maternal recreational physical activity and they are summarized in table 2.2. Two of these studies also assessed the development of gestational hypertension. Six studies included three cohort studies, two case-control studies, and one nested case-control study. Findings are mixed: some studies (Marcoux et al. 1989; Sorensen et al. 2003; Saftlas et al. 2004, Rudra et al. 2005) found that recreational activity before and during pregnancy was associated with a slightly reduced risk of preeclampsia, but other studies (Magnus et al. 2008, Rudra et al. 2008, Osterdal et al. 2009) found that recreational activity during pregnancy was not associated with the risk of preeclampsia or even associated with higher risk of preeclampsia. These studies are described and summarized in Table 2-2.

Table 2-2. Observational studies examining the relationship between physical activity and the risk of preeclampsia

Author – Year	Study design and study population	Physical activity measurement	Definition of outcomes	Main results
Marcoux et al. 1989	. Case control study . Six hospitals in Quebec City and four hospitals in Montreal, Canada . 172 women with preeclampsia, 505 controls	. Leisure time physical activity . Interviewed in hospital after delivery . Information was collected on type, frequency and average duration of any LTPA performed regularly during the first 20 weeks of pregnancy . Used intensity codes (estimation of the energy (kcal/min) required for the activity) to calculate and categorize leisure time physical activity	. Gestational hypertension: elevation of diastolic blood pressure to 90 mm Hg or more, after 20 weeks' gestation, on at least two consecutive occasions 4 h or more apart. . Preeclampsia : gestational hypertension plus proteinuria (300 mg total protein or more in 24 urine samples)	. Women who performed regular LTPA had a reduced risk of preeclampsia (aRR 0.67, 95% CI 0.46-0.96) and gestational hypertension (aRR 0.75, 95% CI 0.54-1.05) . The relative risks decreased as the average time spent in LTPA increased OR: 1.00, 0.77 and 0.57, p = 0.01, for low, moderate and high energy expenditure
Sorensen et al. 2003	. Case control study . Swedish Medical Center in Seattle, Washington, and Tacoma General Hospital in Tacoma . 201 pre-eclamptic and 383 normotensive pregnant women	. Recreational physical activity . Structured questionnaire was administered in hospital during postpartum period . Participants provided information about the type, intensity, frequency, and duration of recreational physical activity performed during the first 20 weeks of pregnancy and during the year before pregnancy . Calculated and categorized leisure time physical activity based on MET hours per week	. Preeclampsia: sustained pregnancy-induced hypertension with proteinuria.	. Any regular physical activity vs. inactive OR = 0.65 (95% CI 0.43 – 0.99) . Light or moderate activities vs. inactive OR = 0.76 (95% CI, 0.48 - 1.20). . Vigorous activities vs. Inactive OR = 0.36 (95% CI, 0.27 – 0.79)

Saftlas et al. 2004	. Nested case-control study . 13 private obstetric practices, New Haven, Connecticut 2739 singleton births . 44 pre-eclamptic and 2422 control women	. Work and leisure-time physical activity . Interviewed before 16 weeks' gestation . The interview ascertained occupational factors, and leisure time physical activity during first 16 weeks of gestation and a year before pregnancy . Measures with MET value for each activity	. Gestational hypertension: systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg on at least two occasions taken at least 6 hours apart after 20 weeks' gestation . Preeclampsia: gestational hypertension plus proteinuria (300 mg total protein or more in 24 urine sample, or 2+ in two or more dipsticks)	. Any regular physical activity vs. inactive OR = 0.66 (95% CI 0.35 – 1.22) for preeclampsia . Less, moderate and high intensity of physical activity vs. inactive Ors = 0.62; 0.59; 0.76 for preeclampsia . Leisure time physical activity was not associated with gestational hypertension
Rudra et al. 2005	. Case control study . Swedish Medical Center in Seattle, Washington, and Tacoma General Hospital in Tacoma . 244 pre-eclamptic and 470 normotensive pregnant women	. Perceived exertion of physical activity . Structured questionnaire was administered in hospital during postpartum period . Question "During the year before you became pregnant, when you were exercising in your usual fashion, how would you rate your level of exertion (degree of effort)?" . Measures of perceived exertion (relative intensity) of LTPA. Women selected a score based on the Borg scale of perceived exertion.	. No definition of outcome available.	. Very strenuous to maximal exertion vs. negligible or minimal exertion OR = 0.22 (95% CI 0.11 – 0.44) . Moderate exertion vs. no or weak exertion OR = 0.54, 95% CI 0.26-1.12
Magnus et al. 2008	. Cohort study . Norwegian Mother and Child Cohort Study,	. Recreational physical activity . Self-reported questionnaire was	. Preeclampsia: blood pressure of 140/90 mm Hg after 20 weeks of	. Only recreational activity at highest frequency (25 times or more per month)

	Norway. . 2,315 preeclamptic among 59,573 pregnancies	administered at 14-22 weeks' pregnancy . Only counted the frequency of activities per month during pregnancy among 14 activities the participants performed	gestation combined with proteinuria >=1 dipstick on at least 2 occasions	during pregnancy was associated with reduced risk of preeclampsia OR = 0.79, 95% CI 0.65 – 0.96, compared to inactive women
Rudra et al. 2008	. Cohort study 1996-2003 . . Swedish Medical Center in Seattle, Washington, and Tacoma General Hospital in Tacoma . 111 preeclamptic among 2,241 pregnancies	. Recreational physical activity before and during pregnancy . Structure interview at 15 weeks' gestation. . Questions about activity the subject participated in a year before pregnancy and 7-day recall . Energy expenditure was calculated in perceived and absolute intensity.	. Preeclampsia: blood pressure of 140/90 mm Hg or higher or a sustained 30 mmHg systolic or 15 mmHg diastolic rise above the first trimester values. Proteinuria >=30 mg/dL on two or more random specimens collected at least 4 h apart.	. Recreational activity in the year before pregnancy was associated with reduced preeclampsia risk (OR for any vs none = 0.55, 95% CI 0.30–1.02). . Recreational activity during early pregnancy was not associated with preeclampsia risk (OR for any vs none = 1.07, 95% CI 0.67–1.69). . Recreational activity only in early pregnancy was associated with increased preeclampsia risk (OR = 2.03, 95% CI = 0.71–5.81)
Osterdal et al. 2009	. Cohort study 1996-2002 . 85,139 singleton pregnancies	. Recreational and exercise during pregnancy . Question about type, frequency and duration of any kind of exercise the subject participated during pregnancy. . Total amount of exercise in minutes/week and MET hours/week calculated.	. Diagnosis of preeclampsia was obtained from the Registry. No definition of outcomes was described.	. The two highest physical activity levels were associated with increased risk of severe preeclampsia compared with the non-exercising group, with adjusted odds ratios of 1.65 (95% CI: 1.11–2.43) and 1.78 (95% CI:

				1.07–2.95), whereas more moderate levels of physical activity (1–270 minutes/week) had no statistically significant association with risk of preeclampsia

OR: odds ratio aRR: adjusted risk ratio CI: confidence interval

LTPA: leisure time physical activity

Working during pregnancy

Work activity is another important component of overall activity, including all aspects of working-related status, with both physically demanding activities and working conditions. Inconsistent results were usually found in studies that have examined the relationship between work and pregnancy outcomes such as, small-for-gestational-age, low birth weight, and preterm delivery (Hanke et al. 1999). Lack of standardized definitions and categorization for occupational exposure, potential hazards, and a variety of working conditions among different study populations may explain this inconsistency (Hanke et al. 1999). Many hypothetical mechanisms have been postulated for the relationship between strenuous physical work and adverse pregnancy outcomes. Some physiological changes have been reported, such as redistribution of cardiac output from visceral circulation to exercising muscles and skin, depletion of energy stores, increased body temperature, endocrinal changes. These changes may produce adverse effect on reproductive tract, development of the fetus, placentation, or stimulate abnormal reaction of the uterus (Clapp 1996). However, proposed biological mechanisms underlying this association remain unclear. Several observed results support the notion that increased physical activity during pregnancy is likely to be beneficial relative to some pregnancy outcomes (Shaw 2003).

In a Poland pregnant women population in 1996-1997, only about 25% of all pregnant women worked for more than 6 months during pregnancy, while 34% stopped working within the 1st trimester (Hanke et al. 1999). Also, it should be important to note that there is an inverse relationship between working hours and leisure time physical activity, since women with longer working hours may spend less time in leisure activity (Spinillo et al. 1995). The important characteristics of work during pregnancy that have been studied include level of working intensity, shift work, daily or weekly working hours, work posture, stressful conditions, noise, high temperature, computer operation, exposure to chemicals (Spinillo et al. 1995; Hanke et al. 1999; Mozurkewich et al. 2000; Pompeii et al. 2005).

Studies of work and gestational hypertension/preeclampsia

Although there have not been standardized definitions and classifications of occupational exposure, findings from many pervious studies on the work and development of hypertension/preeclampsia are relatively consistent. In different study populations and at a simple classification, compared with unemployed women, women working during pregnancy had more than 2 times higher risk of preeclampsia (Marbury et al. 1984; Klebanoff et al. 1990; Eskenazi et al. 1991). This finding was also found in later studies. Spinillo et al. (Spinillo et al. 1995) found a 2-fold greater risk of severe preeclampsia among women reporting moderate to high work activity compared to no work or mild physical activity at work during pregnancy. Also, they found a significant linear trend relating the degree of physical activity at work to the risk of preeclampsia. Higgins et al.(Higgins et al. 2002) found a high risk (OR = 4.1) for preeclampsia among women at work compared to those not working. Particularly, mean daytime systolic, mean daytime diastolic, and 24 hour systolic pressure were higher among women at work. For the outcome as hypertension or preeclampsia, physically demanding work was associated with 1.6 times higher risk in a meta-analysis (Mozurkewich et al. 2000).

However, some associations were found in previous studies. Two studies by Marcoux et al.(Marcoux et al. 1989) and Saftlas et al. (Saftlas et al. 2004) examined the simultaneous associations between leisure-time activity and occupational physical activity and preeclampsia risk. Frequent walking or standing during work hours was associated with a decreased risk of preeclampsia, even after controlling for LTPA during pregnancy (Marcoux et al. 1989, Saftlas et al. 2004). A combination of LTPA and occupational activity showed consistently reduced risk with various categorizations of these two exposures, although not statistically significant, for the development of preeclampsia (Saftlas et al. 2004). These studies are described and summarized in Table 2-3.

Maternal work in pregnancy might be associated with an increased risk of preeclampsia. However, neither plausible mechanisms nor possible explanation for that association have been determined in literature. Some challenges include: very little known about the etiology, no specifically biologic markers, inherent complexity and variability of physical activity at work. Some possible mechanisms were discussed such as stressful occupation or potentially psychologically stressful (Klebanoff et al. 1990; Saftlas et al. 2004), poor placental perfusion together with other risk factors (obesity, family history of pregnancy-induced hypertension), hyperlipemia, hypertriglyceridemia (Wergeland & Strand 1997), and sympathetic overactivity (Walker et al. 2001; Higgins et al. 2002).

Table 2-3. Observational studies examining the relationship between occupational activity and the risk of hypertensive disorders during pregnancy.

Author – Year	Study design and study population	Physical activity measurements	Definition of outcomes	Main results
Marbury et al. 1984	. Cross-sectional study . Brigham and Women's Hospital 1977 – 1980 . 11,173 deliveries	. Interviewed in hospital after delivery using a questionnaire . Working status was categorized into: "Housewife", "Worked month 1 – month 8", "Worked to term"	. Preeclampsia : no definition available.	. "Worked month 1-month 8" vs. "Housewife": aRR 1.3, 95% CI 0.97-1.75 . "Worked to term" vs. "Housewife": aRR 0.76, 95% CI 0.54-1.08
Marcoux et al. 1989	. Case control study . Six hospitals in Quebec City and four hospitals in Montreal, Canada . 172 women with preeclampsia, 505 controls	. Interviewed in hospital after delivery using a questionnaire . Leisure time and occupational physical activity	. Gestational hypertension: elevation of diastolic blood pressure to 90 mm Hg or more, after 20 weeks' gestation, on at least two consecutive occasions 4 h or more apart. . Preeclampsia: gestational hypertension plus proteinuria (300 mg total protein or more in 24 urine sample)	. Worked vs. no worked: aRR 0.80, 95% CI 0.52-1.21 for preeclampsia and aRR 1.16, 95% CI 0.78-1.73 for gestational hypertension. . Frequent walking reduced the risk of preeclampsia (aRR 0.61; 95% CI 0.42-0.89)
Klebanoff et al. 1990	. Cross-sectional study . 4412 medical residency women and 4238 wives of medical residency men	. Survey questionnaire . Categorization: "working medical residency" vs. "not"	. Preeclampsia or eclampsia: no definition available.	. Prevalence of preeclampsia or eclampsia among women residents and wives of male residents : 8.8% vs. 3.5% (p <0.001)
Eskenazi et al. 1991	. Case-control study . Northern California Kaiser Permanente medical Centers 1984-1985 . 139 preeclamptic	. Information abstracted from medical charts . Categorization: "worked during pregnancy" vs.	. Preeclampsia: elevation of mean arterial pressure to 105mm Hg or more, or a change in mean arterial	. Worked vs. unemployed: aOR 2.1 95% CI 1.1 – 4.4

	women and 132 controls	"unemployed"	pressure >= 20mm Hg plus proteinuria (300 mg total protein or more in 24 urine sample, or at least 1+ on two separate occasions), after 20 weeks' gestation.	
Saurel-Cubizolles et al. 1991	.Cross-sectional study . 7 hospitals in Paris, France 1979-1981 . 621 female hospital employees	. Type of work, type of working department, working conditions . Interviews during medical visits and after delivery.	. High blood pressure: systolic blood pressure >130mm Hg and/or diastolic blood pressure >80mm Hg on at least one occasion during pregnancy	. Long standing-up position, carrying heavy loads, and heavy cleaning tasks were associated with high blood pressure during pregnancy ($p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively)
Spinillo et al. 1995	. Case control study . Department of Obstetrics and Gynecology of the University of Pavia . 160 women with severe preeclampsia, 320 controls	. Type of employment and level of physical activity sustained at work . Scored by type of work, physical intensity, posture at work and weekly working hours into 4 levels: minimum, mild, moderate and high effort. . Interviewed in hospital after delivery using a questionnaire	. Severe preeclampsia: elevation of systolic blood pressure to 160mm Hg or more, or elevation of diastolic blood pressure to 110mm Hg or more, and proteinuria (>300 mg/dL) after 20 weeks' gestation.	. Clerical workers vs. unemployed: aOR 0.53; 95% CI 0.30-0.96 . Significant linear trend relating the degree of physical activity at work . Moderate/high physical activity at work vs. mild activity: aOR 2.08, 95% CI 1.11-3.88
Wergeland & Strand 1997	. Cross-sectional study . Norway (October-November 1989) . 5438 singleton pregnancies	. Type of work, working condition, physical work load . Self-administered questionnaire after delivery in maternity institutions.	. Preeclampsia: hypertension during pregnancy plus proteinuria diagnosed on more than one occasion or hospitalized due to hypertension.	. aORs from 1.4 – 2.0 for work involving lifting of heavy loads, hectic work pace, work with hands above shoulder level, shift work. . No association with standing/walking, twisting bending gesture

Walker et al. 2001	. Cohort study . Melbourne (Astralia) . 100 normotensive, singleton pregnancies who work outside from home, with more than 30 weeks' gestation	. Work days vs non-work days. No details in job description.	. Blood pressure: diastolic, systolic and mean arterial blood pressure . Gestational hypertension: two blood pressure reading at least 140/90 or one isolated reading at least 160/100 . Preeclampsia: gestational hypertension plus at least 300 mg proteinuria per 24 hours or at least ++ on two separate occasions	. Systolic, diastolic and mean arterial blood pressure was significantly higher on work days than on non-work days. . Change in mean arterial at work vs. no change: aOR 1.24, 95% CI 1.07-1.43 for pregnancy induced hypertension (either gestational hypertension or preeclampsia)
Higgins et al. 2002	. Cohort study . Rotunda hospital, Dublin, Ireland . 933 normotensive, singleton pregnancies enrolled between 18-24 weeks' gestation	. Categorized as: working, not working, and normally employed but not working	. Blood pressure: diastolic, systolic blood pressure . Hypertension: one diastolic blood pressure reading of greater than or equal to 110 or two consecutive diastolic pressure of greater than or equal to 90 at least 4 hours apart. . Preeclampsia: hypertension plus proteinuria at least 300 mg proteinuria per 24 hours or at least ++ on two separate occasions at least 4 hours apart)	. Work vs. no work: aOR 5.48, 95% CI 1.08-27.76 for preeclampsia . Work vs. no work: aOR 1.25, 95% CI 0.52-3.00 for gestational hypertension.
Saftlas et al. 2004	. Nested case-control study . 13 private obstetric practices, New Haven, Connecticut 2739 singleton births . 44 pre-eclamptic	. Work and leisure-time physical activity . Interviewed before 16 weeks' gestation . The interview ascertained	. Gestational hypertension: systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg on at	. Unemployed vs. employed with highest sitting: aOR 0.64, 95% CI 0.21-2.00 for preeclampsia . Unemployed vs. employed with highest sitting: aOR 1.18, 95%

	and 2422 control women	occupational factors, and leisure time physical activity during first 16 weeks of gestation and a year before pregnancy	least two occasions taken at least 6 hours apart after 20 weeks' gestation . Preeclampsia: gestational hypertension plus proteinuria (300 mg total protein or more in 24 urine sample, or 2+ in two or more dipsticks)	CI 0.70-1.98 for gestational hypertension.

aOR: adjusted odds ratio aRR: adjusted risk ratio CI: confidence interval

Clinical trials: Exercise, rest, and preeclampsia

There is some evidence from observational studies on the association between LTPA and reduced risk of preeclampsia. It has been suggested that exercise may help prevent preeclampsia and its complications. Several clinical trials have been conducted to confirm this hypothesis. Kramer and McDonald (Kramer & McDonald 2006) conducted a systematic review of clinical trials assessing the effects of regular aerobic exercise on pregnancy outcome among healthy pregnancies. This analysis included two randomized clinical studies by Erkkola (Erkkola 1976), and Collings et al. (Collings et al. 1983) with a total of 82 participants in two groups: engaging and not engaging in programmed exercise. The result showed no significant association. Avery et al. (Avery et al. 1997) and Yeo et al. (Yeo et al. 2000) conducted randomized clinical studies among pregnant women who were at risk of preeclampsia (having gestational diabetes, mild hypertension or a previous personal or family history of hypertension). These two small trials with a total of 45 participants compared moderate intensity aerobic exercise vs. normal physical activity during pregnancy. No significant decreased risk was found among group engaging in moderate exercise.

