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Volume of physical activity and hemostatic variables in pregnant women

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Volume of Physical Activity and Hemostatic Variables in Pregnant Women

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A thesis submitted to the Graduate Faculty of

JAMES MADISON UNIVERSITY

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Abstract

Purpose: This study investigated the relationship between blood coagulation and fibrinolytic potential and physical activity. Physical activity levels to predict blood coagulation and fibrinolytic potential were also examined. **Methods:** Twenty-three pregnant women, aged 19-34 yrs, had a fasted blood draw between 6 and 10 a.m. analyzed for tPA antigen, tPA activity, PAI-1 antigen, and vWF antigen. Trimester specific volume of leisure time physical activity was assessed by the Modifiable Activity Questionnaire (MAQ) and converted to METmin/wk. Based on MAQ results, women were grouped as meeting (“active”) or not meeting (“sedentary”) physical activity recommendations established by American College of Obstetrics and Gynecology. Average daily step count was calculated from 2 week pedometer logs and women were categorized as “sedentary” (<5,000 steps/day) or “at least low active” (5,000+ steps/day) according to step count. **Results:** PAI-1 and tPA antigen were higher and tPA activity was lower during the 3rd trimester of pregnancy versus 2nd trimester. ANCOVA suggests gestational age produced an statistically significant model for predicting PAI-1, tPA activity, and tPA antigen, but not vWF; average METmin/wk and step count groupings did not produce a statistically significant model predicting PAI-1, tPA antigen, tPA activity, or vWF but approached statistical significance for tPA antigen (METmin/wk $p = 0.073$ and steps/day $p = 0.057$). METmin/wk predicted tPA antigen, during pregnancy, in a forward stepwise multiple regression. Linear regressions based on physical activity groups resulted in a significant y-intercept difference ($p=0.047$) for tPA antigen using step count classifications. No significant y-intercept or slope differences were seen in vWF in relationship to volume of physical activity using a linear regression model.

Conclusion: It appears this is the first study to explore the relationship between hemostasis and volume of physical activity during pregnancy, thus providing an impetus for further cross sectional and longitudinal studies in this area. Future research is needed because pregnant women are predisposed to a number of thromboembolic complications and other health related issues related to hypercoagulation. Physical activity may enhance fibrinolytic and blood coagulation potential during pregnancy, as it can in non-pregnant adults.

Chapter I

Introduction

The blood coagulation and fibrinolytic cascades involve an intricate series of steps and reactions to either enhance the potential to produce fibrin (blood coagulation), the key protein in blood clots, or to break down fibrin (fibrinolysis). Pregnancy is defined as a hypercoagulant state, and is characterized by a decrease in fibrinolytic activity and an increase in blood coagulation enzymes, resulting in a 2-fold increase in coagulation potential in late pregnancy; in healthy women this hypercoagulant state is normalized 3-6 weeks postpartum (Choi, 2002; Kruithof, 1987).

The pattern of increased coagulation potential and reduced fibrinolytic capacity during pregnancy may protect pregnant women against the hemostatic challenges of placental separation (Bremme, 2003). However, these changes also present an increased risk for thromboembolic complications and hypercoagulability. The risk for pregnancy associated venous thromboembolism (VTE) increases 5.5-6 times compared to thromboembolism risk in non-pregnant women of childbearing age (McColl, 1997; Macklon, 1996; McColl, 1999; Ishii, 1994). Pre-eclampsia, characterized by an altered state of hemostasis, is the second leading cause of death during pregnancy and predisposes women to an increase in coronary heart disease risk later in life (Walter, 2000; Sattar, 2002). The majority of miscarriages are associated with combination with coagulation issues and are specifically due to placental vessel thrombosis and infarction (Bick, 2000). Additionally, hemostatic disturbances may lead to poor maternal-fetal circulation and ultimately restrict fetal growth (Holmes, 2005; Greer, 2002; Greer, 2003)

and markers of fibrinolytic inhibition (plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA) antigen) have been linked to gestational diabetes (Farhan, 2006; Morimitsu, 2007).

This issue is complicated by the fact that women are becoming pregnant at higher starting weights and gaining weight beyond healthy gestational recommendations (Huang, 2007; Waller, 2007). Obesity is known to increase cardiovascular disease risk and decrease fibrinolytic potential, increase coagulation potential, and increase atherosclerosis (Gaal, 2006) and being overweight/obese is a key risk factor of VTE (McColl, 1997; Macklon, 1996; McColl, 1999; Ishii, 1994). Fat cells synthesize and release PAI-1, inhibiting the body's potential to lyse blood clots. Obese individuals have greater PAI-1, and elevated fibrinogen levels and other coagulation factors versus healthy-weighted people (Rauramaa, 1999). Stewart et al. (2007) reported that obese women are in a greater coagulatory state during the first trimester of pregnancy due to fibrinolysis inhibition as seen in the PAI-1/PAI-2 ratio. Although this ratio improved among obese women as pregnancy advanced, inability to rebound from this impairment could explain elevated maternal risk of pre-eclampsia and hypertension (Stewart, 2007).

Participation in regular physical activity (PA) may help an individual reduce excess body fat and improve overall body composition (Thompson, 2009; HHS, 1996). In addition, regular PA is known to enhance the fibrinolytic profile (Regensteiner, 1995; Helmrich, 1991; Dempsey, 2004). Greater leisure time physical activity (LTPA) and endurance training have been shown to decrease PAI-1 and fibrinogen while enhancing tPA activity (Eliasson, 1996; Boman, 1994).

To date, it appears as though there has only been one study investigating the relationship between hemostasis and volume of physical activity during pregnancy. This study, by KovalcĀ-kovĀĵ (1975), is written in Slovak and not available in English, and thus little is known about the topic.

The purpose of the current study was to 1.) study markers of blood coagulation and fibrinolysis based on trimester, in pregnant women 2.) determine whether volume of physical activity predicts PAI-1, tPA activity, tPA antigen, and vWF in pregnancy and 3.) investigate the relationship between volume of physical activity during pregnancy on PAI-1, tPA activity, tPA antigen, and vWF. It was hypothesized that tPA activity would be lowest and tPA antigen, PAI-1, and vWF highest in the 3rd trimester and that the extent of hypercoagulation during pregnancy would be lower in physically active women, versus sedentary women at comparable gestational ages.

Chapter II

Review of Literature

Markers of blood coagulation and fibrinolysis are associated with a number of pregnancy complications including miscarriage, intrauterine growth restriction, gestational diabetes, venous thromboembolism, and pre-eclampsia. Figure 1 provides an overview of the interaction between the fibrinolytic and blood coagulation cascades. Tables 1 and 2 are summaries of studies investigating changes in blood coagulation and fibrinolytic systems during pregnancy and postpartum. Specifically, data on tissue plasminogen activator (tPA) antigen and activity, and plasminogen activator inhibitor-1 (PAI-1) (fibrinolytic variables) and the blood coagulation cascade (vonWillebrand factor; vWF) are presented. The research studies presented in the tables demonstrates a general trend towards a hypercoagulatory state at the end of pregnancy, which returns to non-pregnant levels by 4-6 weeks postpartum. Though values for each of these variables have been studied in healthy men and women and the general trends are well established in healthy pregnant women, the pattern and extent of change to a hypercoagulatory state has not been studied in relation to maternal physical activity level during pregnancy and postpartum. Only one known study, available only in Slovok, has investigated the relationship between exercise and hemostasis during pregnancy. Further information regarding the effect of physical activity on fibrinolysis and blood coagulation can be seen in tables 3-5.

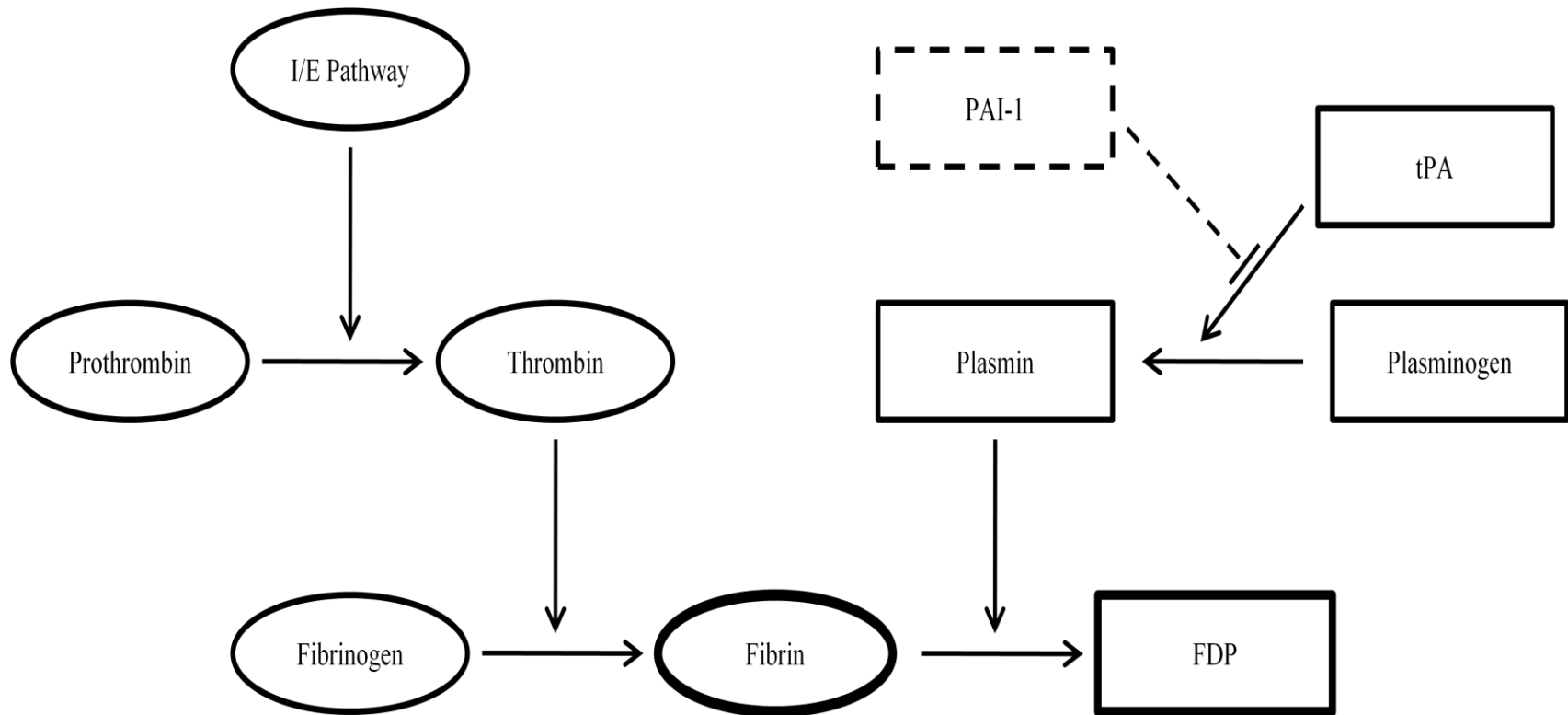


Figure 1. An overview of the fibrinolytic and blood coagulation systems. Ovals = blood coagulation; rectangles = fibrinolysis; dotted lines = inhibitor.