The effect of rest was explored in two clinical trials (Herrera 1993, Spinapolice et al. 1983). These trials included 106 pregnant women at moderate risk of preeclampsia (having previous preeclampsia, nulliparous with over 35 years old, or with family history of preeclampsia, or with obesity, or with positive roll-over test, or with abnormal uterine Doppler scan). The trials compared rest and unrestricted activity, or rest plus nutrient supplementation and unrestricted activity plus placebo. The results showed a significant reduction in the relative risk of preeclampsia with rest as compared to physical activity. Again, with the small sample size, current evidence is insufficient to support recommending rest or reduced activity to women for preventing preeclampsia and further complications. The clinical trials reviewed herein had small sample sizes and no standardized training regimen. In a systematic review, Meher & Duley (Meher & Duley 2006) concluded that there was not enough evidence to determine if exercise is helpful in preventing preeclampsia and its complications.

Limitation of previous studies and future research

There are several notable limitations of existing studies of the effect of physical activity on gestational hypertension/preeclampsia. First, evaluation of physical activity is mainly based on retrospective self report, and thus subject to potential measurement errors, especially in the case of long term recall (Leiferman & Evenson 2003; Ning et al. 2003). Second, no standardized and consistent method was used in evaluation of physical activity, and many instruments used were not validated (Leiferman & Evenson 2003). This makes it difficult to compare across studies. Third, not all aspects of physical activity (LTPA, occupational, and daily living activities) were ascertained (Weissgerber et al. 2004; Dempsey et al. 2005). Also, the physical activity questionnaire lacked detail about type, intensity, and duration of specific activity (Leiferman & Evenson 2003; Ning et al. 2003). Last, existing studies did not adequately control for pre-conceptual and/or prenatal exercise or activity (Weissgerber et al. 2004).

Initial findings from physiological and epidemiological studies as well as clinical trials suggest that future investigations should be designed to study in greater detail the type, frequency, duration, and pattern of overall physical activity in relation to the development of hypertensive disorders and preeclampsia during pregnancy in large populations. Studies need to evaluate the joint and potentially divergent effects of occupational physical activity, together with other daily living activity (e.g., transportation and child care). Evaluation should be prospectively conducted at several times during pregnancy.

C. PART C: Physical activity - Uteroplacental and Umbilical circulation and Doppler velocimetry waveforms

Maternal-fetal circulation and blood pressure in normal pregnancy.

The intervillous circulation of maternal blood is likely to be established progressively between 8 to 12 weeks' gestation (Carbillon et al. 2001). The uteroplacental blood flow increases ten-fold during pregnancy (van Asselt et al. 1998). A decrease in systematic vascular resistance exists throughout pregnancy (Artal & O'Toole 2003). Maternal adaptations including changes in vascular tone, trophoblast invasion, and adrenergic response lead to low vascular impedance in the area of placenta and decreased placental vascular resistance (Carbillon et al. 2001; Clapp 2006). These fundamental changes result in a systematic transition from a low-volume and high-resistance to a high-volume and low-resistance circulation established in uteroplacental vessels during the first trimester. The trophoblast invasion into the endothelium of the spiral arteries changes the musculoelastic structure of the vessel walls into distended, low-resistance channels. All of these changes are to provide adequate perfusion of the intervillous space, which is fundamental for the growth of the fetus (Tekay & Campbell 2000).

Figure 2-3. Flow velocity waveform from uterine artery in a non-pregnant woman and a pregnant woman (Figure 4-11 and 4-12 in Harrington and Campbell 1995 page 118, used with permission from Oxford University Press)

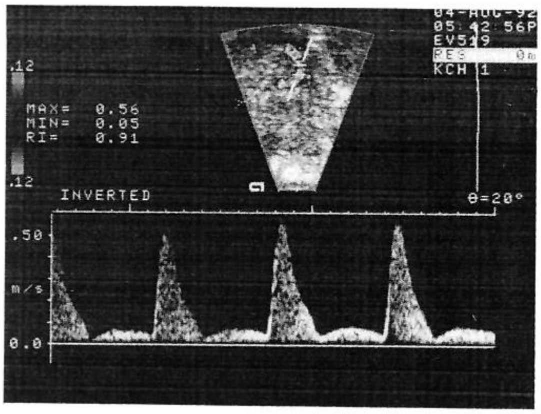


Fig. 4.11
A flow velocity waveform (FVW) obtained from a uterine artery in a non-pregnant patient. The characteristic shape of this waveform shows a steep systolic slope, an early diastolic notch, and a small amount of diastolic flow. Although the waveform changes in the menstrual cycle, with more flow in the luteal phase, the waveform remains essentially high resistance in the non-pregnant state.

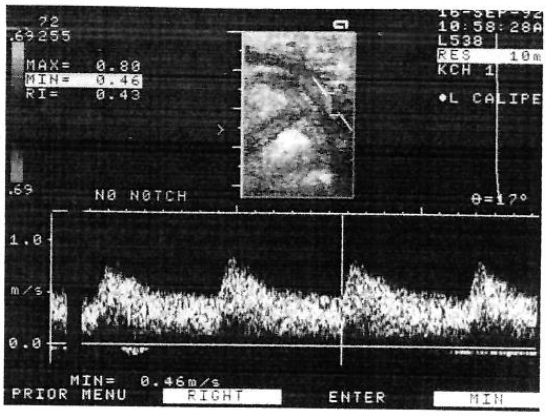


Fig. 4.12
FVW in established pregnancy at 20 weeks. Placentation typically results in a low resistance FVW, the disappearance of the notch and an abundance of diastolic flow (compare with the FVW from the non-pregnant patient in Fig 4.11) Failure of this physiological modification is associated with the development of pre-eclampsia and intrauterine growth retardation.

Because blood flow in diastole is mostly passive, the umbilical arterial diastolic flow decreases when placental impedance increases that results from abnormal physiological changes among preeclamptic pregnancy. Increased vascular resistance in the capillaries of the terminal villi leads to low, absent, or even reversed end-diastolic artery velocities that can be observed by Doppler velocimetry wave forms (Alfirevic & Neilson 1995; Divon 1996; Ebrashy et al. 2005). At mid-second trimester, mean arterial pressure decreases 5–10 mm Hg and then gradually increases back to pre-pregnancy levels, in normal pregnancy (Artal & O'Toole 2003).

Rationale of using Doppler velocimetry indices in measures of uteroplacental blood flow

Placental blood flow and degree of vascular resistance in the uteroplacental circulation can reflect current status of the fetus and predict several adverse pregnancy outcomes. It is difficult and impractical to measure directly uteroplacental circulation in human. This leads to the development of surrogate sensitive, safe, and noninvasive measures, such as Doppler ultrasound of the uterine and umbilical artery (Chappell & Bewley 1998). Multiple publications have reviewed the utility of Doppler studies of the uterine artery and umbilical artery as a test for prediction of the onset of preeclampsia and other pregnancy outcomes (Bewley et al. 1991, Bower et al. 1993, Irion et al. 1998, van Asselt et al. 1998, Antsaklis et al. 2000, Aquilina et al. 2000, Chien et al. 2000, Parretti et al. 2003, Phupong et al. 2003, Axt-Fliedner et al. 2005, Gomez et al. 2005, Guzin et al. 2005, Ohkuchi et al. 2000, Herskovitz et al. 2005, Papagheorghiou et al. 2005). Persistent abnormalities in the uterine artery Doppler waveform in 12-20 weeks of gestation can reflect inadequate placental development and an increased risk of developing preeclampsia (Antsaklis et al. 2000; Lyell et al. 2003; Weissgerber et al. 2004). An abnormal umbilical artery blood flow pattern reflects the presence of a structural placental lesion, which in turn is associated with adverse fetal outcome in high-risk pregnancies (Divon 1996). The meta-analysis by Alfirevic (Alfirevic & Neilson 1995) showed that assessment of umbilical artery waveforms by Doppler ultrasonography after 20 weeks' gestation in high-risk pregnancies reduces the odds of perinatal death by 38%. Doppler indexes of the uterine and umbilical artery can be used for the prediction of intrauterine growth retardation, hypertensive disorders of pregnancy, cesarean section for fetal distress, meconium, fetal asphyxia, admission to the neonatal intensive care unit, and perinatal mortality (Divon 1996; Herskovitz et al. 2005). Although no single marker is currently adequate to predict the development of preeclampsia, uterine artery Doppler velocimetry at mid-gestation is considered a very sensitive predictor for the development of preeclampsia, and some authors stated that it would currently be the best predictive test (van Asselt et al. 1998; Raijmakers et al. 2004; Parra et al. 2005), especially in combination with some other biomarkers for endothelial and placental function (e.g. PAI-1/PAI-2 ratio, leptin, placental growth factor) (Raijmakers et al. 2004). Umbilical artery Doppler velocimetry is considered most predictive of intrauterine growth retardation and fetal distress (Harville 2006, unpublished). However, application of Doppler velocimetry in clinical use is still controversial, because of its low positive predictive value in low risk population (Coleman et al. 2000).

Doppler flow velocity waveform indices in uterine and umbilical artery.

Doppler ultrasound in medical imaging consists of a continuous wave Doppler (CW), pulsed wave Doppler (PW), and color Doppler imaging (CDI) (Harrington & Campbell 1995). When ultrasound is reflected from movements of a target, such as red blood cells, the frequency shift of the targets will be detected. The final Doppler signal displayed on the monitor is a waveform representing the Doppler shifts creating by circulating red cells during a cardiac cycle. In a typical and normal shape of flow waveform, several measures are presented in Figure 2-4:

Figure 2-4. Flow velocity waveforms (FVW) with measures (Figure 24-6 and 24-7 in Tekay & Campbell 1988 page 328, used with permission from Oxford University Press)

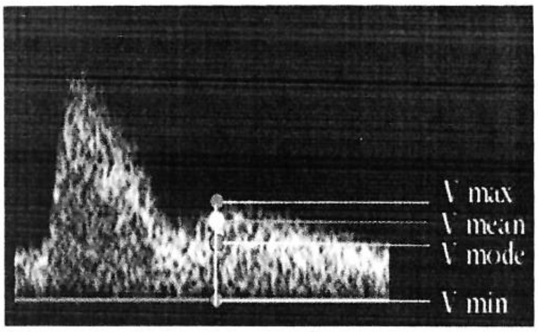


FIGURE 24–6. Flow velocity waveform of the uterine artery with mode, mean, minimum (min), and maximum (max) velocity (V) highlighted. Note the broad range of velocities of different magnitude indicated by a considerable difference between the Vmin and Vmax and Vmean. Compare with Figure 24–9.

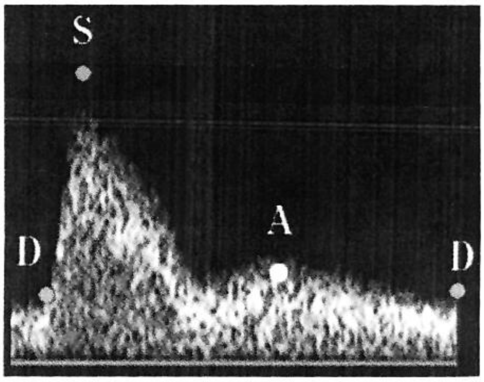


FIGURE 24–7. Flow velocity waveform with S (maximum peak systolic frequency), D (end-diastolic velocity), and A (mean Doppler shift frequency) highlighted. By using these, the pulsatility (PI = S−D/A) and resistance (RI, *Pourcelot index* = S−D/S) indices can be calculated.

S: maximum peak systolic frequency
D: end-diastolic frequency
A: mean Doppler shift frequency during a cardiac cycle

In clinical diagnosis in obstetrics, the most common indices are:

Pourcelot's resistance index (a.k.a the resistance index, or resistive index) (Pourcelot 1974)

RI = (Peak systolic height – Minimum diastolic height)/ Peak systolic height = (S-D)/S

As diastolic falls, the value of the RI increases, if there is no diastolic flow, the RI=1. RI values greater than 1 are possible, if there is reversed diastolic flow.

Pulsatility index (Gosling and King 1975)

Pulsatility index (PI) = (Peak systolic height – Minimum diastolic height)/Mean waveform height = (S-D)/Mean or (S-D)/A

PI and RI directly reflect the downstream flow impedance. PI may be more informative than RI since PI takes the entire waveform into account and not just the maximum and minimum frequencies, as does RI.

S/D ratio (Stuart et al. 1980)

Systolic/Diastolic Ratio (A/B ratio, S/D ratio) = S/D: as diastolic falls, S/D increase, when there is no diastolic flow, the S/D ratio is infinity. Given the absent end-diastolic flow velocity, S/D will not be measurable.

Early diastolic notch:

Because of trophoblast invasion, in the uterine artery flow velocity waveform the diastolic notch gradually disappears during early second trimester. By 20 weeks of pregnancy, the majority of women have low resistance uterine artery FVWs with 20% retaining a notch in either uterine artery FVW. At 24 weeks the number of women with notching is 9% (Harrington & Campbell 1995)

Reverse flow at the end of diastole:

A substantial increase in the vascular resistance of the uteroplacental unit leads to a decrease in end-diastolic flow velocity or its absence in the FVW, even reverse flow at the end of diastole appears.

Time for applying Doppler ultrasound for the prediction of preeclampsia

Previous studies used uterine artery Doppler examination at different times during pregnancy for the prediction of preeclampsia and hypertensive disorders during pregnancy. The predictive values of the Doppler as a screening test (sensitivity, specificity, positive predictive value, and negative predictive value) change as gestational age increases. Several studies applied the test at around 20 weeks' gestation (Campbell et al. 1986, Bowers et al. 1993, Aquilina et al. 2000). Others have applied it at around 24 weeks' gestation (Antsaklis et al. 2000, Coleman et al. 2000, Phupong et al. 2003, Hershkovitz et al. 2005) or anytime during second trimester at 16-28 weeks' gestation (Irion et al. 1998, Ohkuchi et al. 2000, Axt-Fliedner et al. 2005). Testing women at around 20 weeks may produce higher false positive result for the test (Aquilina et al. 2000, Antsaklis et al. 2000), but it is also very good time to routinely perform scan for fetal anomalies. Performing the test at 28-32 weeks' gestation has highest predictive value (Antsaklis et al. 2000), but it is too late to apply prophylactic treatment to modify the disease (Aquilina et al. 2000). Some researchers performed the test at early pregnancy as 11-14 weeks' gestation (Gomez et al. 2005) and found uterine artery PI at early pregnancy can be predictive for the disease, but single measurement for screening purpose in unselected early pregnancy populations has limited clinical value.

Uterine artery Doppler for the prediction of preeclampsia.

Although a reliable method of measuring placental blood flow directly is not available at present, the uterine artery Doppler velocimetry is a good alternative by enabling detection of high uterine vascular resistance attributable to inadequate uteroplacental blood circulation in preeclampsia (Tekay & Campbell 2000). High impedance in the uterine arteries in preeclampsia, presented by high resistance index value along with the persistence of an early diastolic notch, can be detected by Doppler ultrasound.

A number of studies with varying results (sensitivity, specificity, positive predictive value, and negative predictive value) have been published (Bewley et al. 1991, Irion et al. 1998, van Asselt et al. 1998, Antsaklis et al. 2000, Aquilina et al. 2000, Parretti et al. 2003, Axt-Fliedner et al. 2005). This variation can be explained, in part, because of differences in the timing, site, and evaluation of Doppler studies, by the different equipment used or techniques, by small number of patients, varying sampling sites, different gestational age of participants, as well as different criteria for the classification of Doppler indices. The different cutoff levels used for Doppler indices in studies have lead to vary the results, for example the cut-points for RI varied from 0.52 – 0.62.

Doppler indices can be categorized into quantitative measures (Pulsatility Index, Resistance Index, S/D ratio) or qualitative measures (early diastolic notch, reverse diastolic flow). The value of quantitative assessment can be assessed in either absolute measures (specific cut-point at specific gestational age) or relative measures (based on percentile of the value distribution in the study population). The following table 2-4 shows selected studies with artery Doppler indices and various cut-off levels.

Table 2-4. Selected studies with uterine artery Doppler indices and cut-off levels used for prediction of preeclampsia.

Study - Year	Gestational age that the ultrasound was performed	Predictor
Campbell et al. 1986	20 weeks	RI > 0.58
Bewley et al. 1991	16-24 weeks	Mean RI > 95th percentile
Harrington et al. 1991	20 weeks	RI > 95th percentile and/or diastolic notch
Bower et al. 1993	18-22 weeks	RI > 95th percentile and/or diastolic notch
North et al. 1994	19-24 weeks	RI > 95th percentile RI > 0.53 – 0.57
Harrington et al. 1996	24 weeks	RI > 95th percentile and/or unilateral or bilateral notch
Irion et al. 1998	18-19 weeks & 26-27 weeks	RI > 0.58 A/B (S/D) ratio > 90th percentile Diastolic notch
Aquilina et al. 2000	20 weeks	Bilateral notch/mean RI >=0.55 (median) Unilateral notch/mean RI >= 0.65 (85th percentile) A/B (S/D) ratio >= 2.65
Antsaklis et al. 2000	20 weeks, 24 weeks, and 32 weeks	Diastolic notch: unilateral or bilateral
Coleman et al. 2000	22-24 weeks	RI >=0.58: abnormal RI>=0.70: very abnormal Diastolic notch
Paretti et al. 2003	24 weeks	Mean RI>=0.58
Phupong et al. 2003	22-28 weeks	Diastolic notch
Axt-Fliedner et al. 2005	19-26 weeks	RI>=0.58: abnormal RI>=0.70: very abnormal Uni/bilateral notching
Herskovitz et al. 2005	23-24 weeks	PI > 95th percentile Diastolic notch
Papagheorghiou 2005	23 weeks	Mean PI >1.6 (>95 percentile)

RI: Resistance index PI: Pulsatility index

A/B (S/D) ratio: Systolic/Diastolic ratio

Diastolic notch

A high-amplitude wave from the placental bed can result from increased uteroplacental circulation, which produces a notch in the uterine artery Doppler during diastole. A number of studies found that when an early diastolic notch is noted, irrespective of its depth in relation to peak systolic flow, the woman was considered at risk for developing preeclampsia. These studies used notching as only one index for abnormal uterine artery Doppler measures (Antsaklis et al. 2000, Lyell et al. 2003, El-Hamedi et al. 2005).

In clinical screening for preeclampsia, the early diastolic notch has a high specificity and negative predictive value, but a poor sensitivity and positive predictive value (Lyell et al. 2003). In unselected women, the presence of a diastolic notch is reported to perform better in predicting preeclampsia than an elevated resistance index (Coleman et al. 2000, Axt-Fliedner et al. 2005) or systolic/diastolic ratio (Coleman et al. 2000). However, a large, multi-centre observation study (Papagheorghiou et al. 2005), found that mean PI performs better than early diastolic notching in predicting preeclampsia.

Umbilical artery Doppler and pregnancy outcome

The role of umbilical artery Doppler flow velocimetry in relation to pregnancy outcome has been studied for more than 20 years. It has been widely accepted that an abnormal Doppler umbilical artery waveform is a strong and independent predictor of adverse perinatal outcome in high-risk pregnancies, but still controversial on the role of these measures in unselected populations. In high risk populations (diagnosis of preeclampsia, small-for gestational age, or post dates pregnancy), abnormal umbilical artery velocimetry (absent or reverse diastolic flow, or PI above 95th percentile, high mean S/D ratio) was strongly associated with a higher rate of complications, including cesarean section, fetal distress, preterm delivery, low Apgar score, admission to the neonatal intensive care unit (NICU), significant neonatal morbidity, and perinatal death (Rochelson et al. 1987, Brar et al. 1989, Fischer et al. 1991, Devoe et al. 1992, Ogunyemi et al. 1992, Yoon B et al. 1993, Yoon B et al. 1994, Todros et al. 1996, Zelop et al. 1996, Soregaroli et al. 2002). In a randomized clinical trial, the use of umbilical Doppler velocimetry did not show clinical and economical benefit with regard to maternal admission rate and duration of neonatal admission (Omtzigt et al. 1994). In a meta-analysis, Goffinet et al. (Goffinet et al. 1997) found no significant difference between the Doppler and control groups for antenatal hospitalization, obstetric outcome or perinatal morbidity in unselected and low risk population. Recent studies (Seyam et al. 2002, Kwon et al. 2006) have confirmed the significant role of abnormal umbilical Doppler velocimetry (absent end-diastolic flow, S/D ratio greater than 3.0) in prediction of adverse perinatal outcomes.

Previous studies on exercise and uteroplacental and umbilical circulation

Several randomized clinical trials have attempted to evaluate the immediate effect of maternal exercise on uteroplacental blood flow with Doppler velocimetry. Most measurements were taken before and soon after exercise. These measurements have been performed with varying results because they used different gestational ages, study populations, and tests applied. In women at 35-38 weeks' gestation performing a submaximal bicycle test, Erkkola et al. (Erkkola et al. 1992) observed a significant increase in the S/D ratio from the baseline value to the first measurement during the recovery 1 minute after cessation. This result showed that the impedance of the uterine circulation increased with intensity of exercise. However, the S/D ratio in the umbilical artery remained unchanged before and after exercise. Kennelly et al. (Kennelly et al. 2002) found only modest changes in the uterine artery pulsatility index and no change in the umbilical artery pulsatility index among women at 30-34 weeks' gestation with exercise, consistent with results from the study by Morrow et al. (Morrow et al. 1989). Ertan et al. (Ertan et al. 2004) reported no significant changes in the umbilical and uterine artery Doppler after cycling in normal pregnancies and in pregnancy with IUGR, consistent with results from the studies by Steegers et al. (Steegers et al. 1988), and Moore et al. (Moore et al. 1988)

Rafla (Rafla & Etokowo 1998, Rafla 1999, Rafla 1999) conducted a series of measurements of uterine and umbilical artery Doppler velocimetry at different time points after exercise in women with normal and IUGR pregnancies. The results showed a transient increase, followed by a significant decrease later (compared to baseline) in the uterine artery pulsatility index (Rafla & Etokowo 1998). In the umbilical artery, the results showed a significant decrease in pulsatility index at two to four minutes of recovery after cycling (Rafla 1999). A different pattern was seen among women with IUGR pregnancy: the umbilical artery pulsatility index decreased initially, then increased even late after exercise (Rafla 1999).

To date, the literature does not provide satisfactory information on the effects of exercise on the uteroplacental and umbilical circulation. Randomized clinical trials provided some evidence of immediate effects. However, we are not aware of any epidemiological studies that report a long-term effect of exercise or physical activity during pregnancy on Doppler flow measurements of the uteroplacental unit.

Summary

This chapter reviews the literature regarding the etiology of gestational hypertension and preeclampsia, the role of physical activity in relation with the development of gestational hypertension and preeclampsia, and the associations between physical activity and maternal-fetal circulation during mid-pregnancy. We propose a study to address the hypothesis that physical activity is associated with lower resistance in uterine and/or umbilical arteries and a lower risk of hypertensive disorders during pregnancy.

III. STATEMENT OF SPECIFIC AIMS AND STUDY HYPOTHESES

We conducted a study using data from the Pregnancy, Infection, and Nutrition (PIN) 3 Study with 2006 women. The present study seeks to accomplish the following:

Specific Aim 1:

To examine the association of moderate to vigorous physical activity (work, recreational, exercise, and total) during pregnancy on the uteroplacental and umbilical circulation, measured by uterine and umbilical artery Doppler flow velocimetry waveforms.

Hypothesis 1: Engaging in moderate to vigorous work, recreational, exercise, and total activity at 17-22 weeks' gestation will be associated with a higher proportion of normal uterine and umbilical artery Doppler velocimetry indices measured at 15-10 and 24-29 weeks' gestation.

Specific Aim 2:

To examine the relationship between regular vigorous exercise before pregnancy and moderate to vigorous physical activity (work, recreational, exercise, and total) during pregnancy on the development of gestational hypertension/preeclampsia.

Hypothesis 2a: Women who engage in vigorous leisure-time physical activity three months prior to pregnancy, and/or continuing during pregnancy, will be at lower risk for the development of gestational hypertension and preeclampsia.

Hypothesis 2b: Women who engage in moderate to vigorous work, recreational, exercise, and total physical activity at 17-22 weeks' gestation will be at lower risk for the development of pregnancy-induced hypertension and preeclampsia.

IV. RESEARCH MATERIALS AND METHODS

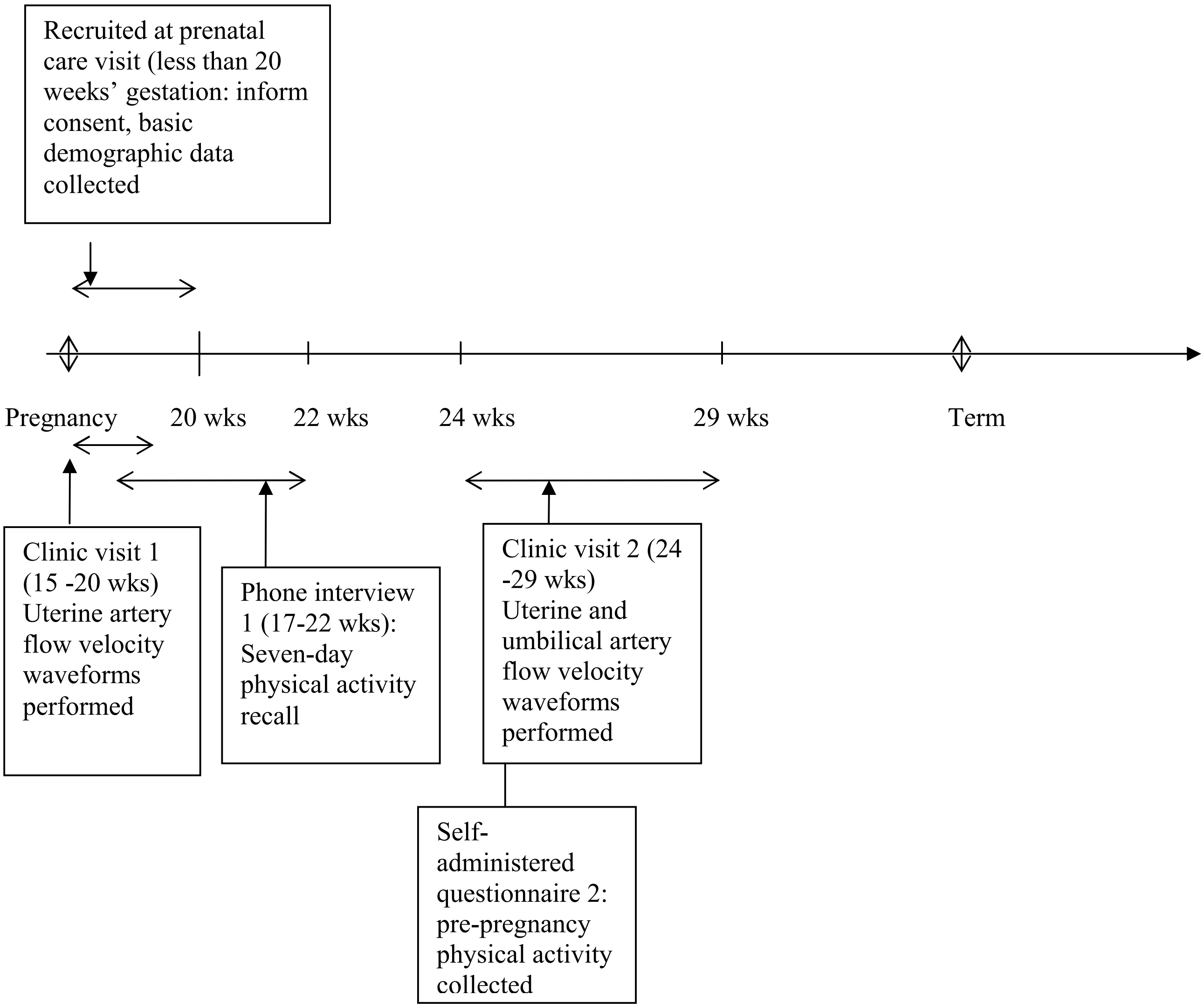
Overview

We conducted a secondary data analysis from the third phase (PIN3) Study of 2006 women who enrolled for prenatal care at UNC Hospital in Chapel Hill, North Carolina, US from January 2001 to June 2005. The parent study - PIN (Pregnancy, Infection, and Nutrition) was designed to identify etiologic factors for preterm delivery. Women were recruited for enrollment at less than or equal to 20 weeks' gestation at their second prenatal visit. Study staff described the study and asked women to participate and sign the informed consent form if they agreed. Also, some basic demographic and pregnancy-related data were recorded into a computerized tracking file used to date the pregnancy and track study participation.

Detailed information on occupational, recreational, household, and other activities in the past week was collected through 2 telephone interviews at 17-22 weeks' gestation and 27-30 weeks' gestation. Information on exercise before pregnancy was collected through a self-administered questionnaire at the second clinic visit at 24-29 weeks' gestation. Diagnoses of gestational hypertension and preeclampsia were made through information collected at prenatal care visits. Two clinic visits provided evaluation of uteroplacental and umbilical circulation by uterine artery Doppler velocimetry at 15-20 weeks' gestation, and by uterine and umbilical artery Doppler velocimetry at 24-29 weeks's gestation. Other information on sociodemographic, medical and reproductive history, health behaviors during pregnancy, current pregnancy factors, and clinical assessment was collected and assessed as potential confounders. Figure 4-1 provides the data collection timeline for information used in this study.

We used multivariable linear regression and log linear regression to assess the effect of work, recreational, exercise, and total physical activity on the patterns of Doppler flow velocity waveforms in uterine and umbilical artery. For longitudinal measures of uterine artery Doppler velocimetry, Generalized Estimating Equations (GEE) was used for modeling. We used logistic regression to examine relative risk of engaging in moderate or vigorous work, recreational, exercise, and total activity on the development of gestational hypertension and preeclampsia. All analyses will be adjusted for gestational age at examination and relevant confounding factors.

Figure 4-1: The PIN3 Study – Data collection timeline for information used in this study.



Study population

Study population in PIN3 Study

The PIN3 Study prospectively enrolled a cohort of pregnant women seeking prenatal care at UNC hospital in Chapel Hill, North Carolina, US. Women were recruited at their second prenatal visit if they were less than or equal to 20 weeks' gestation. Recruitment began in January 2001 and ended in June 2005 with the total of 2006 women included. Women were excluded if they were less than age 16, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or do not have a telephone from which they can complete phone interviews.

Population for analysis 1: Physical activity and maternal-fetal circulation measured by Doppler ultrasound in mid-pregnancy

This analysis investigated the associations of physical activity and uteroplacental and umbilical circulation measured by Doppler flow velocity waveforms. Among the total of 2006 women, 897 (45%) women were examined with Doppler ultrasound and had available data on either or both measures of uterine and umbilical Doppler indices at the first or second clinical visit, and 1823 (91%) women completed the first phone interview. This analysis included 874 women who completed with Doppler ultrasounds of either or both of uterine and umbilical artery at two clinic visits, and completed the first phone interview with information from a one-week physical activity recall.

Population for analysis 2: Physical activity and the risk of gestational hypertension and preeclampsia

This analysis investigated the association between physical activity before and during first half pregnancy and the risk of gestational hypertension/preeclampsia. Among 2006 women, 1856 (93%) women had gestational hypertension/preeclampsia outcome information available from prenatal care visits, and 1823 (91%) completed the first telephone interview with information on one-week physical activity recall. We excluded 129 women who were diagnosed with chronic hypertension or experienced hypertension before 20 weeks of gestation. The analysis included a total of 1586 women who had both information on gestational hypertension/preeclampsia and physical activity, after excluding one observation with an extreme outlier in work activity.

Measurement of physical activity

Assessment of exercise before and during pregnancy

Participants received a take-home questionnaire at 24-29 weeks' gestation. A part of the questionnaire consists of general and knowledge questions about physical activity before and during pregnancy. Women were asked, “Thinking back to 3 months before you got pregnant until now, have there been times when you have done any regular exercise or strenuous activity like aerobic exercise or jogging at least twice a week?” If the woman answered affirmatively, she was asked about participation in selected common vigorous activities (e.g., swimming, jogging) at any of three time periods (three months before pregnancy, the first three months of pregnancy, and the second three months of pregnancy). Women could also report other kinds of exercise or strenuous activity. All of the predefined activities as well as most of the “other” activities required an intensity of at least 6 metabolic equivalents (METs) and were therefore defined as "vigorous". For each of the three time periods, we created a dichotomous variable to indicate whether the woman participated in any of these exercises. For women who completed the questionnaire, their vigorous leisure activity participation was categorized in to “no exercise”, “exercise only before pregnancy”, “exercise before pregnancy through the first trimester”, and “exercise before pregnancy through the second trimester”. In the analysis 2 “Physical activity and the risk of gestational hypertension and preeclampsia”, 28% of women reported no exercise before and during pregnancy, and 38% of women reported engaging in exercise before pregnancy through the second trimester.

One-week recall physical activity measurement

A one-week recall physical activity was obtained from the phone interview at 17-22 weeks' gestation. The questionnaire included six separate sections for work, recreational, outdoor household, indoor household, child/adult care, and transportation. The questionnaire assessed frequency and duration of all moderate and vigorous physical activities the women participated in the past week. For example, the question asking about participation in particular modes of recreational activity was: "In the past-week, did you participate in any non-work, recreational activity or exercise, such as walking for exercise, swimming, dancing, that caused at least some increase in breathing and heart rate?" If the woman answered "Yes", the interviewer asked her to list all types of recreational activities. Then, the woman was asked "How many times in the past week did you participate in that activity?", and "On average, for how many minutes or hours did you usually do that activity at a time?". Finally, the woman was asked to self-evaluate the intensity of that activity "Thinking about your breathing and heart rate, how hard did this usually feel to you?'. The questionnaire took on average 10-20 minutes to administer.

Evaluation of physical activity (one-week recall) was based on two components: *relative intensity* and *absolute intensity*. For each type of activities, the woman reported the number of sessions in the past week, duration of each session, and the self-evaluated level for perceived intensity with three options: "fairly light", "somewhat hard", and "hard or very hard". The perceived intensity categories were modified from the Borg scale (Borg and Linderholm 1974). We calculated five scores regarding relative intensity: 1) number of hours/week in fairly light intensity, 2) number of hours/week in somewhat hard intensity, 3) number of hours/week in hard or very hard intensity, 4) total number of hours/week in work activity, and 5) number of hours/week in moderate to vigorous (somewhat hard + hard or very hard perceived intensity). We used the total number of hours/week overall and in "somewhat hard" and "hard or very hard" intensity (that defines moderate to vigorous intensity). Categorization of each physical activity variable in relative intensity was: 1) no activity, 2) activity but not "somewhat hard/hard or very hard", 3) moderate to vigorous activity less than or equal to the median value among participants who reported at least some "somewhat hard/hard or very hard" activity, and 4) moderate to vigorous activity greater than the median value.

Regarding scoring with absolute intensity, we assigned an intensity code of each activity to a metabolic equivalent (MET) value using published MET tables (Ainsworth et al. 1993, Ainsworth et al. 2000). We calculated two scores in continuous scale: total MET-hours/week for that activity and total MET-hours/week for moderate to vigorous intensity of that activity. We multiplied the hours/week in each activity by its MET value and summed them up to calculate total MET-hours/week and MET-hours/week for moderate to vigorous activity (defined as activities with a MET value >=4.8) (Pollock et al. 1998). Total activity was calculated by summing up all the values of the activity types. Each physical activity variable in the analysis was categorized into four levels: 1) no activity, 2) activity but not moderate to vigorous, 3) moderate to vigorous activity less than or equal to the median value among participants who reported at least some moderate to vigorous activity, and 4) moderate to vigorous activity greater than the median value.