The fibrinolytic and the blood coagulation cascades work in conjunction with each other to maintain hemostasis and react to special situations such as pregnancy. The blood coagulation cascade, initiated through either the intrinsic or extrinsic pathway, involves a series of steps and reactions leading to the formation of a fibrin clot. Specifically, vonWillebrand factor (vWF) is a pro-coagulant protein in the intrinsic pathway found in combination with factor VIII in the intrinsic pathway. The fibrinolytic system involves the process of breaking down blood clots, or in other words, breaking down fibrin into fibrin degradation products (FDPs). The process of fibrinolytic potential begins with the activation of plasminogen to plasmin by tissue-type plasminogen activator (tPA). tPA activity refers to the amount of free tPA that is able to activate plasminogen whereas tPA antigen is the total amount of tPA in the system, free plus bound to its inhibitor, plasminogen activator inhibitor-1 (PAI-1). PAI-1 is the main inhibitor of the fibrinolytic system; PAI-1 creates an irreversible bond with tPA and inhibits the fibrinolytic process.

Table 1. Studies investigating changes in blood coagulation during pregnancy and postpartum.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Coagulation and fibrinolysis changes in normal pregnancy: Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis (Cerneca et al., 1997)	To determine the fibrinolytic and blood coagulation system changes that occur during normal pregnancy and puerperium.	117 normal, healthy, pregnant women and 45 age-matched, non-pregnant controls from Italy.	Fasted blood samples were taken at weeks 10, 20, 30, and 36 gestation and 2 days postpartum between 8:30-9:30AM for prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III activity, protein S activity, protein C activity, tPA antigen, and PAI-1.	There was an increase in procoagulant factors during pregnancy.
Coagulation and fibrinolytic mechanisms during and after normal childbirth (Bonnar et al., 1970)	To examine the changes in the fibrinolytic and coagulation systems during childbirth.	15 women with healthy, full-term pregnancies	Blood samples were taken for fibrinogen, plasminogen, euglobulin lysis time, urokinase sensitivity test, fibrin/fibrinogen degradation products, platelet count, thrombin clotting time, one-stage prothrombin time, factor VIII, factor IX, factor V, factor II, partial thromboplastin time, kaolin-cephalin clotting time, and plastic tube recalcification time at 7 increments between the end of the second stage of labor and 3-5 days after delivery.	There was a sharp increase in coagulation factors during delivery, which decreased with placental separation. Normal, non-pregnant values of fibrin/fibrinogen degradation products were found within an hour of delivery.
Reassessment of von Willebrand factor (VWF), VWF propeptide, factor VIII:C and plasminogen activator inhibitors 1 and 2 during normal pregnancy (Sie et al., 2003)	Use various assays to reassess vWF and factor VIII reference values in pregnant women.	306 healthy pregnant women (about 30 women for every 3 week gestational period).	A blood sample was taken and analyzed for VWF:Ag, VWF:Ag II, Factor VIII:C, PAI-1, and PAI-2.	VWF antigen and VWF:Ag II increased throughout pregnancy.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Reference intervals for plasma levels of fibronectin, von Willebrand factor, free protein S and antithrombin during third-trimester pregnancy (Wickstrom et al., 2004)	Analyze fibrinolytic and blood coagulation markers during pregnancy and establish reference values for some of the studied variables.	132 healthy pregnant women on an iron supplement and at least 1 previous pregnancy. 11/132 smoked during 3 rd trimester (9 smoking < 10 cigarettes/day, 2 smoking >10/day). 97% of women were Swedish. Control intervals are based on 73 non-pregnant women and men (50/50 split; age 20-60).	Blood samples for vWF, antithrombin, free protein S, and fibronectin were collected at 33, 36, and 39 weeks gestation, and 1-3 hours postpartum.	vWF increased from 33 weeks gestation through the postpartum measurement.

Normal pregnancy is associated with an increase in blood coagulation factors, including vonWillebrand factor, contributing to a hypercoagulatory state which peaks during labor. A few researchers have investigated vWF levels at time points throughout pregnancy and postpartum (Wickstrom, 2004; Clark, 1998; Sie, 2003). Values typically begin between 100-150% in the 1st trimester and progress linearly to between 200-250% during 3rd trimester. The data on vWF during postpartum are limited and focus almost exclusively on the early postpartum period. In addition, there is limited evidence available investigating reference values of vWF antigen in healthy populations, let alone special populations such as pregnant women (Wickstrom, 2004). Variance is wide between assays, making it difficult to make determinations of whether values have any clinical relevance (Diapharma).

Table 2. Studies investigating changes in fibrinolytic potential during pregnancy and postpartum.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Fibrinolysis in pregnancy: a study of plasminogen activator inhibitors (Kruithoff et al., 1987)	To study the actions of plasminogen activator inhibitors throughout pregnancy and postpartum.	90 pregnant women with normal pregnancy (10 women for each 4-week gestational period), 10 women soon after delivery (mean time 77 ± 54 minutes), 10 women 3-5 days postpartum, and 10 age-matched non-pregnant women	Blood samples were obtained from the women to test for tPA, uPA, PAI-1, PAI-2, total PA, plasminogen, and α_2 -antiplasmin.	PAI-1 levels were greater than non-pregnant levels (non-significant) with an almost linear increase throughout pregnancy. There was about a 50% decrease in PAI-1 1-hour post-delivery and normal PAI-1 activity was seen 3-5 days postpartum. tPA increased during pregnancy, plateauing in the last 2 trimesters, doubling 1 hour postpartum and, and remaining slightly elevated 3-5 days postpartum.
Coagulation and fibrinolysis changes in normal pregnancy: Increased levels of procoagulants and reduced levels of inhibitors during pregnancy induce a hypercoagulable state, combined with a reactive fibrinolysis (Cerneca et al., 1997)	To determine the fibrinolytic and blood coagulation system changes that occur during normal pregnancy and puerperium.	117 normal, healthy, pregnant women and 45 age-matched, non-pregnant controls from Italy.	Fasted blood samples were taken at weeks 10, 20, 30, and 36 gestation and 2 days postpartum between 8:30-9:30AM for prothrombin time, activated partial thromboplastin time, fibrinogen, antithrombin III activity, protein S activity, protein C activity, tPA antigen, and PAI-1.	There was a decrease in anticoagulants during pregnancy. Fibrinolytic markers of tPA and PAI-1 were increased during pregnancy and decreased in puerperium.
Fibrinolysis during normal human pregnancy: complex inter-relationships between plasma levels of tissue plasminogen activator and inhibitors and the euglobulin clot lysis time (Wright et al., 1988)	To measure fibrinogen, fibrin-fibrinogen degradation products (FDP), D-dimer, PAI-2, tPA, and plasminogen in normal pregnancy.	55 pregnant women and 16 healthy non-pregnant controls (women 20-35 years) from Sweden.	Cross sectional study where blood samples for fibrinogen, FDP, D-dimer, PAI-2, tPA, and plasminogen were collected at 9-11 weeks (n=12), 22-24 weeks (n=16), and 36-38 weeks (n=17) gestation, within 24 hours postpartum (n=5), or between 36-48 hours postpartum (n=5).	Plasminogen was higher than controls and increased throughout pregnancy. Plasminogen fell postpartum to control levels but fibrinogen did not. tPA activity was reduced by the 2 nd trimester, remaining at that level for the remainder of pregnancy.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Sequential studies on components of the haemostatic mechanism in pregnancy with particular reference to the development of pre-eclampsia (Condie & Ogston, 1976)	To look at the development of changes in hemostasis during pregnancy and postpartum in an effort to determine if there are differences in women who have normal pregnancies versus develop preeclampsia.	60 women (age range 18-25 years) in their first pregnancy and 10 never-pregnant controls (< 25 years)	Blood samples for fibrinolytic activity, fibrinolytic capacity, plasma plasminogen, plasma fibrinogen, serum fibrinogen/fibrin related antigen, urinary FR-antigen, and serum α_1 -antitrypsin and α_2 -macroglobulin were taken at 12, 20, 30, and 38 weeks gestation, after placental delivery (30 minutes), 24, 48, 96, 144 hours postpartum and 6 weeks postpartum.	Plasminogen was higher during pregnancy than in controls.
Reassessment of von Willebrand factor (VWF), VWF propeptide, factor VIII:C and plasminogen activator inhibitors 1 and 2 during normal pregnancy (Sie et al., 2003)	Use various assays to reassess vWF and factor VIII reference values in pregnant women.	306 healthy pregnant women (about 30 women for every 3 week gestational period).	A blood sample was taken and analyzed for VWF:Ag, VWF:Ag II, Factor VIII:C, PAI-1, and PAI-2.	PAI-1 increased throughout pregnancy, until the very end, when it fell.
APC resistance and other haemostatic variables during pregnancy and puerperium (Kjellberg et al., 1999)	To investigate the relationship between markers of hemostasis and change in activated protein C ratio during pregnancy, to determine blood coagulation reference values, and to confirm normality in hemostatic balance during pregnancy.	27 nulliparous, 19 primiparous, 2 multiparous women (mean 29 years) without any bleeding disorders.	Prospective, longitudinal study. Blood samples at 10-15, 23-25, 32-34, and 38-40 weeks gestation, within 1 week and during the 8 th week postpartum for Hb, hct, platelet count, tPA, APC ratio, factor VIII, fibrinogen, protein C, free protein S, prothrombin 1+2, fibrin, D-dimer, PAI-1, and PAI-2.	PAI-1 increase significantly with pregnancy progression. PAI-1 decreased by the time women left the hospital following delivery. tPA activity significantly decreased with pregnancy progression.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Enhanced thrombin generation and fibrinolytic activity in normal pregnancy and the puerperium (Bremme et al., 1992)	To study fibrinolytic markers and coagulant inhibitory indices throughout pregnancy.	26 pregnant women (mean age 28, age range 20-38; 12 in their 1st pregnancy, 9 in their 2 nd , and 5 who had have multiple previous pregnancies).	Morning blood draws following a 10-hour fast were taken at weeks 12-15, 24, and 35 gestation, immediately following placental delivery, and 5 week postpartum for platelet count, fibrinogen, prothrombin complex, antithrombin, protein C, protein S (total and free), soluble fibrin, TAT, D-dimers, PAI-1, PAI-2, and cardioplin antibodies positive.	PAI-1 increased during pregnancy, reaching a level of 90 AU/mL at 35 weeks gestation.
Tissue plasminogen activator levels change with plasma fibrinogen concentrations during pregnancy (Choi & Pai, 2002)	To study the fibrinolytic and blood coagulation systems during normal pregnancy	436 women were studied (1 st trimester: 107, 2 nd trimester: 65, 3 rd trimester: 123, postpartum: 109, non-pregnant: 32)	Blood samples were analyzed for markers of coagulation (VII, VIII, IX, X, XI, XII, fibrinogen), prothrombin time, activated partial thromboplastin time, antithrombin III, tPA, PAI-1, D-dimer, and protein S.	Levels of tPA antigen, and plasma fibrinogen levels were greater in the 3 rd trimester than the 1 st trimester, and tPA antigen and plasma fibrinogen had decreased, in comparison to peak pregnancy levels, 5-8 weeks postpartum.
tPA activity in peripheral blood obtained from pregnant women (Ishii et al., 1994)	Use a new method to clarify changes in fibrinolysis potential that occur throughout pregnancy.	Pregnant women (unspecified number).	Blood samples were taken in women between 10 and 11am for tPA activity, tPA antigen, and PAI activity. Study layout is unspecified (longitudinal vs. cross sectional) but control blood samples as well as samples from 8, 12, 16, 20, 24, 28, 32, 36, 40 weeks gestation, and within 2 days puerperium were taken.	tPA activity dramatically decreased during pregnancy and increased to almost non-pregnant levels by 48 hours postpartum. tPA antigen gradually increased during pregnancy and decreased to almost non-pregnant levels by 48 hours postpartum. PAI-1 increased during pregnancy and decreased to non-pregnant levels by 48 hours postpartum.
Source of increased plasminogen activators during pregnancy and puerperium (Shimada et al., 1989)	To examine uPA and tPA antigen levels during pregnancy, delivery, and postpartum.	43 non-pregnant women of child-bearing age, 73 healthy pregnant women, and 54 postpartum women	Cross sectional study with women grouped by trimester, stage of delivery, or postpartum. 3 women were studied at multiple time points.	There were no significant changes in tPA from 1 st to 2 nd trimester, with both increasing significantly during the 3 rd trimester. tPA antigen continued to rise immediately after childbirth before dropping.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Fibrinolysis changes in normal pregnancy (Bellart et al., 1997)	To study changes in tPA, PAI-1, PAI-2, and D-dimer during pregnancy, delivery, and 3 days postpartum.	60 pregnant women with healthy pregnancy (mean age 29 years).	In 60 women, blood samples for tPA, PAI-1, PAI-2, and D-dimer were taken during each trimester of pregnancy. 20 of these women also had blood samples taken during delivery and 3 days postpartum.	tPA increased during pregnancy, exceeding the normal non-pregnant range after 1 st trimester and reaching peak levels at delivery, returning to normal 3 days postpartum. PAI-1, though remaining within normal non-pregnant range, were significantly higher 2 nd and 3 rd trimester and during delivery.