To examine test-retest reliability of the physical activity questionnaire, 109 women from the PIN3 Study were asked to repeat the physical activity recall within 48 hours of the initial assessment. The result presents a substantial agreement, based on ratings suggested by Landis and Koch (Landis and Koch 1977). For example, the intraclass correlation coefficient (ICC) for total number of minutes of moderate to vigorous activity based on the women's perception was 0.84 and the total number of MET minutes per week based on existing MET tables was 0.84.

To explore validity of the physical activity questionnaire, 177 women who were recruited separately from PIN3 were asked to wear an accelerometer and keep a diary of their physical activity for seven days to compare with their physical activity report from an interview. The result presents a moderate agreement. For example, the intraclass correlation coefficient was 0.43, 0.48, and 0.44 for total minutes per week of moderate activity, total minutes per week of moderate to vigorous physical activity, and total MET minutes per week of moderate to vigorous physical activity, respectively.

Measures of outcome: Doppler velocimetry waveform indices

During the first clinic visit, at 15-20 weeks' gestation, the sonographer performed Doppler ultrasonography to obtain flow velocity waveforms in the uterine arteries (left and right). During the second clinic visit, at 24-29 weeks' gestation, Doppler ultrasonography was performed in both uterine arteries and the umbilical artery. The woman lay in a semi-recumbent position, and both uterine arteries were examined at their crossing with the external iliac artery using a 3.5 MHz transabdominal probe. For the umbilical artery, Doppler velocity waveforms were obtained from the free-floating loop of the umbilical cord during fetal quiescence. Doppler waveform indices were calculated from computerized planimetry including:

S/D ratio (peak systolic velocity/end-diastolic velocity),

PI (pulsatility index = (peak systolic velocity – end-diastolic velocity)/time-averaged maximum velocity)

RI (resistance index = (peak systolic velocity – end-diastolic velocity)/peak systolic velocity).

Also, presence of an early diastolic notch in the uterine arteries or umbilical artery, presence and direction of diastolic flow in umbilical artery, and location of the placenta were recorded.

For the uterine artery analysis, 823 women had Doppler flow velocimetry waveforms performed in either or both left and right uterine arteries at the first clinic visit, and 836 women had Doppler flow velocimetry waveforms performed in either or both left and right uterine arteries at the second clinic visit. PI was chosen as a continuous outcome measure with the most information because it incorporated the mean and the systolic and diastolic velocity and did not have many outliers. The mean of the left and right artery PI measurements was used for the final analysis. Presence of an early diastolic notch in either or both the left and right uterine arteries was chosen as a dichotomous variable.

For the umbilical artery analysis, 832 women had Doppler flow velocimetry waveforms performed in the umbilical artery at the second clinic visit. RI was chosen as a continuous outcome measure because of its most commonly used in clinical practice. With only few participants with adverse outcomes such as early diastolic notch present or reversed diastolic flow, we did not include these categorical variables for analysis.

Measure of outcome: gestational hypertension and preeclampsia

We obtained information on hypertensive disorders during pregnancy from prenatal care visits and urine tests. Gestational hypertension and preeclampsia were two categories of hypertensive disorders defined according to the criteria proposed by the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy (NHPEP 2000). Gestational hypertension was defined as systolic blood pressure level of 140 mm Hg or higher or diastolic blood pressure level of 90 mm Hg or higher that occurred after 20 weeks' gestation in a woman with previously normal blood pressure, without proteinuria. Preeclampsia was defined as gestational hypertension accompanied by urinary excretion of 0.3g protein or higher. Among 2006 women, 150 did not have available information on hypertensive disorders during pregnancy.

Covariate measurement

Other information on participants was obtained from the first phone interview at 17-22 weeks' gestation and medical records. Socio-demographic variables included age at enrollment, race (white, black, other), marital status, completed years of education, and household percentage of poverty for 2001 (Proctor and Dalaker 2001). Pre-pregnancy body mass index was calculated from self-reported weight and measured height (kg/m^2) and categorized based on the Institute of Medicine guidelines (IOM 1990). Adequacy of total weight gain was calculated as a ratio of observed weight/expected weight based on the Institute of Medicine guidelines (IOM 1990). Pregnancy and medical history variables included parity, chronic hypertension, pre-existing diabetes, and bleeding during pregnancy. Lifestyle behaviors included smoking, alcohol consumption, and drug use since month before pregnancy. Gestational age at the ultrasound measurements was calculated. The covariates and their categorizations are described in Table 4-1.

Table 4-1. Potential confounders considered in the analysis

Variable	Categorization
Demographic characteristics	
Age in years	<=20 21-34 >=35
Mother's race	White Black Other
Marital status	Married Unmarried
Education in years	High school or less (<=12) Some college (13-15) College graduation
Income (percent of poverty line)	<100% 100-200% >200%
Obstetric and chronic disease history	
Parity	Nulliparous Multiparous
Chronic hypertension	Yes No
Pre-existing diabetes	Yes No
Current pregnancy assessment	
Body mass index before pregnancy	Underweight < 19.8 kg/m^2 Normal: 19.8 – <26.0 kg/m^2 Overweight: 26 – <29.0 kg/m^2 Obese: >=29.0 kg/m^2
Adequacy of total weight gain (ratio of observed weight/expected weight based on IOM guidelines)	<1 1-2 >2
Ever bleeding during pregnancy	Yes No
Gestational age at the time of assessment	In number of weeks
Life style / Behavioral	
Smoking	Non smoker Past smoker Current smoker
Alcohol use since month before pregnancy	Yes No
Drug use since month before pregnancy	Yes No

Statistical analyses

Statistical analyses for study 1: Physical activity and maternal-fetal circulation measured by Doppler ultrasound in mid-pregnancy

Multiple linear regression modeling was performed for the umbilical RI and started with full models, including physical activity, all covariates as previously described, gestational age at the time of ultrasound, and placental location. We used a backward elimination approach to step-by-step remove variables from the model (Kleinbaum et al. 1998). Two criteria were used for elimination of a variable: 1) p-value for the t-test in the model exceeded 0.10 indicating the variable did not contribute meaningfully to the prediction of umbilical RI, and 2) removal of this variable from the model did not change the estimate of coefficients for the umbilical RI by 10% indicating the variable was not a potential confounder. We retained any confounder found in one model in all final models, together with gestational age at the second clinic visit. Lastly, to account for other types of physical activity, we included a variable "other physical activity" defined by subtracting of the specific exposure activity value of interest from the total activity value in the final models. We reported regression coefficients and p-values for physical activity variables in each model.

Data analyses for uterine artery Doppler indices started with a series of multiple linear regression modeling for the right and left uterine artery, at two time points, separately, using the same approach as described for the umbilical RI. Then, we repeated the same modeling techniques with the mean PI. The purpose of initial models was to evaluate the separate association between physical activity and uterine PI indices at different time points and uterine artery location. Finally, Generalized Estimating Equation (GEE) models were fit to the uterine artery Doppler data using PROC GENMOD with REPEAT statement in SAS for the continuous outcome as mean uterine PI, measured twice. We reported regression coefficients with 95% confidence intervals and p-value for physical activity variables in each model. The presence of a notch in either or both uterine arteries, measured twice, was the dichotomous outcome, and we reported crude and adjusted relative risk (RR) with their confidence intervals. All final models were adjusted for appropriate confounders, gestational age at the first and second clinic visit, placental location at the second visit, and “other physical activity”.

Statistical analyses for study 2: Physical activity and the risk of gestational hypertension and preeclampsia

Gestational hypertension and preeclampsia were considered separately for identifying appropriate covariates of interest for all statistical models. Frequency distributions of sociodemographic, lifestyle, and pregnancy characteristics of women with gestational hypertension or with preeclampsia were compared to women without those conditions. We then assessed the relationship between each specific physical activity mode and intensity with gestational hypertension or preeclampsia by calculating the relative risk as odds ratio (OR) with 95% confidence intervals (CI), using multivariate logistic regression with the SAS GENMOD procedure (SAS/STAT software, SAS Institute Inc., Cary, NC). Women without the specific activity served as the reference category.

Evaluation of confounders in all models started with listing risk factors based on previous studies and the hypothesized etiology of these diseases. Potential confounders were evaluated for their associations with physical activity and pregnancy outcomes using directed acyclic graphs (Greenland et al. 1999). Potential confounders were examined and retained in the model if there was a change by 10% or more in the crude estimate of the effect measure between physical activity and gestational hypertension or preeclampsia. For consistency, any variable that was identified as a confounder in a model between a specific physical activity and an outcome was included in all final models of that outcome. All final models regarding either perceived or absolute activity intensity measures used the same confounders, plus gestational age at the time interview. Lastly, to account for energy expenditure other than the specific activity of interest, we included a variable “other physical activity” defined by subtracting of the specific exposure activity value of interest from the total activity value in the final models, and these further adjustments did not make much difference of estimates in all the final models.

V. MANUSCRIPT 1: PHYSICAL ACTIVITY AND MATERNAL-FETAL CIRCULATION MEASURED BY DOPPLER ULTRASOUND IN MID-PREGNANCY

Introduction

The American College of Obstetricians and Gynecologists (ACOG) encourages pregnant women, in the absence of either medical or obstetric complications, to engage in regular, moderate intensity physical activity (1). This recommendation is based on the scientific evidence that physical activity during pregnancy is not associated with adverse fetal and maternal outcomes and may have some benefits (5,16,28). However, some concerns remain about the sufficiency and the modification of the uteroplacental and umbilical circulation in relation to physical activity (12). To date, the literature does not give satisfactory information on this issue.

Regular physical activity and exercise during pregnancy may introduce physiological effects on the maternal haemodynamic system and placental function (12,13,29) that lead to modification of maternal-fetal blood flow (14,23) which might be beneficial to the fetus (12). Doppler ultrasound provides a non-invasive way to examine uteroplacental blood flow and placental vascular resistance, enabling inferences about the adequacy of maternal-fetal and placental circulation (18,37). For example, when placental impedance increases, the uterine and umbilical arterial diastolic flow decreases, which is associated with persistence of a diastolic notch in uterine arteries or with either low, absent, or even reversed end-diastolic blood flow in the umbilical artery that can be detected by Doppler ultrasound (6,10,18). Numerous studies have established an association between abnormal Doppler velocimetry waveforms in the uterine and umbilical arteries and adverse pregnancy outcomes such as pre-eclampsia, intrauterine growth retardation, and prediction of fetal distress, perinatal mortality, or admission to the neonatal intensive care unit (4,10,1518,22,35,38).

Several randomized clinical trials have evaluated the immediate effect of maternal exercise on maternal-fetal circulation with Doppler velocimetry. Most measurements were taken before and soon after exercise. Findings included no meaningful changes in uterine artery Doppler indices (20,26,36), an increase in uterine artery Doppler indices (19,24,27), or no change in umbilical artery Doppler indices in relation to exercise (19,20,24,27). In a series of measurements of uterine and umbilical artery Doppler velocimetry at several time points after an exercise session in women with normal and intra-uterine growth retardation (IUGR) pregnancies, Rafla et al. (32,33,34) found an increase followed by a decrease of the uterine artery Doppler indices, and an opposite pattern in the umbilical artery Doppler indices.

We are not aware of any observational studies that reported associations between physical activity during pregnancy and persistent changes of Doppler flow measurements of the uteroplacental unit. The present study provides a comprehensive analysis of overall physical activity and several component sources of physical activity on maternal-fetal circulation during mid-pregnancy.

Methods

Study population

This analysis includes participants in the third phase of the PIN (Pregnancy, Infection, and Nutrition) Study, a prospective study examining etiologic factors (physical activity, stress, and placental vascular compromise) for preterm delivery. Women seeking services before 20 weeks' gestation from prenatal clinics at the University of North Carolina Hospitals between January 2001 and June 2005 were asked to participate. Exclusion criteria included being less than age 16, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or not having a telephone for the phone interviews. During the course of pregnancy, the women were asked to complete two research clinic visits, two telephone interviews, and two self-administered questionnaires. A total of 2006 women recruited for this phase. This analysis included 874 women, who completed with Doppler ultrasounds of either or both of uterine and umbilical artery at two clinic visits, and completed the first telephone interview with information from a one-week physical activity recall.

One-week recall physical activity measurement

A one-week recall physical activity was obtained from the phone interview at 17-22 weeks' gestation. The questionnaire included six separate sections for work, recreational, outdoor household, indoor household, child/adult care, and transportation. The questionnaire assessed frequency and duration of all moderate and vigorous physical activities the women participated in during the past week. For example, a question regarding participation in particular modes of recreational activity stated: "In the past-week, did you participate in any non-work, recreational activity or exercise, such as walking for exercise, swimming, dancing, that caused at least some increase in breathing and heart rate?" If the woman answered "Yes", the interviewer asked her to list all types of recreational activities. For each type of activity, the woman reported the number of sessions in the past week, duration of each session, and her perception of the intensity classified as: "fairly light", "somewhat hard", and "hard or very hard". The perceived intensity categories were modified from the Borg scale (8). Regarding scoring with absolute intensity, we assigned an intensity code for each activity to a metabolic equivalent (MET) value using published MET tables (2,3).

In this analysis, we focused on two typical types of physical activity that required routine daily movement of at least moderate intensity (work, recreational activity), and total activity that included all physical activities. Regarding relative intensity, for each type of activity, we calculated the total number of hours/week overall and in "somewhat hard" and "hard or very hard" intensity (that defines moderate to vigorous intensity). Regarding absolute intensity, we multiplied the hours/week in each activity by its MET value and summed them up to calculate total MET-hours/week and MET-hours/week for moderate to vigorous activity (defined as activities with a MET value >=4.8, which corresponds to moderate intensity for women 20-39 years of age) (30). Total activity was calculated by summing up all the values for all activity types. Each physical activity variable in the analysis was categorized into four levels: 1) no activity, 2) activity but not moderate to vigorous, 3) moderate to vigorous activity less than or equal to the median value among participants that reported that activity, and 4) moderate to vigorous activity greater than the median value. The only exception was for moderate to vigorous work activity, which had a low prevalence, so we collapsed it into three categories.

Measures of outcome

During the first clinic visit, at 15-20 weeks' gestation, the sonographer performed Doppler ultrasonography to obtain flow velocity waveforms in the uterine arteries (left and right). During the second clinic visit, at 24-29 weeks' gestation, Doppler ultrasonography was performed in both uterine arteries and the umbilical artery. The woman lay in a semi-recumbent position, and both uterine arteries were examined at their crossing with the external iliac artery using a 3.5 MHz transabdominal probe. For the umbilical artery, Doppler velocity waveforms were obtained from the free-floating loop of the umbilical cord during fetal quiescence. Doppler waveform indices were calculated from computerized planimetry as systolic/diastolic (S/D) ratio, pulsatility index (PI), and resistance index (RI). Also, presence of an early diastolic notch in the uterine arteries or umbilical artery, presence and direction of diastolic flow in umbilical artery, and location of the placenta were recorded.

For the uterine artery analysis, PI was chosen as a continuous outcome measure with the most information because it incorporated the mean and the systolic and diastolic velocity and did not have many outliers. The mean of the left and right artery PI measurements was used for the final analysis. We also used a dichotomous variable that indicated the presence of an early diastolic notch in either or both the left and right uterine arteries. For the umbilical artery analysis, RI was chosen as a continuous outcome measure because of its most commonly used in clinical practice. With only few participants with adverse outcomes such as notch present or reversed diastolic flow, we did not analyze these categorical variables. Doppler waveform indices used in this study and their clinical implications are presented in Table 1.

Covariate measurement

Other information on participants was obtained from the first phone interview at 17-22 weeks' gestation and medical records. Socio-demographic variables included age at enrollment, race (white, black, other), marital status, completed years of education, and household percentage of poverty for 2001 (31). Pre-pregnancy body mass index was calculated from self-reported weight and measured height (kg/m^2) and categorized based on the Institute of Medicine guidelines (21). Adequacy of total weight gain was calculated as a ratio of observed weight/expected weight based on the Institute of Medicine guidelines (21). Pregnancy and medical history variables included parity, chronic hypertension, pre-existing diabetes, and bleeding during pregnancy. Lifestyle behaviors included smoking, alcohol consumption, and drug use since month before pregnancy. Gestational age at the ultrasound measurements was included in the analysis.

Statistical analyses

Multiple linear regression modeling was performed for the umbilical RI and started with full models, including physical activity, all covariates as previously described, gestational age at the time of ultrasound, and placental location. We used a backward elimination approach to step-by-step remove variables from the model (25). Two criteria were used for elimination of a variable: 1) p-value for the t-test for the presence of this variable in the model exceeded 0.10 indicating the variable did not contribute meaningfully to the prediction of umbilical RI, and 2) removal of the variable from the model did not change the estimate of coefficients for the umbilical RI by more than 10% indicating the variable was not a confounder. We retained any confounder identified in any of the three physical activity models in all final models, together with gestational age at the second clinic visit. Lastly, to account for other types of physical activity when examining the association with work and recreational activity, we included a variable "other physical activity" defined by subtracting of the specific exposure activity value of interest from the total activity value in the final models. We reported regression coefficients and p-values for physical activity variables in each model.

We fit generalized estimating equation (GEE) models to the uterine artery Doppler data using PROC GENMOD with REPEATED statement in SAS (SAS Institute Inc., Cary, NC) for the continuous outcome as mean uterine PI, measured twice (17). We reported regression coefficients with 95% confidence intervals and p-value for physical activity variables in each model. Also using GEE models for the presence of a notch in either or both uterine arteries, as a dichotomous outcome, measured twice, we reported crude and adjusted relative risk (RR) with their confidence intervals. All final models were adjusted for appropriate confounders, gestational age at the first and second clinic visit, placental location at the second visit, and "other physical activity". Further adjustment for "other physical activity" did not meaningfully change the estimates in the final models. Reproductive history (parity, history of stillbirths, miscarriages, and abortions), bleeding during pregnancy, adequacy of maternal weight gain, alcohol use and drug use were not confounders in any model, and thus are not presented in the result tables.

Results

Distribution of sociodemographic, lifestyle, and pregnancy characteristics of study participants are presented in Table 2. Women were mostly white, married, and well-educated. Almost 40% of women were overweight or obese. We compared characteristics of women who were included in the analysis (n=874) and those who were eligible, but were not included (n=1132), among the total of 2006 women in the PIN3 study (data not shown). Chi-square statistics were used for comparison. We found no differences between both groups ($p<0.05$) on most characteristics (e.g., age, race, education, marital status, general health, BMI before pregnancy, parity, maternal weight gain, and smoking). Also, no differences between the groups were found regarding regular exercise before pregnancy, and during the first and second trimester of pregnancy. However, women who were included in the analysis were more likely to have a lower percent below poverty and better adequacy of prenatal care.

At the first clinic visit the mean uterine PI was 1.15 (SD=0.45), and 28% had an early diastolic notch present in either or both uterine arteries. At the second clinic visit the mean uterine PI was 0.85 (SD=0.26), and 10% had a notch present in either or both uterine arteries, and the mean umbilical RI was 0.65 (SD=0.06). Seventy percent of women did not engage in any work activity and

37% of women did not engage in any recreational activity. The median value of intensity among women who reported at least some moderate to vigorous total physical activity was 9.3 MET-hours/week and the median value of intensity among women who reported at least some moderate to vigorous recreational activity was 10.9 MET-hours/week.

Table 3 displays GEE models for the relationship between physical activity, measured using perceived intensity, with the two outcomes (mean uterine PI and any uterine notching at either or both first and second clinic visit). About 65% of women reported "somewhat hard or hard/very hard" total physical activity, 30% reported "somewhat hard or hard/very hard" work activity, and 39% reported "somewhat hard or hard/very hard" recreational activity. "Somewhat hard or hard/very hard" total physical activity and recreational activity above the median were associated with higher uterine PI (beta coefficient = 0.092 and 0.067, respectively). "Somewhat hard or hard/very hard" work activity was associated with lower uterine PI (beta coefficient = -0.100). The risk of any uterine notching was increased among women reporting "somewhat hard or hard/very hard" recreational activity above the median (adjusted RR = 1.71, 95% CI 1.12 – 2.62).

Focusing on the same two outcomes, table 4 displays the results for physical activity measured in absolute intensity. The results corroborated findings with the GEE models using physical activity measured with perceived intensity (Table 3). About 35% of women reported moderate to vigorous total physical activity, only 5% reported some moderate to vigorous work activity, and 20% reported moderate to vigorous recreational activity. Mean uterine PI was slightly decreased among those who reported moderate to vigorous work activity (beta coefficient = -0.076), but increased among those who reported moderate to vigorous total physical activity above the median (beta coefficient = 0.095). A modest increased risk of any uterine notching was found among those who reported moderate to vigorous recreational activity above the median (adjusted RR = 1.49, 95% CI 0.91 – 2.46).

The multiple linear regression models between physical activity measured in both perceived and absolute intensity and the umbilical RI are described in Table 5. Total, work and recreational physical activity at any level of intensity measured in either perceived or absolute intensity were not associated with changes of the umbilical Doppler RI.

Discussion

This is the first epidemiologic study to investigate the association of physical activity with vascular resistance in the uterine and umbilical artery blood flow. Our study found no associations between types of physical activity, including work and recreational activity, at any level of intensity with any changes of umbilical Doppler resistance index. Findings from randomized trials assessing acute response (19,20,24,27) showed no changes in umbilical Doppler indices (measured as S/D ratio, PI, or RI) after exercise. However, some associations between physical activity and uterine artery blood flow were observed with the magnitude varied by type of physical activity and level of intensity. Overall, moderate to vigorous total physical activity above the median was associated with a higher mean uterine PI. Interestingly, we observed a lower mean uterine PI among women engaging in moderate to vigorous work activity, suggesting a reduction of impedance in uterine circulation. We observed a slightly higher mean uterine PI among those reporting recreational activity above the median, which was in agreement with previous randomized trials (19,24,27). Appearance of an early diastolic notch is considered a persistent alteration, rather than an immediate effect, and we found a small increased risk of the presence of any uterine notching among women engaging in moderate to vigorous recreational activity above the median, indicating somewhat higher chronic impedance of uterine artery circulation. However, all the associations we found in this analysis are relatively small, indicating that physical activity did not appear to be associated with meaningful changes of Doppler flow measurements of the uteroplacental unit.

A link between physical activity and resistance in the placenta is plausible biologically. In normal pregnancy, maternal haemodynamic adaptations, including changes in vascular tone, increase of placental bed blood flow through hormonally mediated vascular growth and remodeling, and decreased adrenergic response, lead to low vascular impedance in the placenta and decreased placental vascular resistance (11,14,37). Among women engaging in exercise during pregnancy, many other biological effects are observed including increased resting maternal plasma volume, intervillous space blood volume, enhanced fetoplacental growth, placental function and vascularity (12,13). Observations in the placental biopsy after delivery revealed a significantly greater total vascular volume and total capillary volume in the placental villi among women engaging in exercise (23). Other important findings in the placental biopsy included increased total villous surface area, increased cell proliferation, and reduced fraction of nonfunctional tissue (7,23). The chronic effects on these physiological and functional changes increase overall placental perfusion, placental bed blood flow at rest, oxygen and substrate delivery (13,23). All of these changes imply a reduction of resistance in the placental blood flow among women engaging in exercise during pregnancy; however, our results did not support the association between recreational activity and reduced resistance in the placental blood flow, but did show the reduced resistance among working women at moderate to vigorous level.

Our data indicated an agreement in findings across perceived and absolute intensity measures of physical activity. However, we noted some differences in categorization levels of physical activity. Measures of physical activity in perceived intensity were based on participant's perception of the specific activity using the definitions of "fairly light", "somewhat hard", and "hard or very hard". The participant's perception of the intensity of physical activity could change through pregnancy and also differ person to person, as some people may tolerate higher intensity activity better than others. Measures of physical activity in absolute intensity were based on actual activities reported, with the assignment to MET values for those activities. The MET value cut-point for defining "moderate to vigorous" physical activity as of >= 4.8 was based on non-pregnant adult, age of 20-39 (Pollock et al. 1998), higher than the cut-point used for general adult population (>= 3 METs) (39). As a result, the category "no activity" remains similar in both perceived and absolute intensity, but fewer participants were classified as "moderate to vigorous" in absolute intensity than participants who were classified as "somewhat hard or hard" in perceived intensity. Despite differences in categorization, findings remained relatively similar, indicating only a small effect of physical activity on uteroplacental circulation.

A large cohort of pregnant women helped us to study physical activity during pregnancy on blood flow in uterine and umbilical arteries measured by Doppler ultrasound. Physical activity was collected through a one-week recall questionnaire to capture comprehensive information on the type, frequency, duration, and intensity of all types of physical activity during pregnancy. The questionnaire was validated and had high test-retest reliability (9). We assessed the intensity of each activity using both perceived exertion and measures of energy expenditure (i.e., MET value), based on the compendium of physical activities (3), the most common basis for scoring. Outcome data such as uterine artery Doppler indices were measured at two different time points during pregnancy, taking into account the variability of these measures along with gestational age. Information on key confounders was collected in detail, allowing us to evaluate the effects of specific types of physical activity and we were able to control for other activities simultaneously.

Several limitations of this study should be noted. Although the physical activity questionnaire was validated and showed high test-retest reliability, measurement errors are inevitable because of self-reporting. Physical activity is variable over a short period of time, so that physical activity measured in a one-week period may not represent a longer interval of pregnancy. Such misclassification of exposure is likely to be random with respect to the outcomes and therefore, it may bias any relationships toward the null. Doppler velocimetry indices were also subject to some variances between and within operators. The study included 93 duplicate women (who were recruited for more than one time because they had two or more deliveries during the study period) in the total of 874 women. The study analysis did not account for the correlation introduced because some women participated more than once in the PIN3 Study. The findings could also be biased by inadequate adjustment for unmeasured confounding effect such as nutrition status or stress during pregnancy. Timing between measures of physical activity and Doppler ultrasound exams may introduce some biases due to variable patterns of physical activity during pregnancy, making the causal inference somewhat uncertain.

This study provided evidence regarding the associations of physical activity, by mode and intensity, and maternal-fetal circulation measured by Doppler ultrasound. Our findings indicate that physical activity during pregnancy does not appear to be associated with meaningful changes of resistance in uterine and umbilical arteries that would be related to maternal-fetal haemodynamics and blood volume delivery. Future studies might consider multiple prospective measurements of physical activity during pregnancy, following by multiple measurements of Doppler indices in the short time, and the time-series analysis.

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Table 5-1. Doppler waveform indices used in this study and clinical implications

Arteries examined	Outcome Indices	Time of measurement	Calculation	Clinical implication
Uterine arteries	Mean of Pulsatility Index (PI)	Measured twice at 15-20 and 24-29 weeks' gestation	PI = (S-D)/A	High PI indicates increased resistance in uteroplacental blood flow
	Any early diastolic notch in either or both uterine arteries	Measured twice at 15-20 and 24-29 weeks' gestation	Yes or No	A notch indicates increased resistance in uteroplacental blood flow
Umbilical artery	Resistance Index (RI)	Measured once at 24-29 weeks' gestation	RI = (S-D)/S	High RI indicates increased resistance in umbilical blood flow

PI: Pulsatility Index
RI: Resistance Index
S: Peak systolic velocity
D: End-diastolic velocity
A: Time-averaged maximum velocity

Table 5-2. Selected sociodemographic, lifestyle and pregnancy characteristics of the study participants (N = 874).

	Number	Percent
Age in years		
<=20	81	9.3
21-34	670	76.6
>=35	123	14.1
Race		
White	615	70.4
Black	180	20.6
Other	79	9.0
Marital status		
Not married	241	27.6
Education		
College and higher	671	76.8
Income (percent of the poverty line)		
<100	131	15.6
100 – 200	111	13.3
>200	595	71.1
Body mass index before pregnancy		
Underweight < 19.8 kg/m^2	120	14.0
Normal: 19.8 – <26.0 kg/m^2	407	47.3
Overweight: 26 – <29.0 kg/m^2	103	12.0
Obese: >=29.0 kg/m^2	230	26.7
Chronic hypertension	72	8.6
Preexisting diabetes	43	5.2
Smoking		
Non-smoker	554	70.1
Past smoker	111	14.1
Current smoker	125	15.8

Table 5-3. GEE models for past week physical activity using perceived intensity at 17-22 weeks of pregnancy and mean uterine artery pulsatility index and the risk of any uterine notching at both Doppler measurements (N = 874).

			Outcome as mean uterine artery PI [a]			Outcome as the risk of any uterine notching	
	N	%	Beta	95% CI of Beta	p-value	RR unadjusted (95% CI)	RR adjusted (95% CI) [b]
Total physical activity (median = 2.9 hrs/wk)							
No activity [c]	57	6.5	Reference			1.00	1.00
Activity but not SH+H	252	28.8	0.064	(-0.020, 0.148)	0.13	0.91 (0.51, 1.64)	1.08 (0.54, 2.19)
SH+H activity below the median	283	32.4	0.064	(-0.018, 0.146)	0.12	0.91 (0.51, 1.63)	1.26 (0.63, 2.53)
SH+H activity above the median	282	32.3	0.092	(0.010, 0.175)	0.03	1.13 (0.63, 2.01)	1.57 (0.78, 3.14)
Recreational activity (median = 2.0 hrs/wks)							
No recreational activity [c]	327	37.4	Reference			1.00	1.00
Recreational activity but not SH+H	210	24.0	0.033	(-0.026, 0.092)	0.28	1.03 (0.72, 1.49)	1.17 (0.78, 1.76)
SH+H activity below the median	194	22.2	0.043	(-0.017, 0.103)	0.16	1.16 (0.80, 1.69)	1.38 (0.92, 2.05)
SH+H activity above the median	143	16.4	0.067	(0.003, 0.131)	0.04	1.56 (1.05, 2.31)	1.71 (1.12, 2.62)
Work activity							
No work activity [c]	613	70.1	Reference			1.00	1.00
Work activity but not SH+H	160	18.3	-0.013	(-0.069, 0.042)	0.64	1.05 (0.74, 1.49)	1.22 (0.84, 1.78)
Some SH+H work activity	101	11.6	-0.100	(-0.154, -0.043)	0.00	0.72 (0.46, 1.11)	0.77 (0.47, 1.26)

SH+H: Activity that was self-evaluated as "somewhat hard" and "hard or very hard".
Median among participants who reported at least some SH+H activities.
[a] Adjusted for household percentage of poverty (<100, 100-200, >200), pre-existing diabetes (yes, no), smoking (no, past, current), gestational age at first and second visit (weeks), and other physical activity.
[b] Adjusted for household percentage of poverty (<100, 100-200, >200), pre-existing diabetes (yes, no), smoking (no, past, current), gestational age at first and second visit (weeks), placental location at second visit (anterior, posterior, other) and other physical activity.
[c] referent group, women with no specific activity.
In all models, all variables with more than two levels were coded as indicator variables.

Table 5-4. GEE models for past week physical activity using absolute intensity at 17-22 weeks of pregnancy and mean uterine artery pulsatility index and the risk of any uterine notching at both Doppler measurements (N = 874).

			Outcome as mean uterine artery PI [a]			Outcome as the risk of any uterine notching	
	N	%	Beta	95% CI of Beta	p-value	RR crude (95% CI)	RR adjusted (95% CI) [b]
Total physical activity (median = 9.3 MET - hrs/wk)							
No activity [c]	57	6.5	Reference			1.00	1.00
Activity but not MV	510	58.4	0.070	(-0.008, 0.147)	0.08	0.94 (0.54, 1.63)	1.26 (0.64, 2.47)
MV activity below the median	152	17.4	0.067	(-0.025, 0.159)	0.15	0.90 (0.47, 1.69)	1.14 (0.54, 2.42)
MV activity above the median	155	17.7	0.095	(0.005, 0.186)	0.04	1.25 (0.68, 2.29)	1.68 (0.81, 3.49)
Recreational activity (median = 10.9 MET - hrs/wk)							
No recreational activity [c]	327	37.4	Reference			1.00	1.00
Recreational activity but not MV	369	42.2	0.038	(-0.010, 0.087)	0.12	1.13 (0.83, 1.55)	1.36 (0.96, 1.91)
MV activity below the median	89	10.2	0.057	(-0.029, 0.144)	0.19	1.40 (0.86, 2.27)	1.36 (0.80, 2.34)
MV activity above the median	89	10.2	0.062	(-0.014, 0.138)	0.11	1.34 (0.84, 2.16)	1.49 (0.91, 2.46)
Work activity							
No work activity [c]	613	70.1	Reference			1.00	1.00
Work activity but not MV	211	24.2	-0.037	(-0.086, 0.012)	0.14	0.89 (0.65, 1.24)	1.04 (0.73, 1.48)
Some MV work activity	50	5.7	-0.076	(-0.150, 0.001)	0.05	1.02 (0.59, 1.76)	1.06 (0.58, 1.94)

MV: moderate to vigorous, defined as activity with a MET value >=4.8.
Median among participants who reported at least some MV activities.
[a] Adjusted for household percentage of poverty (<100, 100-200, >200), pre-existing diabetes (yes, no), smoking (no, past, current), gestational age at first and second visit (weeks), and other physical activity.
[b] Adjusted for household percentage of poverty (<100, 100-200, >200), pre-existing diabetes (yes, no), smoking (no, past, current), gestational age at first and second visit (weeks), placental location at second visit (anterior, posterior, other) and other physical activity.
[c] referent group, women with no specific activity.
In all models, all variables with more than two levels were coded as indicator variables.

Table 5-5. Multiple linear regression for past week physical activity using perceived and absolute intensity at 17-22 weeks of pregnancy and umbilical artery resistance index at 24-29 weeks of pregnancy (N = 874).

Modeling with physical activity in perceived intensity [a]	Beta (95% CI)	p-value	Modeling with physical activity in absolute intensity [a]	Beta (95% CI)	p-value
Total physical activity (median = 2.9 hrs/wk)			Total physical activity (median = 9.3 MET - hrs/wk)		
No activity [b]	Reference		No activity [b]	Reference	
Activity but not SH+H	0.004 (-0.015, 0.023)	0.67	Activity but not MV	0.004 (-0.014, 0.022)	0.68
SH+H activity below the median	0.008 (-0.011, 0.027)	0.39	MV activity below the median	0.009 (-0.011, 0.029)	0.39
SH+H activity above the median	0.006 (-0.013, 0.025)	0.53	MV activity above the median	0.013 (-0.007, 0.033)	0.20
Recreational activity (median = 2.0 hrs/wk)			Recreational activity (median = 10.9 MET - hrs/wk)		
No recreational activity [b]	Reference		No recreational activity [b]	Reference	
Recreational activity but not SH+H	-0.004 (-0.015, 0.007)	0.47	Recreational activity but not MV	-0.004 (-0.014, 0.005)	0.36
SH+H activity below the median	0.001 (-0.010, 0.012)	0.87	MV activity below the median	0.007 (-0.007, 0.022)	0.33
SH+H activity above the median	-0.003 (-0.015, 0.009)	0.59	MV activity above the median	-0.001 (-0.016, 0.013)	0.85
Work activity			Work activity		
No work activity [b]	Reference		No work activity [b]	Reference	
Work activity but not SH+H	-0.003 (-0.013, 0.008)	0.64	Work activity but not MV	-0.006 (-0.015, 0.004)	0.27
Some SH+H work activity	-0.002 (-0.015, 0.011)	0.80	Some MV work activity	0.010 (-0.007, 0.028)	0.23

SH+H: Activity that was self-evaluated as "somewhat hard" and "hard or very hard".
MV: moderate to vigorous, defined as activity with a MET value >=4.8.
Median among participants who reported at least some SH+H or MV activities.
[a] Adjusted for household percentage of poverty (<100, 100-200, >200), weight gain ratio of observed weight/expected weight based on IOM guidelines (<1, 1-<2, >=2), gestational age at second visit (weeks), placental location at second visit (anterior, posterior, other), and other physical activity.
[b] referent group, women with no specific activity.
In all models, all variables with more than two levels were coded as dummy variables.