Healthy pregnancy is associated with a decrease in fibrinolytic enzymes, including tPA activity, and an increase in markers of fibrinolytic inhibition, including PAI-1 and tPA antigen. These changes help contribute to a hypercoagulant state which peaks during labor and return to non-pregnant levels post-partum.

PAI-1 activity values begin between 7.4 and 10.25 AU/mL in first trimester, progressing to between 11.26 and 14.9 AU/mL in 2nd trimester, and then vary greatly in 3rd trimester, with values of 22.41 and 37.8 AU/mL. Despite the differences in the 3rd trimester, there is an increase in PAI-1 in the 3rd trimester compared to the 2nd trimester. In contrast, studies investigating PAI-1 levels in healthy non-pregnant women suggest wide variability in average values, but all normal values do fall below 15 AU/mL (Holmes, 2005; Kruithoff, 1987; Cerneca, 1997; Ranby, 1990; Eliasson, 1993). Kruithoff et al. (1987) found an almost linear increase in PAI-1 throughout pregnancy. Cerneca et al. (1997) studied 117 pregnant women from Italy and took blood samples between 8:30-9:30am. Stirling et al. (1984) studied 72 women of various races (59 whites, 6 Asians, 4 blacks, and 3 Chinese) with no time listed for when the blood draws occurred. It is possible that differences in these 2 studies during the 3rd trimester are consequence of diurnal variation in PAI-1 activity or could be an effect of race; obtaining blood samples between 7 and 10 a.m. minimizes diurnal variation. Postpartum values are not all shown due to vague time points but do conform to a general trend in a rapidly decreasing PAI-1 activity level following delivery, returning to non-pregnant levels by 3-5 days postpartum.

Healthy, non-pregnant values for tPA activity range between 0.1-1.5 IU/mL (Kjellberg, 1999; Wimer, 1985; Eliasson, 1993). Kjellberg et al. (1999), investigated tPA

activity levels during pregnancy and postpartum, finding an almost linear decrease from 1st to 3rd trimester,

returning to pre-pregnancy levels postpartum. Data is more limited here as many studies look at plasminogen, but not specifically tissue-type plasminogen activator activity.

A number of studies investigated tPA antigen levels at time points throughout pregnancy and postpartum (Bellart, 1997; Kruithof, 1987; Shimada, 1989; Cerneca, 1997; Choi, 2002). The majority of the studies listed begin with values between 2.5-4.5 ng/mL for the 1st semester with an increase to between 6-8 ng/mL by the end of 3rd trimester. Postpartum values show a marked decrease in tPA antigen initially with values back down to non-pregnant or 1st trimester levels by 6 weeks postpartum. Studies investigating non-pregnant levels of tPA antigen report mixed results. Studies analyzing healthy, non-pregnant tPA antigen levels using ELISA kits show a small range in findings. Choi and Pai (2002), Eliasson et al. (1993), and the Imubind® tPA ELISA Kit (American Diagnostica) studied 32 women (mean age 26.7), 72 women age 25-34, and 95 healthy women, respectively, finding a mean tPA antigen level between 3.9-4.0 ng/mL. A study looking at non-pregnant women in Italy found much higher tPA antigen levels (7.1 ± 5.5 ng/mL) and a study of 10 healthy women found lower levels (2.2 ± 0.8 ng/mL; Cerneca, 1997). An earlier study using an immunoradiometric assay found lower values for tPA antigen in healthy non-pregnant women (2.2 ± 0.8 ng/mL; Kruithoff, 1987).