VI. MANUSCRIPT 2: PHYSICAL ACTIVITY AND THE RISK OF GESTATIONAL HYPERTENSION/PREECLAMPSIA

Introduction

Gestational hypertension, characterized by the new development of hypertension after 20 weeks of pregnancy, and preeclampsia (gestational hypertension plus proteinuria), are among the leading direct causes of maternal death, responsible for approximately 15 - 18 % of maternal mortality in the United States.[1,2] The literature has demonstrated benefits from regular physical activity for preventing or delaying the development of high blood pressure, as well as reduced blood pressure among those with hypertension in non-pregnant populations.[3] Among pregnant women, physical activity has been hypothesized to prevent preeclampsia through enhanced placental growth and vascularity, reduction of oxidative stress, reversal of endothelial dysfunction, reduced plasma triglycerides, and increased high-density lipoprotein.[4,5]

Associations between various types of physical activity and the risk of gestational hypertension and preeclampsia have been found in previous studies. Regular recreational activity was associated with a somewhat reduced risk of preeclampsia[6-9] and gestational hypertension,[6] in some but not all[10-12] cohort studies. Similarly, work activity has been variably related to hypertensive disorders during pregnancy.[6,8,13-20] Findings from small randomized trials did not find preventive effects of structured exercise on the development of preeclampsia among healthy pregnancies,[21,22]or among pregnant women at high risk for preeclampsia.[23,24]

Previous studies of the associations of physical activity with gestational hypertension and preeclampsia have several limitations, including reporting physical activity from periods in the distant past, a lack of a standardized, validated and consistent method for physical activity assessment, not ascertaining all types of physical activity (such as recreational, occupational, and other activities), and omission of details about the intensity and duration of specific activities.[4,5,25-27] The present study addresses these gaps in the literature with a cohort study in which the components of physical activity were collected during pregnancy to examine the relationship to the risk of gestational hypertension and preeclampsia.

Methods

Women from prenatal clinics at the University of North Carolina Hospitals (Chapel Hill, NC) were recruited for enrollment at less than or equal to 20 weeks' gestation. Recruitment began in January 2001 and ended in June 2005. The study protocol was approved by the Institutional Review Board at the University of North Carolina – Chapel Hill. Participants were asked to complete two research clinic visits, two telephone interviews, and several self-administered questionnaires. During the clinic visits, specimens (saliva, blood, and genital tract swabs) were collected and ultrasounds with Doppler measurements were performed. Exclusion criteria included being less than 16 year of age, non-English speaking, not planning to continue care or deliver at the study site, carrying multiple gestations, or not having a telephone for the phone interviews. Overall, 2006 women were enrolled. Of those, 1856 (93%) women had gestational hypertension/preeclampsia outcome information available from prenatal care visits, and 1823 (91%) completed the first telephone interview with information on the one-week physical activity recall. We excluded 148 women who were diagnosed with chronic hypertension or experienced hypertension before 20 weeks of gestation. The analysis included a total of 1586 women who had information on both gestational hypertension/preeclampsia and physical activity, after excluding one an extreme outlier in work activity.

We obtained information on hypertensive disorders during pregnancy from prenatal care visits and urine tests. Gestational hypertension and preeclampsia were defined according to the criteria proposed by the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy.[28] Gestational hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher that occurred after 20 weeks' gestation in a woman with previously normal blood pressure, without proteinuria.

Preeclampsia was defined as gestational hypertension accompanied by urinary excretion of 0.3 g of protein or higher.

Brief assessment of exercise before and during pregnancy

A take-home questionnaire was given to the participant at 24-29 weeks' gestation in which women were asked, “Thinking back to 3 months before you got pregnant until now, have there been times when you have done any regular exercise or strenuous activity like aerobic exercise or jogging at least twice a week?” If the woman answered affirmatively, she was asked about participation in selected common vigorous activities (e.g., swimming, jogging) at any of three time periods (three months before pregnancy, the first three months of pregnancy, and the second three months of pregnancy). Women could also report other kinds of exercise or strenuous activity. All of the predefined activities as well as most of the “other” activities required an intensity of at least 6 metabolic equivalents (METs) and were therefore defined as "vigorous". For the 1170 women who completed the questionnaire, their vigorous leisure activity participation was categorized into “no exercise”, “exercise only before pregnancy”, “exercise before pregnancy through the first trimester”, and “exercise before pregnancy through the second trimester”.

One-week recall of physical activity

The telephone interview at 17-22 weeks’ gestation included six separate sections for work, recreational, outdoor household, indoor household, child/adult care, and transportation activity. It assessed frequency and duration of all physical activities the women participated in during the past week. For example, the question asking about participation in particular modes of recreational activity was: “In the past week, did you participate in any non-work, recreational activity or exercise, such as walking for exercise, swimming, dancing, that caused at least some increase in breathing and heart rate?” If the woman answered “Yes”, the interviewer asked her to list all types of recreational activities. For each type of activity, the woman reported the number of sessions in the past week, duration of each session, and the level of perceived intensity with three options: “fairly light”, “somewhat hard”, and “hard or very hard”. The perceived intensity categories were modified from the

Borg scale.[29] We also assigned intensity codes for each activity to a MET value using published MET tables in order to obtain measures using absolute levels of intensity.[30,31]

In the analysis, we focused on two typical types of physical activity of at least moderate intensity (work, recreational activity), and total activity that included all physical activities. For each type of activity, regarding perceived intensity, we calculated the total number of hours/week in "somewhat hard" and "hard or very hard" intensity (which we defined as moderate to vigorous intensity activity). To characterize absolute intensity, we multiplied the hours/week in each activity by its MET value and summed them up to calculate total MET-hours/week and MET-hours/week for moderate to vigorous activity (defined as activities with a MET value >=4.8, which corresponds to moderate intensity for women 20-39 years of age).[32] Total moderate to vigorous activity was calculated by summing up all the values of the activity types at least 4.8 METs. Each physical activity variable in the analysis was categorized into four levels: 1) no activity, 2) activity but not moderate to vigorous, 3) moderate to vigorous activity less or equal the median value among participants that reported that activity, and 4) greater than the median value. The only exception was for moderate to vigorous work activity, which had a low prevalence, so we collapsed it into three categories.

Measurement of covariates

Sociodemographic variables included age at enrollment, race (white, black, other), marital status, completed years of education, and household percentage of poverty level for 2001.[33] Pre-pregnancy body mass index was calculated from self-reported weight and measured height (kg/m^2) and categorized based on Institute of Medicine guidelines.[34] Adequacy of total weight gain was calculated as a ratio of observed weight/expected weight based on Institute of Medicine guidelines.[34] Pregnancy and medical history variables included parity, previous miscarriages, previous abortions, previous stillbirth, pre-existing diabetes, and bleeding during pregnancy. Lifestyle behaviors included self-reported smoking, alcohol consumption, and drug use since month before pregnancy.

Statistical methods

Gestational hypertension and preeclampsia were considered separately for identifying appropriate covariates of interest for all statistical models. Frequency distributions of sociodemographic, lifestyle, and pregnancy characteristics of women with gestational hypertension or with preeclampsia were compared to women without those conditions. We then assessed the relationship between each specific physical activity mode and intensity (perceived and absolute) with gestational hypertension or preeclampsia by calculating an odds ratio (OR) with 95% confidence intervals (CI), using multivariate logistic regression with the SAS GENMOD procedure (SAS/STAT software, SAS Institute Inc., Cary, NC). Women without the specific activity served as the reference category.

Evaluation of confounders in all models started with determination of risk factors based on previous studies and the hypothesized etiology of these diseases. Potential confounders were evaluated for their associations with physical activity and pregnancy outcomes using directed acyclic graphs.[35] Potential confounders were examined and retained in the model if there was a change by 10% or more in the crude estimate of the effect measure between physical activity and gestational hypertension or preeclampsia. For consistency, any variable that was identified as a confounder in a model between a specific physical activity and an outcome was included in all final models of that outcome. All final models regarding either perceived or absolute activity intensity measures used the same confounders, plus gestational age at the time interview. Lastly, to account for energy expenditure other than the specific activity of interest for recreational and work activity, we included a variable "other physical activity" defined by subtracting of the specific exposure activity value of interest from the total activity value in the final models, and these further adjustments did not meaningfully change the estimates in all the final models. Reproductive history (history of stillbirths, miscarriages, and abortions), bleeding during pregnancy, smoking, alcohol use, and drug use did not confound any of the associations and were thus not included in the analysis.

Results

We identified 270 (17%) women as having gestational hypertension, 49 (3%) women with preeclampsia, and 1267 women who had neither. Selected distributions of demographic, lifestyle, and pregnancy characteristics of women with and without gestational hypertension and preeclampsia are presented in Table 6-1. The women with gestational hypertension or preeclampsia were more likely to be overweight, have pre-existing diabetes, and gain more weight than expected during pregnancy. Lower levels of education and income were each associated with preeclampsia, but not with gestational hypertension. Women with gestational hypertension were less often nulliparous and more likely to be Black.

We compared characteristics of women who were included in the analysis (n=1586) and those who were eligible, but were not included (n=272) (data not shown). Chi-square statistics were used for comparison. Women who were included were more likely to be older, married, White, nulliparous, report better general health, higher income, lower obesity, and lower weight gain during pregnancy, compared to women who were not included. In addition, women who were included were more likely to report regular exercise during the first and the second trimester of pregnancy. We found no differences in both groups regarding adequacy of prenatal care, pre-existing diabetes, and regular exercise before pregnancy.

More than two-thirds of the women engaged in regular exercise before or during pregnancy (Table 6-2). After adjustment, exercise before pregnancy through the second trimester was associated with a slightly reduced risk of gestational hypertension (adjusted OR = 0.7 [95% CI 0.4, 1.1]), but with increased, albeit imprecise, risk of preeclampsia (adjusted OR = 2.7 [95% CI 0.9, 8.1]). A similar pattern was found for exercise before pregnancy only, but not for exercise before and during the first trimester only.

Detailed analyses of total, work, and recreational activity using perceived intensity at 17-22 weeks' gestation in relation with gestational hypertension and preeclampsia are presented in Table 6-3. Total and recreational activities at any level of intensity were not associated with the risk of gestational hypertension or preeclampsia. We found a slightly increased risk of gestational hypertension among women reporting some work activity (adjusted OR = 1.3 [95% CI 0.9, 1.4]), but no association with preeclampsia.

Table 6-4 displays the result from similar models for total, work, and recreational activity using absolute intensity. Similar to the regression results for perceived activity (Table 6-3), the estimates for absolute intensity of activity were attenuated by adjustment for confounding factors, mostly due to prepregnancy body mass index. Total and recreational moderate to vigorous activity above the median was associated with a reduced risk of gestational hypertension (adjusted OR = 0.4 [95% CI 0.2, 0.9] and OR = 0.6 [95% CI 0.3, 1.0], respectively), but not with the risk of preeclampsia. Similar to the perceived intensity measures, the middle work category was associated with an increased risk of gestational hypertension (adjusted OR = 1.4 [95% CI 1.0, 1.9]). We found a higher risk of preeclampsia among women engaging in moderate to vigorous recreational activity below the median (adjusted OR = 2.7 [95% CI 1.0, 7.6]), but no change in risk among women engaging these activity at higher level of intensity. The risk estimates for preeclampsia were less precise than for gestational hypertension, but did appear to follow a different pattern in the magnitudes and direction of association.

We reran our analyses using the cut-point of >= 3 METs for moderate to vigorous physical activity in the analysis, rather than >=4.8 METs. We found weaker associations between physical activity and the risk of gestational hypertension and preeclampsia. For example, total moderate to vigorous physical activity above the median level was found to be associated with a reduced risk of gestational hypertension (OR = 0.6 [95% CI 0.3, 1.1]), but the OR was closer to the null.

Discussion

We evaluated physical activity and hypertensive disorders during pregnancy in a large cohort with detailed data on differing indicators of physical activity. We found distinctive magnitudes and direction of association with gestational hypertension and preeclampsia, suggesting differing effects of moderate to vigorous physical activity on two these disorders. Our results suggested that regular exercise before pregnancy and through the second trimester of pregnancy was associated with a *reduced* risk of gestational hypertension, but with an *increased* risk of preeclampsia. Saftlas et al.[8] found no association between leisure-time physical activity before and during pregnancy with the risk of gestational hypertension, and Sorensen et al.[7] found a decreased risk of preeclampsia among women regularly participating in any recreational physical activity before and during the first 20 weeks of pregnancy, neither consistent with our results.

Moreover, our findings document an association between moderate to vigorous total physical activity in the highest category and a reduced risk of gestational hypertension, but no association with the risk of preeclampsia. We observed a lower risk of gestational hypertension among women who reported moderate to vigorous recreational activity above the median level, consistent with Marcoux et al.[6]. However, Saftlas et al.[8] found no change in risk of gestational hypertension among women engaging in leisure-time physical activity, even at the highest level of intensity, compared to inactive women. Previous studies[6-9] generally reported an inverse association between recreational activity and the risk of preeclampsia, but findings from more recent studies suggests differences. Magnus et al.[11] found a decreased risk of preeclampsia only among women engaging in recreational activity with highest frequency. A study by Rudra et al.[10] reported no association between recreational activity during early pregnancy and preeclampsia risk. Osterdal et al.[12] reported that recreational activity at highest level was associated with an increased risk of preeclampsia, in agreement with our findings for moderate to vigorous recreational activity below the median level.

The relationship between occupational physical activity and the development of preeclampsia and gestational hypertension has been investigated in a variety of populations, using varying definitions and categorizations for work activity, and characteristics of work (intensity, shift work, work posture, stressful conditions, noise, high temperature, exposure to chemicals). We found no association between moderate to vigorous work activity and preeclampsia, unlike some previous studies that reported a decreased risk among workers.[6,17] Others reported an increased risk[8,13-15,19,20] of preeclampsia associated with work activities. For physically demanding work activity, a consistently increased risk of preeclampsia was reported.[16-18] We found a slightly increased risk of gestational hypertension among women reported some work activity, inconsistent with previous studies such as Marcoux et al.[6] who reported a decreased risk among employed women, and some others authors found no change in risk among workers.[8.20]

Classification of physical activity based on perceived (Table 6-3) versus absolute (Table 6-4) intensity yielded somewhat different patterns of association in some cases. The participant's perception could differ based on an individual's tolerance of activity. Measures of physical activity in absolute intensity were based on activities reported with assigned MET values associated with those activities. The MET value cut-point for defining "moderate to vigorous" physical activity was >= 4.8 METs in this study was based on non-pregnant adult age of 20-39 years,[32] higher than the cut-point used for the general adult population of >= 3 METs.[3] As a result, the category "no activity" remains similar in both perceived and absolute intensity, but fewer participants were classified as engaging in "moderate to vigorous" in absolute intensity than the proportion of participants who were classified as "somewhat hard or hard/very hard" in perceived intensity. Overall, our findings suggested stronger associations between physical activity and gestational hypertension or preeclampsia with measures of physical activity in absolute rather than perceived intensity. Our results may differ from previous studies, in part, due to these different classifications. For example, using the cut-point as >= 3 METs for "moderate to vigorous" physical activity in the analysis, we found smaller association between total moderate to vigorous physical activity above the median level and a reduced risk of gestational hypertension (OR = 0.6 [95% CI 0.3, 1.1]).

We acknowledge several limitations of this study. Although the physical activity questionnaire was validated and showed high test-retest reliability,[36] exposure measurement errors are inevitable because of the inherent limitations of self-report. Physical activity at work and in daily living is highly variable over short periods of time, but was measured only at one point in time in the first half of pregnancy. Misclassification of physical activity is likely to be random with respect to the outcomes, therefore, it would be likely to bias the relationship toward the null. The lack of association we identified with work activity may be due to the healthy worker effect, in that women who are healthier are able to remain in jobs involving moderate to vigorous activity during pregnancy. The study included 109 duplicate women (who were recruited for more than one time because they had two or more deliveries during the study period) in the total of 1586 women. The study analysis did not account for the correlation introduced because some women participated more than once in the PIN3 Study. In this study population, few cases of preeclampsia were found (n = 49), resulting in imprecise estimates of the association with physical activity. Furthermore, there may be selection bias due to differences found in those included in the analysis compared to those who were eligible for the study but not included in the analysis. However, some of these differences may be due to the fact that by design we excluded 148 women who were diagnosed with chronic hypertension or experienced hypertension before 20 weeks of gestation.

This study suggests that moderate to vigorous total and recreational activity may be associated with a reduced risk of gestational hypertension, but not with the risk of preeclampsia. Work activity was also not associated with the risk of gestational hypertension or preeclampsia. A larger population is necessary to have more precise estimates of associations with preeclampsia. Multiple measurements of physical activity over the course of pregnancy, starting early, might also help to better elucidate these associations.

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Table 6-1. Selected sociodemographic, lifestyle and pregnancy characteristics of study participants by pregnancy outcomes – PIN3 Study (N = 1586)

	Normotensive n (%)	Gestational hypertension n (%)		Preeclampsia n (%)	
Overall	1267	270		49	
Age in years					
<=20	99 (7.8)	20 (7.4)		5 (10.2)	
21-34	961 (75.9)	218 (80.7)		35 (71.4)	
>=35	207 (16.3)	32 (11.9)		9 (18.4)	
Race					
White	921 (72.7)	198 (73.3)	*	32 (65.3)	
Black	216 (17.0)	58 (21.5)		14 (28.6)	
Other	130 (10.3)	14 (5.2)		3 (6.1)	
Education					
College or more	1020 (80.5)	210 (77.8)		33 (67.4)	*
Income (percent of the poverty line)					
<100	137 (11.2)	28 (10.9)		10 (21.7)	*
100 – 200	152 (12.5)	31 (12.0)		7 (15.2)	
>200	930 (76.3)	199 (77.1)		29 (63.1)	
Body mass index before pregnancy					
Underweight < 19.8 kg/m^2	212 (17.0)	24 (9.0)	**	2 (4.1)	**
Normal: 19.8 – <26.0 kg/m^2	700 (56.2)	107 (40.2)		17 (34.7)	
Overweight: 26 – <29.0 kg/m^2	137 (11.0)	36 (13.6)		3 (6.1)	
Obese: >=29.0 kg/m^2	196 (15.8)	99 (37.2)		27 (55.1)	
Adequacy of total weight gain (ratio of observed weight/expected weight based on IOM guidelines)					
<1	306 (24.6)	45 (16.9)	**	10 (20.4)	**
1 – 2	757 (61.0)	143 (53.8)		12 (24.5)	
>2	179 (14.4)	78 (29.3)		27 (55.1)	
Preexisting diabetes (yes)	24 (1.9)	12 (4.4)	*	8 (16.3)	**
Nulliparous (yes)	689 (54.4)	116 (43.0)	**	26 (53.1)	

*Chi-square test p <0.05 for general association.
**Chi-square test p <0.01 for general association.

Table 6-2. Self-reported regular exercise before and during the first and second trimesters of pregnancy and the risk of gestational hypertension and preeclampsia - PIN3 Study (N = 1088).

			Gestational hypertension		Preeclampsia	
	N	%	OR unadjusted [95% CI]	OR adjusted[a] [95% CI]	OR unadjusted [95% CI]	OR adjusted[b] [95% CI]
Exercise before and during the first and second trimester of pregnancy						
No exercise[c]	306	28.1	1.0	1.0	1.0	1.0
Exercise only before pregnancy	181	16.7	0.7 [0.4, 1.1]	0.7 [0.4, 1.1]	1.4 [0.4, 4.2]	1.7 [0.5, 6.6]
Exercise before pregnancy through the 1st trimester	182	16.7	0.9 [0.6, 1.4]	0.9 [0.6, 1.5]	0.7 [0.2, 2.7]	1.0 [0.2, 4.6]
Exercise before pregnancy through the 2nd trimester	419	38.5	0.6 [0.4, 1.0]	0.7 [0.4, 1.1]	1.5 [0.6, 3.7]	2.7 [0.9, 8.1]

[a]Adjusted for: age (<=20, 21-34, >=35), race (White, Black, Other), prepregnancy BMI (<19.8, 19.8-<26.0, 26-<29.0, >=29.0 kg/m^2), parity (0, >=1), and weight gain ratio of observed weight/expected weight based on IOM guidelines (<1, 1-2, >2).

[b]Adjusted for: age, prepregnancy BMI, weight gain, pre-existing diabetes (yes, no), household poverty percentage (<100, 100-200, >200), and education (high school or less – yes, no).

[c]referent group.

In all models, variables with more than two levels were coded as dummy variables.

Table 6-3. Past week physical activity in perceived intensity (number of hours per week) at 17-22 weeks of gestation and the risk of gestational hypertension and preeclampsia - PIN3 Study (N = 1586).

			Gestational hypertension		Preeclampsia	
	N	%	OR unadjusted [95% CI]	OR adjusted[a] [95% CI]	OR unadjusted [95% CI]	OR adjusted[b] [95% CI]
Total activity (median = 2.74 hrs/wk)						
No activity[c]	85	5.4	1.0	1.0	1.0	1.0
Activity but not SH+H	445	28.0	0.8 [0.4, 1.5]	0.6 [0.3, 1.2]	0.7 [0.2, 2.5]	0.5 [0.1, 2.7]
SH+H activity below the median	528	33.3	0.8 [0.4, 1.5]	0.6 [0.3, 1.2]	0.9 [0.3, 3.1]	0.9 [0.2, 4.3]
SH+H activity above the median	528	33.3	1.0 [0.6, 1.8]	0.7 [0.4, 1.4]	1.0 [0.3, 3.4]	1.1 [0.2, 5.1]
Work activity						
No activity[c]	1106	69.8	1.0	1.0	1.0	1.0
Work activity but not SH+H	305	19.2	1.2 [0.9, 1.7]	1.3 [0.9, 1.4]	0.7 [0.3, 1.7]	1.0 [0.4, 2.5]
Some SH+H work activity	175	11.0	1.4 [1.0, 2.1]	1.2 [0.7, 1.9]	1.1 [0.5, 2.7]	1.4 [0.5, 3.7]
Recreational SH+H activity (median = 2.0 hrs/wk)						
No activity[c]	527	33.2	1.0	1.0	1.0	1.0
Recreational activity but not SH+H	402	25.6	0.8 [0.6, 1.2]	0.9 [0.6, 1.3]	1.0 [0.5, 2.2]	1.3 [0.5, 3.1]
SH+H recreational activity below the median	375	23.6	1.0 [0.7, 1.4]	0.9 [0.6, 1.3]	1.1 [0.5, 2.2]	1.3 [0.6, 3.1]
SH+H recreational activity above the median	279	17.6	0.9 [0.6, 1.3]	0.8 [0.5, 1.3]	0.9 [0.4, 2.2]	1.4 [0.5, 3.6]

The median value was computed among participants who reported "somewhat hard or hard/very hard" activity.
SH+H: somewhat hard or hard/very hard.
[a]Adjusted for race, prepregnancy BMI, weight gain, parity, gestational age at the interview, and 'other activity" (total activity – specific exposure activity).
[b]Adjusted for prepregnancy BMI, pre-existing diabetes, weight gain, gestational age at the interview, and 'other activity" (total activity – specific exposure activity).
[c]referent group, women with no specific activity.
In all models, variables with more than two levels were coded as dummy variables.

Table 6-4. Past week physical activity in absolute intensity (number of MET-hours per week) at 17-22 weeks of gestation and the risk of gestational hypertension and preeclampsia - PIN3 Study (N = 1586).

			Gestational hypertension		Preeclampsia	
	N	%	OR unadjusted [95% CI]	OR adjusted[a] [95% CI]	OR unadjusted [95% CI]	OR adjusted[b] [95% CI]
Total activity (median = 9 MET-hrs/wk)						
No activity[c]	85	5.4	1.0	1.0	1.0	1.0
Activity but not MV	906	57.1	1.0 [0.6, 1.7]	0.7 [0.4, 1.3]	0.9 [0.3, 2.9]	0.7 [0.2, 3.4]
MV activity below the median	299	18.8	0.8 [0.4, 1.4]	0.6 [0.3, 1.3]	0.8 [0.2, 3.1]	1.1 [0.2, 5.5]
MV activity above the median	296	18.7	0.6 [0.3, 1.2]	0.4 [0.2, 0.9]	0.8 [0.2, 3.0]	0.9 [0.2, 4.8]
Work activity						
No activity[c]	1106	69.8	1.0	1.0	1.0	1.0
Work activity but not MV	362	22.8	1.4 [1.0, 1.9]	1.4 [1.0, 1.9]	0.8 [0.4, 1.7]	1.1 [0.5, 2.5]
Some MV work activity	118	7.4	1.1 [0.6, 1.8]	0.9 [0.5, 1.6]	1.1 [0.4, 3.0]	1.3 [0.4, 4.0]
Recreational activity (median = 10.5 MET-hrs/wk)						
No activity[c]	527	33.2	1.0	1.0	1.0	1.0
Recreational activity but not MV	715	45.1	1.0 [0.7, 1.3]	0.9 [0.6, 1.3]	1.1 [0.5, 2.0]	1.2 [0.6, 2.5]
MV recreational activity below the median	169	10.7	0.8 [0.5, 1.3]	0.9 [0.6, 1.6]	1.3 [0.5, 3.3]	2.7 [1.0, 7.6]
MV recreational activity above the median	175	11.0	0.6 [0.4, 1.0]	0.6 [0.3, 1.0]	0.5 [0.4, 1.8]	0.9 [0.2, 3.4]

The median value was computed among participants who reported moderate to vigorous activities (>=4.8 METs).
MV: moderate to vigorous.
[a]Adjusted for race, prepregnancy BMI, weight gain, parity, gestational age at the interview, and 'other activity" (total activity – specific exposure activity).
[b]Adjusted for prepregnancy BMI, pre-existing diabetes, weight gain, gestational age at the interview, and 'other activity" (total activity – specific exposure activity).
[c]referent group, women with no specific activity.
In all models, variables with more than two levels were coded as dummy variables.

VII. CONCLUSIONS

Overview

This dissertation examined several components of physical activity in relation to uteroplacental and umbilical circulation, and in association with hypertensive disorders during pregnancy. The study hypotheses included: 1) that moderate to vigorous physical activity at 17-22 weeks' gestation would be associated with a higher proportion of normal uterine and umbilical artery Doppler velocimetry indices measured at 15-10 and 24-29 weeks' gestation, 2) that vigorous exercise three months prior to pregnancy, and/or continuing during pregnancy, would be associated with a lower risk of gestational hypertension and preeclampsia, and 3) that moderate to vigorous physical activity at 17-22 weeks' gestation would be associated with a lower risk of gestational hypertension and preeclampsia. These hypotheses were supported by plausible mechanisms, in that physical activity may be associated with a lower resistance in uterine and/or umbilical arteries, which could be associated with a lower risk of hypertensive disorders during pregnancy.

The findings only supported part of these hypotheses. Various types of physical activity (work, recreational, exercise, and total, as we focus in this analysis, and the associations with recreational activity were very similar to that with exercise) were not associated with changes of the umbilical circulation in 24-29 week's gestation measured by the resistance index, consistent with findings by others (Morrow et al. 1989, Erkkola et al. 1992, Kennelly et al. 2002, Ertan et al. 2004). The mean uterine artery pulsatility index was lower among women reporting some moderate-to-vigorous work activity, but higher among those reporting moderate-to-vigorous recreational activity and exercise, consistent with findings in some clinical trials (Morrow et al. 1989, Erkkola et al. 1992, Kennelly et al. 2002). However, other clinical trials (Moore et al. 1988, Steegers et al. 1988, Ertan et al. 2004) reported no changes in uterine artery Doppler indices in association with exercise. The risk of an early diastolic notch in the uterine artery was slightly higher among women reporting recreational activity or exercise. The modest changes in the uterine artery resistance without a significant change in the umbilical circulation resistance indicated that physical activity during pregnancy does not appear to be associated with major changes of maternal-fetal circulation. Interestingly, we found a tendency towards lower blood vessel resistance with work activity and higher blood vessel resistance with recreational activity and exercise.

Our data suggested differing patterns of associations between physical activity and the development of gestational hypertension and preeclampsia. For gestational hypertension, a lower risk was found among women engaging in total moderate-to-vigorous physical activity, recreational activity, and exercise in the highest category. We also found a lower risk of gestational hypertension among women reporting exercise before and during pregnancy through the second trimester. Total, work, and recreational activity had no association with the risk of preeclampsia, except a modest increased risk found with recreational activity and exercise with inconsistent dose-response gradients. This finding was also supported by an analysis with exercise before and during pregnancy through the second trimester. Moreover, reporting at least some work activity at moderate-to-vigorous levels was not associated with the risk of either gestational hypertension or preeclampsia. We hypothesized that physical activity would be associated with gestational hypertension or preeclampsia by different mechanisms, in which recreational activity or exercise may play a role in some stages of reduced blood pressure only, but associated with the presence of proteinuria. Our findings were inconsistent with previous reports (Marcoux et al. 1989; Sorensen et al. 2003; Saftlas et al. 2004, Rudra et al. 2005) in that recreational activity before and during pregnancy was associated with a slightly reduced risk of preeclampsia, but in agreement with recent cohort studies (Magnus et al. 2008, Rudra et al. 2008, Osterdal et al. 2009) that recreational activity during pregnancy was not associated with the risk of preeclampsia or even associated with higher risk of preeclampsia.

Previous studies proposed a biological link between exercise and resistance in the placental (Clapp et al. 2002; Clapp 2003, Jackson et al. 1995, Bergmann et al. 2004). A reduction of resistance in the placental blood flow results from many physiological and functional effects in maternal haemodynamics found among women engaging in exercise during pregnancy. We found slightly increased impedance in uterine artery blood flow among women with exercise; therefore our study did not show evidence to support these mechanisms. Also, physical activity is proposed to play a crucial role in preventing some key stages of the development of preeclampsia through many plausibly complicated mechanisms (Weissgerber et al. 2004, Dempsey et al. 2005). We found physical activity was associated with a reduced risk of gestational hypertension only, not with the risk of preeclampsia; therefore our data have only supported some of these mechanisms. The reasons for the discrepancies are discussed.

Study population and outcome definition

The PIN3 Study enrolled 2006 eligible women. The final analysis of physical activity and the risk of gestational hypertension and preeclampsia included a total of 1586 women (79% of the study population) who had both information on gestational hypertension/preeclampsia and physical activity, after excluding 148 women who were diagnosed with chronic hypertension or experienced hypertension before 20 weeks of gestation. After these exclusions, we identified 270 women who had gestational hypertension, 49 women who had preeclampsia and 1267 women who remained norrmotensive. Comparison of characteristics of women who were included in the analysis sample to that of women who were eligible but not included is in Table A-2. We utilized a comparison between cases (gestational hypertension/preeclampsia women) and controls (normotensive women), as a traditional approach, which took into account and clearly targeted only the associations of physical activity and the new onset of hypertension after 20 weeks' gestation, with and without proteinuria, and eliminating the confounding effect of chronic hypertension.

We initially proposed to analyze the data as a cohort study. By this approach, we considered pregnancy-induced hypertension (including gestational hypertension and preeclampsia after 20 weeks' pregnancy, n = 343) and preeclampsia (including preeclampsia after 20 weeks' pregnancy and super-imposed preeclampsia upon chronic hypertension, n = 94) as two outcomes of interest. By this approach, we could describe the association between physical activity and pregnancy-induced hypertension, emphasizing hypertension only, and the association between physical activity and preeclampsia, emphasizing hypertension (both new onset and chronic) with presence of proteinuria. However, we presented the case-control analysis approach because it was clear and informative for interpretation, without confusion of overlapping groups between two outcomes (see Figure 2-1), although the results were more imprecise, due to small number of cases for preeclampsia.

The final analysis of physical activity and uteroplacental and umbilical circulation included a total of 874 women (44% of the study population) who completed with Doppler ultrasounds of either or both of uterine and umbilical artery at two clinic visits, and completed the first telephone interview with information from a one-week physical activity recall. Comparison of characteristics of women who were included in the analysis sample to that of women who were eligible but not included was presented in Table A-1. Doppler waveform indices for uterine arteries were available including S/D ratio, pulsatility index, and early diastolic notch in both left and right arteries, measured twice at two clinical visits. Doppler waveform indices for the umbilical artery were available including S/D ratio, resistance index, umbilical vein notch, and reversed diastolic flow. S/D ratio, with a very broad range of values and many outliers, was not chosen as an outcome. We found only a few participants with umbilical vein notching and reversed diastolic flow, thus these indices were not explored as outcomes. Finally, the pulsatility index, early diastolic notching in the uterine artery, and the resistance index in the umbilical artery were chosen as outcomes because they were informative measures, stable, and did not have as many outliers as other considered measures. Initially, we planned to use separate values of the left and right uterine artery in analysis models with hierarchical data; however, the mean of the left and right artery PI measurements was used for the final analysis because it is most commonly used in clinical practice and in previous studies (Aquilina et al. 2000, Paretti et al. 2003, Papagheorghiou et al. 2005).

We found some strong confounders in the analyses. Body mass index before pregnancy appeared to confound associations between physical activity and both uteroplacental and umbilical blood flow, and the risk of gestational hypertension and preeclampsia. The prevalence of obesity (>=29 kg/m^2) among the gestational hypertension group and preeclamptic group was two to three times higher compared to the normotensive group. Adjustment of obesity resulted in attenuation of most associations. Although race was a confounder in several previous case-control analyses (Sorensen et al. 2003, Rudra et al. 2005), it was not in our study analysis with gestational hypertension and preeclampsia.

Study strengths

This project has several strengths, including the prospective design for measurements of outcomes. Measurement of physical activity was recalled one week prior, which was retrospective but framed with a short recall period. It has also been shown to be a valid and reliable instrument (Borodulin et al. 2008). The one-week recall questionnaire was designed to capture information on the type, frequency, duration and intensity of all types of physical activity during pregnancy. This is the first epidemiological study investigating the associations between total activity and exercise on the development of gestational hypertension and preeclampsia. This is also the first epidemiological study investigating the associations of physical activity and changes of uteroplacental and umbilical circulation, and our findings corroborated results from previous clinical trials that evaluated the effects of exercise on uterine and umbilical artery Doppler indices. We assessed the intensity of each activity using both perceived exertion and measures of energy expenditure (i.e., MET value), based on the compendium of physical activities (Ainsworth et al. 2000), the most common basis for scoring. Outcome data, such as uterine artery Doppler indices were measured longitudinally, taking into account the variability of these measures along with gestational age. Information on key confounders was collected in detail, allowing us to evaluate the effects of specific types of physical activity and we were able to control for other activities simultaneously.

Study limitations

We acknowledge several limitations of this study. The sample size was adequate to assess the associations between physical activity and uteroplacental and umbilical blood flow, and the risk of gestational hypertension, but was inadequate for the outcome of preeclampsia. The estimates of statistical power for the analysis of the association between physical activity and uteroplacental and umbilical blood flow ranged from 92% to 100%, and for the analysis of association between physical activity and gestational hypertension ranged from 84% to 90%. The estimate of statistical power for analysis of preeclampsia (outcome including new onset preeclapmsia and super-imposed preeclampsia upon chronic hypertension) ranged from 78% to 86% in the initial proposal. However, in the final analysis with the outcome including only new onset preeclamptic women (n = 49), the estimate of statistical power reduced to 62% to 67%, resulting in less precision and wide confidence intervals of the estimates, especially after adjustment for confounding effects. In this case, interpretations of the findings regarding preeclampsia were somewhat uncertain because of these statistical power issues.

Although the physical activity questionnaire was validated and showed high reliability, exposure measurement errors are inevitable because of the inherent limitations of self-report. Physical activity collected during a one week period may not reflect actual behavior over time. However, misclassification of physical activity is likely to be random with respect to the outcomes, therefore, it may bias the relationship toward the null.

One important limitation should be noted. The PIN3 study population (n=2006) included some women (n=131) who were recruited for more than one time because they had two or more deliveries during the study period. There were 93 duplicate women who were included in the total of 874 women for the analyses using doppler ultrasound and 109 duplicate women who were included in the total of 1586 women for the analyses on preeclampsia. These analyses did not account for the correlation introduced because some women participated more than once.

We used logistic regression to estimate the associations between physical activity and the risk of gestational hypertension and preeclampsia. Other regression analysis may be more appropriate, such as survival analysis with Cox proportional hazard models, if we could determine the date of diagnosis of the outcomes. Another potential limitation, which may have influenced the findings: lack of associations with work activity may be due to the healthy worker effect, in that women who are healthier are able to remain in jobs involving moderate-to-vigorous activity during pregnancy.

Lastly, the physical activity questionnaire was collected at 17-22 weeks' pregnancy, so some women with early symptoms or onset of pregnancy-induced hypertension were reporting activity that may be affected by their condition. This phenomenon, called "reverse causality", can lead to some misinterpretations of the findings.