Table 3. Cohort studies investigating the acute effects of exercise on blood coagulation and fibrinolytic markers, independent of pregnancy.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Activation and disturbance of blood hemostasis following strenuous physical exercise (Lin et al., 1998)	Investigate markers of fibrinolysis and blood coagulation immediately and 24 hours post-exercise using modern analytical techniques.	11 moderately active participants (mean 24.2 years)	Cycle ergometer test. 5 min WU at 120W, 35 min at 70% VO_{2max} . Blood was taken at baseline, 2, 6, and 24 hours post-exercise for tPA activity and antigen, PAI-1 activity, total fibrin/fibrinogen degradation products.	tPA activity and antigen significantly increased at end-exercise versus rest, returning to baseline by the 2 hr post blood draw. PAI-1 activity was significantly decreased during exercise and returned to resting levels 2 hours post exercise.
The effect of different exercise intensities on the fibrinolytic system (Molz et al., 1993)	To investigate the effect of exercise intensity on fibrinolytic markers	10 untrained women and 10 untrained men (22-34 years)	Cycle ergometer test (begin at 50W and increase 10W/min until HR of 120 bpm. Hold that intensity for 30 minutes, then increase 25W every 2 min until exhaustion or HR 180-190 bpm. Before and after the exercise test blood samples were taken for Hb, tPA activity and antigen, D-dimer, PT, APPT.	tPA activity was increased after moderate and maximal exercise, dropping by 30 min post-exercise. A greater increase was seen immediately following the maximal exercise.
Blood fibrinolytic activity in man (Rosing et al., 1970)	To determine the relationship between magnitude of fibrinolytic response and intensity of exercise as well as to look at diurnal variations in fibrinolytic markers	2 healthy women and 12 healthy men (19-30 years)	Maximal exercise = running speed that exhausted the person in 5 minutes. 40% and 70% of max exercise were investigated. Blood samples were taken every 2-3 hours over a 24 hour span and exercise blood measures were taken before exercise and every 5 minutes during exercise for fibrinogen, fibrinolytic activity, plasminogen.	Fibrinolytic activity increased from 8AM to 3PM. Fibrinolytic activity increased during each exercise bout and quickly returned to normal following exercise.
Acute dynamic exercise increases fibrinolytic activity (Rankinen et al., 1995)	To compare how tPA and PAI are effected by submaximal and max exercise (acute).	9 healthy men (23-37 years)	VO_{2max} , anaerobic and aerobic threshold tests on a cycle ergometer. Blood taken at rest 3-4 hours after a standard breakfast, IPE, and 24 hours post-exercise for plasma fibrinogen, tPA activity, PAI-1.	tPA activity increased IPE and returned to baseline at 24 h post-exercise in all 3 exercise conditions, with a greater increase seen during the VO_{2max} and anaerobic threshold tests. PAI-1 activity decreased IPE during the VO_{2max} and anaerobic threshold tests but no in the aerobic threshold test. PAI-1 returned to baseline 24 h post-exercise.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Effects of exercise intensity, duration, and time of day on fibrinolytic activity in physically active men (Szymanski & Pate, 1994)	To determine the effect of time of day on fibrinolytic responses to submaximal exercise and to determine how duration, intensity, and caloric expenditure during submaximal exercise are related to fibrinolytic responses.	12 healthy men (28-43 years) who had jogged 3-5 d/wk for 30 min over the past 3 months.	Treadmill VO_{2max} , 30 minute morning and afternoon sessions at 50% VO_{2max} and 80% VO_{2max} (4 submax trials). Blood samples were taken before, during, and IPE for Hb, hct, tPA activity, PAI-1.	tPA activity increased during all exercise sessions but was insignificant during the 50% morning session and greater increases were found in the 80% sessions. PAI-1 response was not different due to intensity but did show significant decreases in PAI-1 activity in all but the 50% afternoon session.
Balanced activation of coagulation and fibrinolysis after a 2-h triathlon (Bartsch et al., 1995)	To investigate whether fibrin, thrombin, and plasmin in vivo are effected by strenuous, prolonged exercise.	10 men (age 19-38) participating in a short triathlon.	Triathlon (1.7 km swim, 40 km bike, 10 km run). Blood was taken 1 day pre-race, IPE, and 2, 8, and 21 hr post-triathlon for beta-thromboglobulin, fibrinopeptide A, APTT, ELT, F1+2, TAT, antithrombin III, plasminogen, α -2- antiplasmin, tPA, PAI-1, FbDP.	tPA antigen was highest IPE, returning to baseline 21 hrs post-exercise. PAI-1 antigen was highest 2 hrs post-exercise and returned to baseline by 8 hrs post-exercise.
Changes in the fibrinolytic system associated with physical conditioning (Paz, 1992)	To determine the fibrinolytic response to maximal exercise.	23 healthy men (20-24 years); 10 who do not engage in any sport, 12 middle distance runners running >80 km/wk	VO_{2max} test (Bruce protocol). Blood was studied for plasminogen, α 2-antiplasmin, antithrombin III, fibrinogen, fibrinogen degradation products, tPA and PAI activity and tPA and PAI antigen.	Runners had increased tPA activity and decreased PAI activity at rest. Post-exercise, tPA activity and antigen were increased in both groups; tPA antigen increased to a greater extent in runners.
Fibrinolytic and hemostatic changes during and after maximal exercise in males (Davis et al., 1976)	To study hemostatic and fibrinolytic changes in 10 healthy males in response to a maximal exercise test on a bicycle ergometer.	10 healthy men (22-27 years)	VO_{2max} test (bicycle ergometer). Blood was taken for fibrinogen, factor VIII, cholesterol, triglycerides, hematocrit, white blood cell count, fibrinolytic activity.	Little change occurred before 50-60% VO_{2max} / 70-80% HRmax. The greatest fibrinolytic response was evident at HRmax. Fibrinolytic activity decreased in an almost linear fashion within the 1 st 10 minutes post-exercise. Factor VIII rose during exercise and peaked 5-10 minutes post-exercise.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Evaluation of clotting and fibrinolytic activation after protracted physical exercise (Prisco et al., 1998)	To examine the duration and extent of fibrinolytic and blood clotting activation after a marathon.	12 healthy male marathon runners (25-47 years)	International Marathon of Florence (Italy). Blood was taken the day prior to competition, IPE, 1 day post-marathon, 2 days post-marathon for fibrinogen, F1+2, TAT, ELT, tPA antigen, PAI-1 activity, PAI-1 antigen, D-dimer, FgDP.	PAI-1 antigen, tPA antigen, D-dimer, and FgDP were increased IPE. There was an insignificant decrease in PAI-1 activity IPE. 24 hours post race measures were still altered, they returned to baseline by 48 hours post-marathon.
Increases in factor VIII complex and fibrinolytic activity are dependent on exercise intensity (Andrew et al., 1986)	To determine the relationship between 3 different types of exercise on fibrinolytic markers and the factor VIII complex.	5 men (25-44 years) who are moderately active	VO _{2max} (cycle ergometer), low-intensity steady state exercise, 30 sec max effort test on a cycle ergometer. Blood samples taken prior to each exercise bout, in the last 30 seconds of each stage of the max test, 10 and 60 minutes post-exercise, for plasminogen, FPA, WBC, Hb, APTT, PT, fibrinogen, WBCLT, factors II, V, VIII complex, XII. Factor VIII:vWF measured using human platelets and ristocetin in formaldehyde.	It wasn't until 80% max that changes in factor VIII complex were seen during the max test. There were no major changes in factor VIII complex following steady state. increased following exercise and peaking at 10 minutes post-exercise following the 30 sec exercise.

The studies presented in table 3 include investigations that were designed to determine the effect of an acute bout of exercise on markers of fibrinolysis and blood coagulation. The majority of these studies focused on healthy individuals (primarily males) in their 20's and 30's, many of which were physically active. Though there is more limited data specifically looking at the effect of acute exercise on fibrinolytic and blood coagulation markers in women, there appear to be no substantial differences in the pattern of effect of these markers in men and premenopausal women (Schuit, 1997; Kulaputana, 2005; Eliasson, 1993). The intensity, duration and mode of the acute bout of exercise vary greatly among the investigations with some including an anaerobic threshold test while others included the measurement of VO_{2max} and some included measurements following an hour of exercise at various intensities and modes (triathlons, marathons, and 100 km race and utilizing walking, running, cycling, and swimming).

In response to acute exercise, vWF specifically has not been studied to a great extent, but factor VIII, which in complex includes vWF, has been shown to rise during exercise and peak 5-10 minutes post-exercise, which changes evident in exercise above 80% VO_{2max} (Davis, 1976; Andrew, 1986). Overall, it appears that blood coagulation as a whole increases due to an acute bout of exercise, peaking and remaining elevated for a couple hours following exercise.

The pattern of fibrinolytic response to an acute exercise bout is backed by strong evidence; PAI-1 activity decreases while tPA activity and antigen increase. A greater increase in tPA antigen has been found in runners versus sedentary individuals (Paz, 1992). A greater increase in tPA has also been found with increased intensity, especially at max (Molz, 1993). PAI-1 activity, tPA activity, and tPA antigen all quickly return to

baseline following exercise. This, in conjunction with the increased blood coagulability following an acute bout of exercise, results in a couple hours of increased coagulatory potential following exercise.

Table 4. Cross-sectional and prospective studies investigating the chronic effects of exercise on blood coagulation and fibrinolysis, independent of pregnancy, in cross-sectional studies.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Physical activity and hemostatic and inflammatory variables in elderly men (Wannamethee et al., 2002)	To examine the relationship between inflammation, viscosity, hemostatic variables, and exercise.	3954 men 60-79 years, 30% on aspirin	Questionnaire assessing usual PA under regular cycling/walking, recreational, and sporting (vigorous) activity using frequency and type. Men grouped into 6 categories (1. Inactive, 2. Occasional, 3. Light, 4. Moderate, 5. Moderately vigorous, 6. Vigorous. Blood was tested for clottable fibrinogen, tPA antigen and vWF, D-dimer, CRP, factors VII, VIII, IX, APC resistance, and aPTT.	PA and many hemostatic and inflammatory markers are inversely associated, including vWF and tPA antigen and remain after adjusting for BMI, pre-existing CVD, age, etc. ~40% reduction in high fibrinogen and ~30% reduction in high tPA antigen levels was seen with moderate PA. Men who remained active and became active showed lower hemostatic variables than those currently inactive.
Physical activity status and adverse age-related differences in coagulation and fibrinolytic factors in women (DeSouza et al., 1998)	To determine if there are age related differences in fibrinolytic and blood coagulation factors in women	51 healthy women in 4 groups (11 pre-menopausal sedentary, 13 pre-menopausal active, 14 post-menopausal sedentary, 13 post-menopausal active. The active women are from running clubs.	VO _{2max} . Blood was taken for fibrinogen; tPA antigen, PAI-1 activity and antigen, and D-dimer.	Post-sedentary women had higher PAI-1 activity and antigen and tPA antigen, and lower tPA activity than pre-sedentary women. tPA antigen, PAI-1 activity and antigen were lower and tPA activity was high in post-active women versus post-sedentary women but not in relation to pre-active women.
Regular leisure time physical activity predicts high activity of tissue plasminogen activator: The northern Sweden MONICA study (Eliasson et al., 1996)	To investigate the relationship between physical activity and fibrinolytic variables.	250 women and 250 men in each age group (25-34, 35-44, 45-54, 55-64 years) from Sweden	Self-report LTPA (no/light PA, light PA, moderate PA, moderate/strenuous PA). Blood was taken for tPA activity and mass, PAI-1 activity, triglycerides, and insulin.	tPA activity was higher as physical activity increased but was only significant in men. tPA mass decreased significantly with increased activity in a linear fashion. PAI-1 activity decreased as PA increased.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Lifestyle and hemostatic risk factors for ischemic heart disease: The Caerphilly study (Yarnell et al., 2000)	To examine the effect of lifestyle factors on hemostatic variables.	2398 men (45-59 years)	Minnesota Leisure Time Activity questionnaire. Blood was taken for tPA, PAI-1 activity, clottable fibrinogen, D-dimer, viscosity, and white cell count.	vWF and D-dimer and LTPA were significant related, as LTPA increased, vWF and D-dimer decreased.

A number of studies have used physical activity questionnaires to determine the relationship between physical activity and markers of coagulation (Lakka, 1993; Abramson, 2002; Wanameethee, 2002; Yarnell, 2000; Panagiotakos, 2005; Eliasson, 1996). Wanameethee et al. (2002) and Yarnell et al. (2000) found an inverse relationship between activity level and vWF. As physical activity level increases in cross-sectional studies, fibrinolysis potential is improved. This enhancement can be seen by an increase in tPA activity and a decrease in tPA antigen and PAI-1 (Eliasson, 1996; Wannamethee, 2002).

Table 5. Intervention studies investigating the chronic effects of exercise on blood coagulation and fibrinolysis, independent of pregnancy, in intervention studies.