Public health and clinical practice implication

Etiology of hypertensive disorders during pregnancy, especially preeclampsia, remains unknown in spite of the biologic plausibility and many epidemiologic studies. Many factors are known to play a part in the disease development and the underlying mechanisms have not been resolved in previous studies and this study as well. We did not find sufficient evidence to recommend physical activity as a way of preventing preeclampsia. In a roundtable consensus by the American College of Sports Medicine (ACSM 2006), the panel indicated that physical activity played a role on reduced risk of preeclampsia, based on review of three epidemiologic studies (Marcoux et al. 1989, Sorensen et al. 2003, Saftlas et al. 2004). However, more recent studies (Magnus et al. 2008, Rudra et al. 2008, Osterdal et al. 2009), including this one did not find the same evidence to support its recommendation.

The American College of Obstetricians and Gynecologists (ACOG 2002) recommended pregnant women, in the absence of either medical or obstetric complications, to practice 30 minutes or more of moderate exercise a day on most days of the week. A similar recommendation was introduced in the recent guidelines for Americans by the US Department of Health and Human Services (USDHHS 2008). Our findings are in support in with these recommendations.

The only clinical difference between gestational hypertension and preeclampsia is the presence of proteinuria in diagnosis of preeclampsia. If we consider the two outcomes separately, the implication of this study can be inferred. Findings from this study did not support the hypothesis that recreational physical activity or exercise was associated with reduced risk of preeclampsia. However, we found that total physical activity, recreational physical activity, and exercise at moderate-to-vigorous intensity were associated with a reduced risk of gestational hypertension. This finding corroborated the established knowledge that regular physical activity prevents or delays the development of high blood pressure among non-pregnant women (USDHHS 1996). In addition, work activity at moderate-to-vigorous levels was not associated with the risk of either gestational hypertension or preeclampsia. Therefore, women can at least be encouraged to continue with work, leisure time physical activity, and exercise during pregnancy, without concerns about the development of hypertensive disorders during pregnancy.

However, the recommendation of exercise for pregnant women has not been strongly supported among clinicians. For example, in a survey among 83 private/small group practice obstetricians in the US (Entin and Munhall 2006), the questionnaire asked to what extent obstetricians thought that the performance of regular aerobic exercise would reduce the risk of preeclampsia, and used a Likert scale (1 = not at all, 7 = quite a lot) for response. The mean value for response was only 2.7 ± 1.6, and only 15% of responses to this question were above 4 as the mid-point. Inherently, the majority of interviewed obstetricians remain skeptical about the preventive effect of physical activity on the development of preeclampsia.

There is a tremendous need for a reliable marker or set of markers with high sensitivity to predict preeclampsia. At present, uterine artery Doppler waveforms during the second trimester is considered the best predictor for preeclampsia (Raijmakers et al. 2004; Parra et al. 2005), especially among high risk populations. In this study, a hypothetical link can be established as that moderate to vigorous recreational activity or exercise was associated with slightly higher resistance in blood vessels, shown by higher uterine artery Doppler velocimetry indices and higher risk of early diastolic notch presence, then leading to a higher risk of preeclampsia. Findings from this study suggest that physical activity was associated with no meaningful changes in the uterine artery resistance and was not associated with any changes in the umbilical circulation, implying no further impact on maternal-fetal haemodynamics and blood volume delivery.

Future Research

Physical activity and maternal-fetal circulation

Several randomized clinical trials have evaluated the immediate effect of maternal exercise on uteroplacental blood flow with Doppler velocimetry. Study findings have been mixed, and to date, the literature does not provide satisfactory information on the effects of exercise, especially long term effects, on the uteroplacental and umbilical circulation. This is the first epidemiological study investigating this issue. Cohort study designs will still be appropriate for a future work on this research question, as would randomized clinical trials and laboratory based studies to study more acute effects of physical activity or exercise.

Future studies should be designed with multiple prospective measurements of physical activity, covering at least a set of measurements for each trimester to ensure capturing the variability of physical activity during pregnancy. One-week recall questionnaires would be still appropriate to capture type, frequency, and duration of each activity. An objective measure of physical activity could supplement self-reported information. Also, to avoid a long induction period, multiple measures of maternal-fetal circulation by Doppler ultrasound can be designed at the same time physical activity is assessed. Time-series analysis with time-dependent variables could be used to evaluate changing patterns of physical activity and Doppler velocimetry indices during pregnancy. Biological markers for a hypothetical link could also be measured, such as placental biopsy.

Physical activity and gestational hypertension and preeclampsia

Previous findings on physical activity and gestational hypertension/preeclampsia have been mixed, partly due to a lack of standardized, validated, and consistent methods for assessment of physical activity, especially definitions and categorization for work activity. Two types of study designs to address this association can be considered. A cohort study design is appropriate for future work, but in order to have precise estimates of associations with preeclampsia, a large study population will be needed. Another study design that would be appropriate is a randomized clinical trial to test the role of prenatal physical activity with various regimens as intervention for preeclampsia among diverse populations at low and high risk of hypertensive disorders during pregnancy. For example, future studies need to address the question, "Should women with slightly elevated blood pressures in early pregnancy be encouraged to participate in a supervised physical activity regimen, instead of being directed to go on bedrest?"

Future studies should include multiple prospective measurements of physical activity in the first half of pregnancy, starting early to better elucidate these associations and better capture the variability of physical activity. One-week recall questionnaires would be still appropriate to capture all types, frequency, and duration of each activity in the last week. To avoid misclassification of hypertensive disorders during pregnancy, diagnosis of these diseases should be made multiple times after 20 weeks' gestation.

To the extent that specific biologic pathways linking physical activity to hypertensive disorders of pregnancy can be postulated, future studies should identify and include measurements of promising biomarkers such as antioxidant enzymes. Future studies should also adequately control for preconceptual and/or prenatal exercise.

Conclusion

During the past decade, research addressing hypertensive disorders during pregnancy, especially preeclampsia, has been extensive. However, no fundamental improvement in prevention of these disorders has been made. This study generally provides evidence that self-reported physical activity was not associated with maternal-fetal circulation and few associations were identified for the development of hypertensive disorders. These findings support the public health and American College of Obstetric and Gynecology physical activity guidelines for pregnant women.

VIII. APPENDIX

Table A-1. Descriptive characteristics during pregnancy of completers vs. non-completer
Paper 1: Physical activity and Doppler ultrasound

		In study analysis (n=874)		Not in study analysis (n=1132)		p-value^
		n	%	n	%	
Mother's age in years:						0.2512
	<20	81	9.3	103	9.1	
	20-<35	670	76.6	839	74.1	
	≥35	123	14.1	190	16.8	
Marital status:						0.3675
	Not married	241	27.6	330	29.4	
	Married	633	72.4	792	70.6	
	Missing			10		
Race:						0.4718
	White	615	70.4	767	67.8	
	African American	180	20.6	254	22.5	
	Other	79	9.0	110	9.7	
	Missing			1		
Education:						0.1675
	High school or less	671	76.8	832	74.1	
	College or more	203	23.2	291	25.9	
	Missing			9		
General Health						0.4624
	Excellent	255	29.2	304	32.0	
	Very good	371	42.5	394	41.5	
	Good	198	22.6	190	20.0	
	Fair/Poor	50	5.7	61	6.5	
	Missing			183		
Income (percent of poverty line)						0.0086
	<100	131	15.6	98	10.7	
	100-200	111	13.3	128	14.0	
	>200	595	71.1	691	75.3	
	Missing	47		205		

BMI (kg/m^2):							0.5300
	Low (<18.5)	120	14.0		146	14.1	
	Normal (18.5-<25.0)	407	47.3		523	50.4	
	Overweight (25.0-<30.0)	103	12.0		112	10.8	
	Obese (>30.0)	230	26.7		257	24.7	
	Missing	14			94		
Maternal weight gain ratio (%):							0.4990
	<100	192	23.4		218	22.9	
	100-200	450	54.9		547	57.4	
	>200	178	21.7		188	19.7	
	Missing	54			179		
Adequacy of prenatal care							0.0121
	No	123	14.8		111	10.9	
	Yes	707	85.2		906	89.1	
	Missing	44			115		
Pre-existing diabetes							0.0659
	No	792	94.9		986	96.6	
	Yes	43	5.1		35	3.4	
	Missing	39			111		
Chronic hypertension							0.3509
	No	763	91.4		945	92.6	
	Yes	72	8.6		76	7.4	
	Missing	39			101		
Parity							0.7125
	Nulliparous	398	45.5		503	44.7	
	Multiparous	476	54.5		622	55.3	
	Missing				7		
Pre-eclampsia							0.1533
	No	786	94.1		976	95.6	
	Yes	49	5.9		45	4.4	
	Missing	39			111		
Smoking							0.7085
	Non-smoker	551	70.1		626	71.4	
	Past smoker	111	14.1		125	14.2	
	Current smoker	125	15.8		126	14.4	
	Missing	84			255		
Regular excercise 3-month before pregnancy							0.2809
	No	250	36.2		175	33.2	
	Yes	441	63.8		352	66.8	
	Missing	183			605		

Regular excercise during 1st trimester							0.1531
	No	402	58.2		285	54.1	
	Yes	289	41.8		242	45.9	
	Missing	183			605		
Regular excercise during 2nd trimester							0.5463
	No	443	64.1		329	62.4	
	Yes	248	35.9		198	37.6	
	Missing	183			605		
Note:							
^ p-value from chi-square test							

Table A-2. Descriptive characteristics during pregnancy of completers vs. non-completer, excluding 148 women with diagnosis of chronic hypertension Paper 2: Physical activity and the risk of gestational hypertension and preeclampsia						
		In study analysis (n=1586)		Not in study analysis (n=272)		p-value^
		n	%	n	%	
Mother's age in years:						<0.0001
	<20	124	7.8	51	18.8	
	20-<35	1214	76.5	194	71.3	
	≥35	248	15.7	27	9.9	
Marital status:						<0.0001
	Not married	372	23.5	132	50.2	
	Married	1214	76.5	131	49.8	
	Missing			9		
Race:						<0.0001
	White	1151	72.6	160	59.0	
	African American	288	18.1	78	28.8	
	Other	147	9.3	33	12.2	
	Missing			1		
Education:						<0.0001
	High school or less	1263	79.6	147	55.5	
	College or more	323	20.4	118	44.5	
	Missing			7		
General Health						0.0001
	Excellent	523	33.0	21	20.6	
	Very good	684	43.1	37	36.3	
	Good	303	19.1	33	32.3	
	Fair/Poor	76	4.8	11	10.8	
	Missing			102		
Income (percent of poverty line)						<0.0001
	<100	175	11.5	24	24.2	
	100-200	190	12.5	24	24.2	
	>200	1158	76.0	51	51.6	
	Missing	65		171		
BMI (kg/m^2):						<0.0001
	Low (<18.5)	238	15.3	26	13.1	
	Normal (18.5-<25.0)	824	52.8	79	39.9	
	Overweight (25.0-<30.0)	176	11.3	23	11.6	
	Obese (>30.0)	322	20.6	70	35.4	
	Missing	26		74		
Maternal weight gain ratio (%):						0.0014

	<100	361	23.2		18	23.7	
	100-200	912	58.6		32	42.1	
	>200	284	18.2		26	34.2	
	Missing	29			196		
Adequacy of prenatal care							0.5252
	No	213	13.5		14	11.5	
	Yes	1364	86.5		108	88.5	
	Missing	9			150		
Pre-existing diabetes							0.7453
	No	1542	97.2		118	96.7	
	Yes	44	2.8		4	3.3	
	Missing				150		
Parity							0.0002
	Nulliparous	755	47.6		93	35.1	
	Multiparous	831	52.4		172	64.9	
	Missing				7		
Smoking							<0.0001
	Non-smoker	1086	72.5		46	54.1	
	Past smoker	179	12.1		28	32.9	
	Current smoker	227	15.4		11	13.0	
	Missing	112			187		
Regular excercise 3-month before pregnancy							0.0741
	No	363	33.3		20	40.0	
	Yes	727	66.7		30	60.0	
	Missing	496			222		
Regular excercise during 1st trimester							0.0470
	No	596	54.7		32	64.0	
	Yes	494	45.3		18	36.0	
	Missing	496			222		
Regular excercise during 2nd trimester							0.0103
	No	668	61.3		38	76.0	
	Yes	419	38.7		12	24.0	
	Missing	496			222		
Note:							
^ p-value from chi-square test							

Table A-3. Distribution of selected sociodemographic, lifestyle and pregnancy characteristics of the study participants in the full sample (n=2006), in the paper 1 "Physical activity and Doppler" (n=874), and in the paper 2 "Physical activity and the risk of gestational hypertension/preeclampsia" (n=1586). No major differences were found.

Variables	Full sample (2006) n (%)	Paper 1 (874) n (%)	Paper 2 (1586) n (%)
Age in years			
<=20	184 (9.2)	81 (9.3)	124 (7.8)
21-34	1509 (75.2)	670 (76.6)	1214 (76.5)
>=35	313 (15.6)	123 (14.1)	248 (15.7)
Race			
White	1382 (68.9)	615 (70.4)	1151 (72.6)
Black	434 (21.7)	180 (20.6)	288 (18.2)
Other	189 (9.4)	79 (9.0)	147 (9.3)
Marital status			
Not married	571 (28.6)	241 (27.6)	372 (23.5)
Education			
College and higher	1503 (75.3)	671 (76.8)	1263 (79.6)
Income (percent of the poverty line)			
<100	229 (13.1)	131 (15.6)	175 (11.5)
100 – 200	239 (13.6)	111 (13.3)	190 (12.5)
>200	1286 (73.3)	595 (71.1)	1158 (76.0)
Body mass index before pregnancy			
Underweight < 19.8 kg/m^2	266 (14.0)	120 (14.0)	238 (15.3)
Normal: 19.8 – <26.0 kg/m^2	930 (49.0)	407 (47.3)	824 (52.8)
Overweight: 26 – <29.0 kg/m^2	215 (11.3)	103 (12.0)	176 (11.3)
Obese: >=29.0 kg/m^2	487 (25.7)	230 (26.7)	322 (20.6)
Nulliparous	1098 (54.9)	476 (54.5)	831 (52.4)
Chronic hypertension	148 (8.0)	72 (8.6)	N/A
Preexisting diabetes	78 (4.2)	43 (5.2)	44 (2.8)
Smoking			
Non-smoker	1180 (70.8)	554 (70.1)	1068 (72.5)
Past smoker	236 (14.2)	111 (14.1)	179 (12.1)
Current smoker	251 (15.1)	125 (15.8)	227 (15.4)
Alcohol use	774 (46.4)	341 (43.1)	705 (47.8)
Weight gain during pregnancy			
< 100% weigh gain ratio	410 (23.1)	192 (23.4)	361 (23.2)
100-200%	997 (56.2)	450 (54.9)	912 (58.6)
> 200% weigh gain ratio	366 (20.7)	178 (21.7)	284 (18.2)

Table A-4. Study analysis 1: "Physical activity and maternal-fetal circulation measured by Doppler ultrasound in mid-pregnancy"

Distribution of physical activity, regarding perceived (number of hours per week) and absolute (number of MET-hours per week) intensity by one week recall interview, among study population (N = 874), SH+H: somewhat hard or hard, MV: moderate to vigorous

Perceived intensity (hours/week)				**Absolute intensity (MET-hours/week)**		
Activity	N	%		Activity	N	%
Total physical activity (median = 2.9 hrs/wk)				Total activity (median = 9.3 MET- hrs/wk)		
No activity	57	6.5		No activity	57	6.5
Activity but not SH+H	252	28.8		Activity but not MV	510	58.4
SH+H activity below the median	283	32.4		MV activity below the median	152	17.4
SH+H activity above the median	282	32.3		MV activity above the median	155	17.7
Work activity				Work activity		
No work activity	613	70.1		No work activity	613	70.1
Work activity but not SH+H	160	18.3		Work activity but not MV	211	24.2
Some SH+H work activity	101	11.6		Some MV work activity	50	5.7
Recreational activity (median = 2.0 hrs/wk)				Recreational activity (median = 10.9 MET-hrs/wk)		
No activity	327	37.4		No activity	327	37.4
Activity but not SH+H	210	24.0		Activity but not MV	369	42.2
SH+H activity below the median	194	22.2		MV activity below the median	89	10.2
SH+H activity above the median	143	16.4		MV activity above the median	89	10.2
Exercise activity (median = 2.0 hours/wk)				Exercise activity (median = 10.9 MET-hrs/wk)		
No activity	309	35.4		No activity	309	35.3
Activity but not SH+H	222	25.4		Activity but not MV	373	42.7
SH+H activity below the median	197	22.5		MV activity below the median	96	11.0
SH+H activity above the median	146	16.7		MV activity above the median	96	11.0

Table A-5. Study analysis 2: "Physical activity and the risk of gestational hypertension and preeclampsia"

Distribution of physical activity, regarding perceived (number of hours per week) and absolute (number of MET-hours per week) intensity by one week recall interview, among study population (N = 1586), SH+H: somewhat hard or hard, MV: moderate to vigorous

Perceived intensity (hours/week)				Absolute intensity (MET-hours/week)		
Activity	N	%		Activity	N	%
Total physical activity (median = 2.7 hrs/wk)				Total activity (median = 9 MET- hrs/wk)		
No activity	85	5.4		No activity	85	5.4
Activity but not SH+H	445	28.0		Activity but not MV	906	57.1
SH+H activity below the median	528	33.3		MV activity below the median	299	18.8
SH+H activity above the median	528	33.3		MV activity above the median	296	18.7
Work activity				Work activity		
No work activity	1106	69.8		No work activity	1106	69.8
Work activity but not SH+H	305	19.2		Work activity but not MV	362	22.8
Some SH+H work activity	175	11.0		Some MV work activity	118	7.4
Recreational activity (median = 2.0 hrs/wk)				Recreational activity (median = 10.5 MET-hrs/wk)		
No activity	527	33.2		No activity	527	33.2
Activity but not SH+H	402	25.6		Activity but not MV	715	45.1
SH+H activity below the median	375	23.6		MV activity below the median	169	10.7
SH+H activity above the median	279	17.6		MV activity above the median	175	11.0
Exercise activity (median = 2.0 hours/wk)				Exercise activity (median = 10.5 MET-hrs/wk)		
No activity	506	31.9		No activity	506	31.9
Activity but not SH+H	414	26.1		Activity but not MV	714	45.0
SH+H activity below the median	383	24.2		MV activity below the median	179	11.3
SH+H activity above the median	283	17.8		MV activity above the median	187	11.8

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