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Effects of high and low intensity aerobic conditioning programs on blood fibrinolysis and lipid profile (El-Sayed, 1996)	To examine the effect of low and high intensity exercise interventions on fibrinolytic and lipid markers.	8 untrained females and 10 untrained males (mean age 27.2 years)	Participants were randomly assigned to either a low intensity (30% VO_{2max}) or high intensity (80% VO_{2max}) group. Exercise involved 20 min, 3x/wk for 12 weeks of cycling (Monark bicycle ergometer), plus a 5 minute warm up and cool down. Blood samples were tested for cholesterol, triglycerides, tPA activity and antigen, PAI-1 activity and antigen.	PAI-1 activity was significantly decreased from baseline in the high intensity group.
Effect of strenuous exercise on fibrinogen and fibrinolysis in healthy elderly men and women (Schuit et al., 1997)	To determine the effect of a 6 month exercise intervention on tPA activity, PAI-1, and fibrinogen among the Dutch	116 Dutch women and 113 Dutch men (60-80 years) with blood markers in 94 women and 88 men	Randomly assigned to either an exercise (bicycle) group (48 women, 48 men) or a control group (46 women, 40 men). The exercise group received a home exercise bike and trained 30 min/d, 4 d/wk for 6 months (50% HRmax progressing to 70% as intervention advanced). Blood was analyzed for fibrinogen, PAI-1 antigen, tPA, CRP, HDL, and insulin.	No differences between men and women for fibrinogen, PAI-1 antigen, or tPA activity were found. tPA activity increased to a significantly higher amount and PAI-1 antigen modestly decreased in the exercise group, with the largest changes seen in previously inactive individuals. Fibrinogen was also increased to a greater extent in the exercise group.
Effects of endurance training and seasonal fluctuation on coagulation and fibrinolysis in young sedentary men (van den Burg et al., 1997)	To study the effect of moderate intensity physical training on fibrinolysis and blood coagulation.	40 sedentary men (20-30 years) randomly assigned to either training or control groups (20 in each)	Cycle ergometer VO_{2max} , cycle ergometer 4-part test (gradual increase to 70% VO_{2max} , 15 min steady state, four 1-minute increases in intensity to VO_{2max} , 10 minute active recovery. 12 week intervention supervised training 2x/wk working for 1 hour at 60-70% VO_{2max} . Blood was taken at baseline, after 6 wks, and after 12 weeks for factors VII, VIII, IX, XII, fibrinogen, APTT, prothrombin time, tPA antigen and activity, PAI-1 activity, and uPA antigen.	Factors VII, IX, XII, prothrombin time, and fibrinogen did not change because of the intervention. tPA antigen, PAI-1 activity and antigen decreased in the training group and increased in the control group post-intervention (significant interaction effect).

Articles	Problem/ Question Studied	Participants	Procedures	Findings
Blood coagulability and fibrinolytic activity before and after physical training during the recovery phase of acute myocardial infarction (Suzuki et al., 2002)	To look at the effect of exercise during recovery from MI on markers of blood coagulation and fibrinolysis.	11 women and 75 men (35-82 years) assigned to either exercise group (56) or control (30) depending on if their physician prescribed exercise.	Exercise began 29±3 days post-MI and lasted 31±5 days with 6 d/wk of two 40-minutes sessions (morning and afternoon) with the majority of time spent walking (<120 bpm). Blood samples were taken for PT, APTT, α_1 AT, α_2 MG, fibrinogen, ATIII, plasminogen, α_2 PI, factors VIII:C, vWF:Ag, hct, platelet count, ELT. A subset group (C) was also tested for tPA activity and antigen, PAI-1, TAT, VII:C, P-C:Ag, PIC.	vWF:Ag, VIII:C, ATIII all decreased in the training group while remaining unchanged in the control group. Subset C found a decrease in tPA antigen and PAI-1, in addition to TAT, PIC, P-C:Ag, and VII:C after training and no change in tPA activity.
Effects of a moderate-intensity aerobic program on blood viscosity, platelet aggregation and fibrinolytic balance in young and middle-aged sedentary subjects (Coppola et al., 2004)	To determine if a moderate aerobic exercise program improves fibrinolytic balance in sedentary young and middle-aged people.	15 university students (5 female; mean age 27.9 ± 3 yrs) and 15 professors (4 female)	3x/wk for 12 wks of aerobic activity (10 min WU, 40 min walk or run on treadmill). Blood samples were tested for hct, Hb, blood cell count, fibrinogen, tPA antigen and PAI-1 antigen, and platelet aggregation.	tPA antigen lower in young vs. middle-aged participants. No changes in tPA antigen due to the intervention. PAI-1 antigen was significantly increased in the middle-aged but not the young participants.

Intervention studies looking at the effect of chronic exercise on coagulation and fibrinolysis, reviewed here, range from 1-6 months in length, primarily utilized aerobic modes of activity (walking, running, cycling, Canadian Air force training), and involved a healthy, active individuals, as well to sedentary individuals and post MI patients. A study by Suzuki et al. (1992), found a decrease in vWF following the 1 month intervention in post MI patients.

Summary

The findings of the individual studies above (Suzuki, 1992; van den Burg, 1997; Schuit, 1997) are consistent with a review by Womack et al. (2003) regarding fibrinolytic variables. As an adaptation to exercise, PAI-1 activity and tPA antigen decrease and tPA activity increases, resulting in an enhanced fibrinolytic potential. El-Sayed (1996) found that PAI-1 decreased following a 12 week cycling intervention in a high intensity exercise group (80% VO_{2max}) but not in a low intensity group (30% VO_{2max}), suggesting that intensity of exercise may play a greater role in determining expected fibrinolytic adaptations to exercise.

The normal progression of fibrinolytic and blood coagulation variables in low risk pregnancies has been well established. Markers of blood coagulation (e.g. vWF) and fibrinolytic inhibition (e.g. PAI-1, tPA antigen) increase as pregnancy advances and fibrinolytic markers (e.g. tPA antigen) decrease, creating a hypercoagulant state which peaks at the end of pregnancy and returns to non-pregnant levels by 4-6 weeks postpartum. The changes in blood coagulation and fibrinolytic potential, seen in tables 1 and 2, provide the physiological benefit of protecting the mother against bleeding out in excess during placental separation. However, these changes also predispose the woman to a number of thromboembolic complications and other health related issues related to hypercoagulation including miscarriage, pre-eclampsia, venous thromboembolism, intrauterine growth restriction, and diabetes (Greer, 2003).

The response of fibrinolytic markers to an acute bout of exercise is well established, whereas findings are inconsistent in regards to blood coagulant markers. During an acute bout of exercise, PAI-1 activity decreases while tPA activity and antigen

increase, returning quickly to baseline following exercise. Blood coagulation as a whole increases due to an acute bout of exercise, peaking and remaining elevated for a couple hours following exercise. Together, this results in a couple hours of increased coagulatory potential following exercise.

In contrast to acute bouts of exercise, fibrinolytic potential is enhanced as a result of chronic exercise, as seen by a decrease in PAI-1 activity and tPA antigen and an increase in tPA activity (Eliasson, 1996; Wannamethee, 2002). As with an acute bout of exercise, research involving vWF adaptation to chronic exercise is limited.

The progression of fibrinolytic and blood coagulation markers in low risk pregnancy is well established. In addition, it is well understood that chronic exercise enhances an individual's fibrinolytic profile. Data has been collected regarding exercise in healthy sedentary and active non-pregnant populations, men and women, various disease populations (primarily CVD), but only one known study, not available in English, has investigated the fibrinolytic profile in relationship to exercise during pregnancy (KovalcÅ-kovÅj, 1975). The purpose of the current study was to (1) study differences in markers of blood coagulation and fibrinolysis based on trimester, in this cohort of women and (2) investigate the relationship between volume of physical activity, during pregnancy and postpartum, on blood coagulation potential (vWF) and fibrinolytic potential (tPA activity and antigen, and PAI-1).

Chapter III

Methodology

Research Design

This study had a cross-sectional design and investigated the predictive value of and relationship between physical activity and blood markers for fibrinolytic and blood coagulation potential in pregnant women.

Participants

Women aged 19-34 years living in the Harrisonburg-Rockingham County area and who were currently pregnant. A total of 23 women enrolled and completed this study.

Recruitment

Pregnant and postpartum women living in the city of Harrisonburg, Rockingham County, and Greater Shenandoah Valley, Virginia, were recruited for this study. Investigators met with staff from the Virginia Health Department, the Women Infant Children (WIC) program, local OB-GYN clinicians, and other community organizations to explain the study and recruit volunteers. Informational flyers were distributed on-site at all locations in both English and Spanish and a bulk email was sent out to all James Madison University faculty and staff. All interested individuals were asked to contact the Morrison Bruce Center for the Promotion of Physical Activity for Girls and Women (MBC) on the James Madison University campus or sign up at WIC/OB-GYN clinics to receive a call from the investigation team. Informed consent was obtained from every participant per the James Madison University Institutional Review Board.

Testing Appointment

Women were asked to complete one testing session, between 6am and 10 a.m. following an eight hour fast. After attaining the informed consent, participants were asked to complete a series of questionnaires, measurements, and a venous blood draw. In addition, gestational duration of pregnancy or postpartum were recorded during the appointment. All testing appointments were conducted at the Human Performance Laboratory at James Madison University.

<i>Questionnaire or Form</i>	<i>Appendix</i>
Informed Consent	A
Questionnaire for Blood Draw	B
Supplemental Participant Characteristics	C
Health History	D
Modifiable Activity	E

Anthropometric Measurements

Height was measured, without shoes, to the nearest 0.5 cm using a stadiometer (Seca Weighing and Measuring Systems; Hanover, MD). Weight was measured, without shoes and while wearing light clothing, on a physician type scale to the nearest 0.10 kg (Healthometer Inc.; Bridgeview, IL). Blood pressure was measured using a blood pressure cuff and stethoscope and taken at rest in a seated position (American Diagnostica; Stamford, CT). American College of Sports Medicine standardized procedures for obtaining resting blood pressure were followed (Thompson, 2010). Resting heart rate was taken manually palpating the pulse at the radial artery for 60 seconds.

Venous Blood Draw

Following an 8-hour fast, participants sat in a semi-recumbent position for 15 minutes before a blood sample via venapuncture of the antecubital vein was obtained. Approximately 9 mL of blood was obtained into one 4.5 mL, 0.11 M sodium citrate

collection tube and one 4.5 mL acidified citrate tube. Samples were immediately spun at 10,000 rpm for 20 min at 4°C. Platelet-poor plasma was stored at -80°C until assayed. tPA antigen and von-Willebrand factor antigen (vWF) were measured using enzyme-linked immunoabsorbent assays (ELISA), American Diagnostic and Diapharma, respectively. Tissue plasminogen activator inhibitor activity (tPA activity) and plasminogen activator inhibitor-1 (PAI-1) were measured using Trinity Biotech bio immunoassays. All values for tPA and PAI-1 were used as markers of fibrinolysis. Von Willebrand factor was used as a marker of blood coagulation.

Physical Activity Assessment

The Modifiable Activity Questionnaire (MAQ) was used to recall leisure time physical activity over the past 12 months (Kriska, 1990). Participants selected activities that they engage in from a list of 40 common activities and provided information regarding frequency (per week), duration (per session) of each activity. Results were used to indirectly determine metabolic equivalent (MET) minutes per week of leisure time physical activity (LTPA) by multiplying frequency by duration and estimated METs of each activity, determined by the Compendium of Physical Activity (Ainsworth). Participants were grouped according to whether they met American College of Obstetricians and Gynecologists (ACOG, 2002) and American College of Sports Medicine (Haskell, 2007) physical activity recommendations of 450 METmin/wk (or the equivalent of completed 150 minutes of moderate physical activity each week) at their current state of pregnancy/postpartum (“active”) or not (“sedentary”).

The MAQ has been widely used in the general population as well as in pregnant women (Cramp, 2009; Bauer, 2010) and has shown good validity and reliability in

studies using accelerometers and doubly labeled water (Kriska, 1990; Aaron, 1993; Aaron, 1995; Schulz, 1994). Bauer et al. (2010), compared assisted physical activity diary data during pregnancy and postpartum in 30 women during pregnancy and postpartum with a historical PA recall using the MAQ six years later. The MAQ showed a positive relationship with PAD results at 20 weeks gestation, 32 weeks gestation, and 12 weeks postpartum ($r=0.57$, $r=0.85$, and $r=0.86$ respectively, all $p<0.01$). Bauer's findings are comparable to MAQ validation studies (Kriska, 1990; Aaron, 1993; Aaron, 1995; Schulz, 1994).

Average daily step count using a modified placement of Walk (Walk 4 Life) pedometers was used as an objective measure of physical activity (Walk, Walk 4 Life Inc.). The pedometers were placed on the right midaxillary line at hip level to avoid angling due to a growing fetus and worn for 2 weeks to determine average steps/day. As current literature is inconclusive as to the best placement for pedometers in pregnant women (Ling, 2010), placement was determined by piloting various placement positions (back, right midaxillary line, pants pocket) in pregnant women. Women kept track of their daily step count using a logbook, provided and returned upon convenience of the participant. A total of 19/27 logbooks were returned and used for analysis. Women were categorized as "sedentary" (<5,000 steps/day) or "at least low active" (5,000+ steps/day) as an extension of classifications suggested by Tudor-Locke and Bassett in 2004 ("sedentary" = <5,000 steps/day, "low active" = 5,000 – 7,499 steps/day, "somewhat active" = 7,500 – 9,999 steps/day, and "active" = >10,000 steps/day).

Participant Compensation

For participation in this study, women received two books, an option of either keeping the pedometer or a free pack of diapers, and results from their individual blood tests. The books included the fifth edition of the American College of Obstetricians and Gynecologists' "Your Pregnancy and Childbirth: Month to Month" and the La Leche League's "The Breastfeeding Answer Book."

Reporting Procedures

Each participant had access to data pertaining to her individual measurements and blood test results at any time.

Data Analysis

Descriptive statistics were calculated for all participant variables using frequencies, means and standard deviations. T-tests were used to analyze mean differences in blood markers in the 2nd and 3rd trimesters.

We analyzed physical activity data using the following methods: multiple regression, ANCOVA, and linear regression. Forward stepwise multiple regression investigated whether gestational age, average METmin/wk, and average daily step count were possible predictive variables for PAI-1, tPA activity, tPA antigen, and vWF. ANCOVA analysis was used to determine models to effectively predict PAI-1, tPA activity, tPA antigen, and vWF using physical activity groupings ("active" and "sedentary" based on 450 METmin/wk recommendation; "at least low active" and "sedentary" based on step count classifications of 5,000 steps/day) and gestational age as potential predictors. Scatterplots were used to depict values of our dependent variables over gestational age. From these scatterplots, linear regression equations were used to

assess best fit lines among women meeting/not meeting physical activity recommendations/guidelines. Linear regression equations provided information regarding y-intercept and slope, allowing us to extrapolate pre-pregnancy levels of the dependent variable and analyze mean expected changes in these variables over time. A p value of <0.050 was used to determine statistical significance and a p value of <0.100 was considered to be approaching statistical significance for all statistical analyses.

Chapter IV

Manuscript

Abstract

Purpose: This study investigated the relationship between blood coagulation and fibrinolytic potential and physical activity. Physical activity levels to predict blood coagulation and fibrinolytic potential were also examined. **Methods:** Twenty-three pregnant women, aged 19-34 yrs, had a fasted blood draw between 6 and 10 a.m. analyzed for tPA antigen, tPA activity, PAI-1 antigen, and vWF antigen. Trimester specific volume of leisure time physical activity was assessed by the Modifiable Activity Questionnaire (MAQ) and converted to METmin/wk. Based on MAQ results, women were grouped as meeting (“active”) or not meeting (“sedentary”) physical activity recommendations established by American College of Obstetrics and Gynecology. Average daily step count was calculated from 2 week pedometer logs and women were categorized as “sedentary” (<5,000 steps/day) or “at least low active” (5,000+ steps/day) according to step count. **Results:** PAI-1 and tPA antigen were higher and tPA activity was lower during the 3rd trimester of pregnancy versus 2nd trimester. ANCOVA suggests gestational age produced an statistically significant model for predicting PAI-1, tPA activity, and tPA antigen, but not vWF; average METmin/wk and step count groupings did not produce a statistically significant model predicting PAI-1, tPA antigen, tPA activity, or vWF but approached statistical significance for tPA antigen (METmin/wk $p = 0.073$ and steps/day $p = 0.057$). METmin/wk predicted tPA antigen, during pregnancy, in a forward stepwise multiple regression. Linear regressions based on physical activity groups resulted in a significant y-intercept difference ($p=0.047$) for tPA antigen using

step count classifications. No significant y-intercept or slope differences were seen in vWF in relationship to volume of physical activity using a linear regression model.

Conclusion: It appears this is the first study to explore the relationship between hemostasis and volume of physical activity during pregnancy, thus providing an impetus for further cross sectional and longitudinal studies in this area. Future research is needed because pregnant women are predisposed to a number of thromboembolic complications and other health related issues related to hypercoagulation. Physical activity may enhance fibrinolytic and blood coagulation potential during pregnancy, as it can in non-pregnant adults.

Introduction

The blood coagulation and fibrinolytic cascades involve an intricate series of steps and reactions to either enhance the potential to produce fibrin (blood coagulation), the key protein in blood clots, or to break down fibrin (fibrinolysis). Pregnancy is defined as a hypercoagulant state, and is characterized by a decrease in fibrinolytic activity and an increase in blood coagulation enzymes, resulting in a 2-fold increase in coagulation potential in late pregnancy; in healthy women this hypercoagulant state is normalized 3-6 weeks postpartum (Choi, 2002; Kruithof, 1987).

The pattern of increased coagulation potential and reduced fibrinolytic capacity during pregnancy may protect pregnant women against the hemostatic challenges of placental separation (Bremme, 2003). However, these changes also present an increased risk for thromboembolic complications and hypercoagulability. The risk for pregnancy associated venous thromboembolism (VTE) increases 5.5-6 times compared to thromboembolism risk in non-pregnant women of childbearing age (McColl, 1997;

Macklon, 1996; McColl, 1999; Ishii, 1994). Pre-eclampsia, characterized by an altered state of hemostasis, is the second leading cause of death during pregnancy and predisposes women to an increase in coronary heart disease risk later in life (Walter, 2000; Sattar, 2002). The majority of miscarriages are associated with combination with coagulation issues and are specifically due to placental vessel thrombosis and infarction (Bick, 2000). Additionally, hemostatic disturbances may lead to poor maternal-fetal circulation and ultimately restrict fetal growth (Holmes, 2005; Greer, 2002; Greer, 2003) and markers of fibrinolytic inhibition (plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA) antigen) have been linked to gestational diabetes (Farhan, 2006; Morimitsu, 2007).

This issue is complicated by the fact that women are becoming pregnant at higher starting weights and gaining weight beyond healthy gestational recommendations (Huang, 2007; Waller, 2007). Obesity is known to increase cardiovascular disease risk and decrease fibrinolytic potential, increase coagulation potential, and increase atherosclerosis (Gaal, 2006) and being overweight/obese is a key risk factor of VTE (McColl, 1997; Macklon, 1996; McColl, 1999; Ishii, 1994). Fat cells synthesize and release PAI-1, inhibiting the body's potential to lyse blood clots. Obese individuals have greater PAI-1, and elevated fibrinogen levels and other coagulation factors versus healthy-weighted people (Rauramaa, 1999). Stewart et al. (2007) reported that obese women are in a greater coagulatory state during the first trimester of pregnancy due to fibrinolysis inhibition as seen in the PAI-1/PAI-2 ratio. Although this ratio improved among obese women as pregnancy advanced, inability to rebound from this impairment could explain elevated maternal risk of pre-eclampsia and hypertension (Stewart, 2007).

Participation in regular physical activity (PA) may help an individual reduce excess body fat and improve overall body composition (Thompson, 2009; HHS, 1996). In addition, regular PA is known to enhance the fibrinolytic profile (Regensteiner, 1995; Helmrich, 1991; Dempsey, 2004). Greater leisure time physical activity (LTPA) and endurance training have been shown to decrease PAI-1 and fibrinogen while enhancing tPA activity (Eliasson, 1996; Boman, 1994).

To date, it appears as though there has only been one study investigating the relationship between hemostasis and volume of physical activity during pregnancy. This study, by KovalcĀ-kovĀĭ (1975), is written in Slovak and not available in English, and thus little is known about the topic.

The purpose of the current study was to 1.) study markers of blood coagulation and fibrinolysis based on trimester, in pregnant women 2.) determine whether volume of physical activity predicts PAI-1, tPA activity, tPA antigen, and vWF in pregnancy and 3.) investigate the relationship between volume of physical activity during pregnancy on PAI-1, tPA activity, tPA antigen, and vWF. It was hypothesized that tPA activity would be lowest and tPA antigen, PAI-1, and vWF highest in the 3rd trimester and that the extent of hypercoagulation during pregnancy would be lower in physically active women, versus sedentary women at comparable gestational ages.

Methods

Research Design

This study had a cross-sectional design and investigated the predictive value of and relationship between physical activity and blood markers for fibrinolytic and blood coagulation potential in pregnancy women.

Participants

Women aged 19-34 years living in the Harrisonburg-Rockingham County area and who were currently pregnant were recruited to volunteer for this study. A total of 23 women enrolled and completed this study.

Testing Appointments

Women were asked to complete one testing session, between 6am and 10 a.m. following an eight hour fast. After attaining the informed consent, participants were asked to complete a series of questionnaires, measurements, and a venous blood draw. In addition, gestational duration of pregnancy or postpartum was recorded during the appointment. All testing appointments and measurements were conducted at the Human Performance Laboratory at James Madison University.

Anthropometric Measurements

Height was measured, without shoes, to the nearest 0.5 cm using a stadiometer (Seca Weighing and Measuring Systems; Hanover, MD). Weight was measured, without shoes and while wearing light clothing, on a physician type scale to the nearest 0.10 kg (Healthometer Inc.; Bridgeview, IL). Although pre-pregnancy BMI was calculated using self-report weight, current pregnancy BMI was not reported due to a small sample size that varied across gestational and postpartum age. Blood pressure was measured using a blood pressure cuff and stethoscope and taken at rest in a seated position (American Diagnostica; Stamford, CT). American College of Sports Medicine standardized procedures for obtaining resting blood pressure were followed (Thompson, 2010). Resting heart rate was taken manually palpating the pulse at the radial artery for 60 seconds.

Venous Blood Draw

Following an 8-hour fast, participants sat in a semi-recumbent position for 15 minutes before a blood sample via venapuncture of the antecubital vein was obtained. Approximately 9 mL of blood was obtained into one 4.5 mL, 0.11 M sodium citrate collection tube and one 4.5 mL acidified citrate tube. Samples were immediately spun at 10,000 rpm for 20 min at 4°C. Platelet-poor plasma was stored at -80°C until assayed. tPA antigen and von-Willebrand factor antigen (vWF) were measured using enzyme-linked immunoabsorbent assays (ELISA) from American Diagnostic and Diapharma, respectively. Tissue plasminogen activator inhibitor activity (tPA activity) and plasminogen activator inhibitor-1 (PAI-1) were measured using Trinity Biotech bio immunoassays. All values for tPA and PAI-1 were used as markers of fibrinolysis. vWF was used as markers of thrombosis and blood coagulation.

Physical Activity Assessment

The Modifiable Activity Questionnaire (MAQ) was used to recall leisure time physical activity over the past 12 months (Kriska, 1990). Participants selected activities that they engage in from a list of 40 common activities and provided information regarding frequency (per week), duration (per session) of each activity. Results were used to indirectly determine metabolic equivalent (MET) minutes per week of leisure time physical activity (LTPA) by multiplying frequency by duration and estimated METs of each activity, determined by the Compendium of Physical Activity (Ainsworth). Participants were grouped according to whether they met American College of Obstetricians and Gynecologists (ACOG, 2002) and American College of Sports Medicine (Haskell, 2007) physical activity recommendations of 450 METmin/wk (or the

equivalent of completed 150 minutes of moderate physical activity each week) at their current state of pregnancy (“active”) or not (“sedentary”).

The MAQ has been widely used in the general population as well as in pregnant women (Cramp, 2009; Bauer, 2010) and has shown good validity and reliability in studies using accelerometers and doubly labeled water (Kriska, 1990; Aaron, 1993; Aaron, 1995; Schulz, 1994). Bauer et al. (2010), compared assisted physical activity diary data during pregnancy and postpartum in 30 women during pregnancy and postpartum with a historical PA recall using the MAQ six years later. The MAQ showed a positive relationship with PAD results at 20 weeks gestation, 32 weeks gestation, and 12 weeks postpartum ($r=0.57$, $r=0.85$, and $r=0.86$ respectively, all $p<0.01$). Bauer’s findings are comparable to MAQ validation studies (Kriska, 1990; Aaron, 1993; Aaron, 1995; Schulz, 1994).

Average daily step count using a modified placement of Walk (Walk 4 Life) pedometers was used as an objective measure of physical activity (Walk, Walk 4 Life Inc.). The pedometers were placed on the right midaxillary line at hip level to avoid angling due to a growing fetus and worn for 2 weeks to determine average steps/day. As current literature is inconclusive as to the best placement for pedometers in pregnant women (Ling, 2010), placement was determined by piloting various placement positions (back, right midaxillary line, pants pocket) in pregnant women. Women kept track of their daily step count using a logbook, provided and returned upon convenience of the participant. A total of 19/23 logbooks were returned and used for analysis. Women were categorized as “sedentary” ($<5,000$ steps/day) or “at least low active” ($5,000+$ steps/day) as an extension of classifications suggested by Tudor-Locke and Bassett in 2004

(“sedentary” = <5,000 steps/day, “low active” = 5,000 – 7,499 steps/day, “somewhat active” = 7,500 – 9,999 steps/day, and “active” =>10,000 steps/day).

Data Analysis

Descriptive statistics were calculated for all participant variables using frequencies, means and standard deviations. T-tests were used to analyze mean differences in blood markers in the 2nd and 3rd trimesters.

We analyzed physical activity data using the following methods: multiple regression, ANCOVA, and linear regression. Forward stepwise multiple regression investigated whether gestational age, average METmin/wk, and average daily step count were possible predictive variables for PAI-1, tPA activity, tPA antigen, and vWF. ANCOVA analysis was used to determine models to effectively predict PAI-1, tPA activity, tPA antigen, and vWF using physical activity groupings (“active” and “sedentary” based on 450 METmin/wk recommendation; “at least low active” and “sedentary” based on step count classifications of 5,000 steps/day) and gestational age as potential predictors. Scatterplots were used to depict values of our dependent variables over gestational age. From these scatterplots, linear regression equations were used to assess best fit lines among women meeting/not meeting physical activity recommendations/guidelines. Linear regression equations provided information regarding y-intercept and slope, allowing us to extrapolate pre-pregnancy levels of the dependent variable and analyze mean expected changes in these variables over time. A p value of <0.050 was used to determine statistical significance and a p value of <0.100 was considered to be approaching statistical significance for all statistical analyses.

Results

Participants

Twenty-three pregnant women completed this study (mean age 26.09 ± 3.67 , range 20 – 33 years). Two women were in the 1st trimester, 12 were in the 2nd semester and 9 in the 3rd trimester at the time of their measurement session. Mean pre-pregnancy BMI, assessed using self-reported weight, was 23.54 ± 3.50 kg/m² (range 19.27 – 31.92 kg/m², n = 21). Additional participant characteristics can be found in Table 6.

Table 6. Participant characteristics.

Characteristic	n	%
Number of previous births		
0	14	60.9
1	6	26.1
No response	3	13.0
Race		
White (non-Hispanic)	18	78.3
Hispanic	3	4.3
American Indian/Alaska Native	1	13.0
Asian or Pacific Islander	1	4.3
Marital Status		
Never married	3	13.0
Married or living with partner	20	87.0
Household Income		
< \$20,000	7	30.4
\$20,000 – \$49,000	3	13.0
\$50,000 – \$79,999	7	30.4
\$80,000+	6	26.1
Educational level		
No high school diploma or GED	1	4.3
High school diploma or GED	2	8.7
Training beyond high school but no degree	3	13.0
Two year associate degree	3	13.0
At least one 4-year college degree	7	30.4
At least one graduate degree	7	30.4

Physical Activity

Prior to pregnancy, 95.7% of women met physical activity recommendations and 65.2% of women met recommendations during their current trimester of pregnancy. Classified by step count (n=19), 53.2% women were considered “sedentary” and 36.8% of women “at least low active” during pregnancy. There was a statistically significant

correlation of $r = 0.602$ ($p = 0.006$) between average METmin/wk at the current stage of pregnancy and average daily step count.

Fibrinolytic and Blood Coagulation Markers during Pregnancy and Postpartum

Results for all blood markers were normally distributed. Independent t-tests were run to indicate differences in means between the 2nd and 3rd trimester (Table 7). Mean PAI-1, tPA activity, and tPA antigen showed statistically significant differences between 2nd and 3rd trimester; PAI-1 and tPA antigen were higher and tPA activity was lower in the 3rd trimester versus the 2nd trimester. No statistical differences were found for vWF, though values were higher in 3rd trimester versus 2nd trimester. Lack of statistical significance for vWF may be due to a small sample size which resulted in large standard deviations.

Table 7. Fibrinolytic and blood coagulation variables during the 2nd and 3rd trimester of pregnancy.

Variable	2 nd Trimester (n=11)*	3 rd Trimester (n=9) [†]
PAI-1 (IU/mL)	8.41±5.43	22.91±5.27 ^a
tPA Activity (IU/mL)	0.49±0.26	0.20±0.14 ^a
tPA Antigen (ng/mL)	2.81±1.50	5.11±1.09 ^a
vWF (%)	124.30±39.37	155.71±46.08

*n=12 for tPA antigen, [†]n=7 for PAI-1, ^ap<0.05 vs 2nd trimester

ANCOVA and multiple regression results suggest that gestational age influence PAI-1, tPA activity, and tPA antigen (PAI-1 and tPA antigen are higher and tPA activity lower with increased gestational age; Tables 8 and 9). Gestational age approached statistical significance ($p = 0.088$) as a predictor of vWF in the ANCOVA model using physical activity recommendations, but not in the model using step count classifications.

Table 8. Significance levels based on ANCOVA analysis of fibrinolytic and blood coagulation variables as consequence of time (weeks gestation) and meeting physical activity recommendations/being classified as “at least low active” (A = 450 METmin/wk, B = 5,000 steps/day). All values listed are p values.

Variable	Weeks Gestation (A)	Meeting Recommendations (A)	Weeks Gestation (B)	Meeting “At least low active” Classification (B)
PAI-1 (IU/mL)	<0.001*	0.772	<0.001*	0.175
tPA Activity (IU/mL)	<0.001*	0.607	<0.001*	0.105
tPA Antigen (ng/mL)	0.006*	0.073 [^]	0.007*	0.057 [^]
vWF (%)	0.088 [^]	0.948	0.263	0.226

* = p value <0.050, [^]=p value <0.100 (approaching statistical significance)

Table 9. Multiple regression analysis of fibrinolytic and blood coagulation variables as using weeks gestation, average METmin/wk, and average daily step count as possible predictors. Average METmin/wk were calculated using data from each participant’s current trimester.

Variable	Regression equation	R ²	p value
PAI-1 (IU/mL)	-11.285 + 1.040(weeks gestation)	0.844	<0.001
tPA Activity (IU/mL)	1.195 – 0.032(weeks gestation)	0.569	<0.001
tPA Antigen (ng/mL)	2.001 + 0.096(weeks gestation) – 0.001(METmin/wk)	0.598	0.001
vWF (%)	No equation based off listed predictors	N/A	N/A

Volume of Physical Activity and Fibrinolytic and Blood Coagulation Markers

Meeting physical activity recommendations or being classified as “at least low active” did not significantly predict any of the fibrinolytic or blood coagulation variables based on ANCOVA results (Table 8). Additionally, no significant slope differences were seen among blood coagulation or fibrinolytic markers in relationship to volume of physical activity. A statistically significant difference in y intercept (p=0.047) was found for tPA activity; “at least low active” women had a larger y intercept value versus women classified as sedentary.

Table 10. Differences in slope and y intercept of fibrinolytic and blood coagulation variables during pregnancy based on whether women met physical activity recommendations/ were classified as “at least low active” (A = 450 METmin/wk, B = 5,000 steps/day).

Variable	Slope difference (A)	Y intercept difference (A)	Slope difference (B)	Y intercept difference (B)
PAI-1 (IU/mL)	0.026 (p=0.929)	0.029 (p=0.997)	0.206 (p=0.504)	0.575 (p=0.930)
tPA Activity (IU/mL)	0.013 (p=0.329)	0.392 (p=0.279)	0.033 (p=0.101)	0.871 (p=0.047)*
tPA Antigen (ng/mL)	0.013 (p=0.871)	1.551 (p=0.469)	0.069 (p=0.523)	0.092 (p=0.967)
vWF (%)	0.695 (p=0.778)	19.022 (p=0.774)	4.209 (p=0.207)	58.048 (p=0.411)

* = p value < 0.050

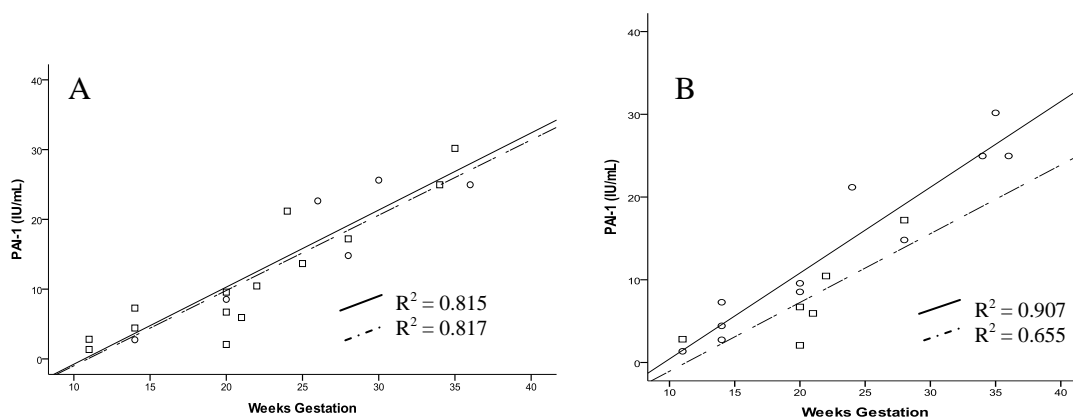


Figure 2. Plasminogen Activator Inhibitor-1 (PAI-1) throughout gestation based on volume of current physical activity. Estimation is based on meeting (\square , dotted line) versus not meeting (\circ , solid line) physical activity recommendations of 450 METmin/wk (A) and step count classifications of 5,000 steps/day (B).

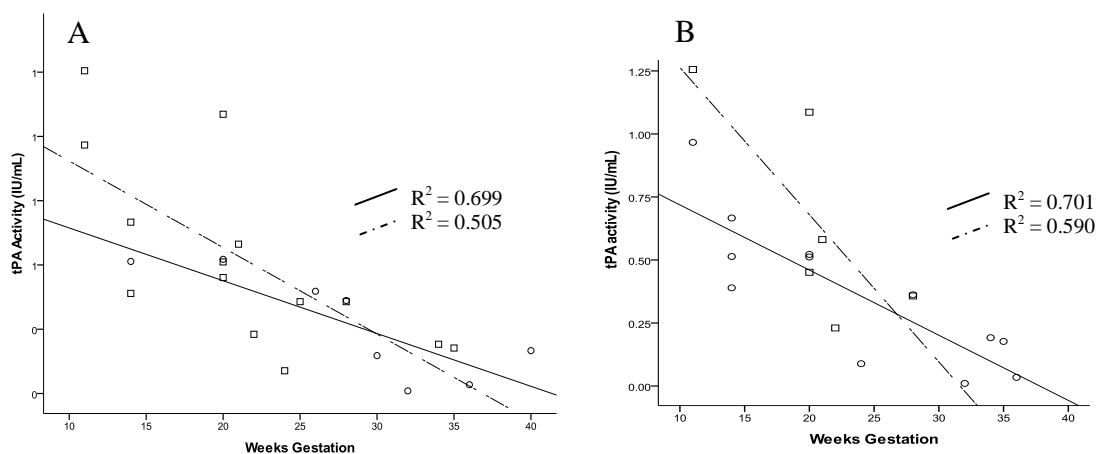


Figure 3. Tissue-type Plasminogen Activator activity (tPA activity) throughout gestation based on volume of current physical activity. Estimation is based on meeting (\square , dotted line) versus not meeting (\circ , solid line) physical activity recommendations of 450 METmin/wk (A) and step count classifications of 5,000 steps/day (B).

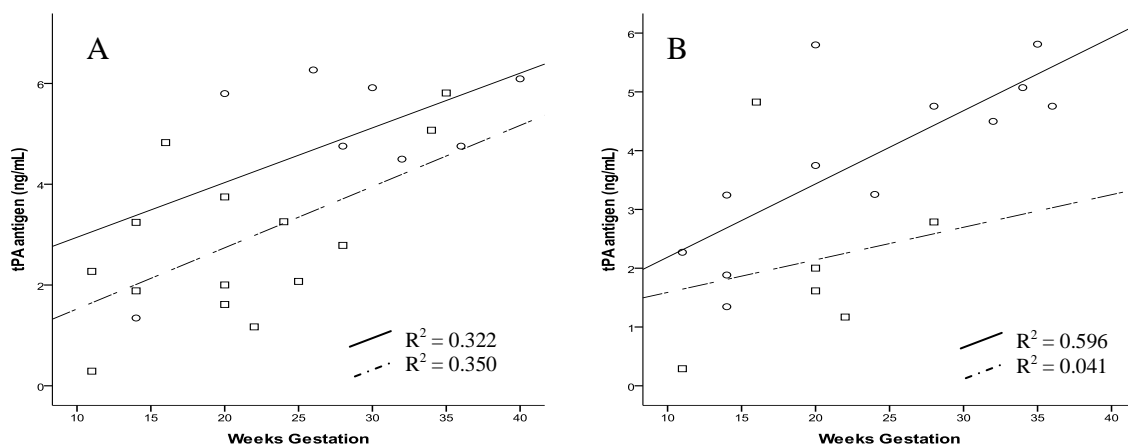


Figure 4. Tissue-type Plasminogen Activator antigen (tPA antigen) throughout gestation based on volume of current physical activity. Estimation is based on meeting (□, dotted line) versus not meeting (○, solid line) physical activity recommendations of 450 METmin/wk (A) and step count classification of 5,000 steps/day (B).

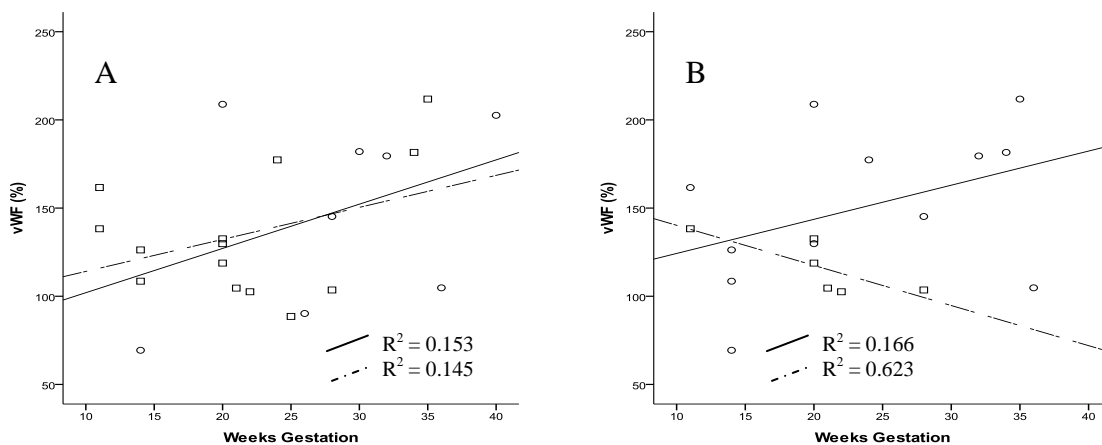


Figure 5. vonWillebrand factor (vWF) throughout gestation based on volume of current physical activity. Estimation is based on meeting (□, dotted line) versus not meeting (○, solid line) physical activity recommendations of 450 METmin/wk (A) and step count classification of 5,000 steps/day (B).

Discussion

Fibrinolytic Activity

Trimester-specific Values and Patterns during Pregnancy

Statistically significantly lower mean values of tPA activity were found in the 3rd trimester versus the 2nd trimester of pregnancy. In addition, ANCOVA results suggest that gestational age negatively affects tPA activity and multiple regression data shows that gestational age is a predictor of tPA activity. Together, these findings support the hypothesis that fibrinolytic activity would be lowest at the end of pregnancy. Our findings are also in agreement with previous longitudinal data showing a reduction in tPA activity with each trimester of pregnancy and a normalization towards pre-pregnancy values postpartum (Kjellberg, 1999). This data provides modest support for the idea that tPA activity is affected by gestational age and this is most apparent in the late stages of pregnancy.

tPA Activity and Volume of Physical Activity

Multiple regression analysis and ANCOVA models show that meeting physical activity recommendations and being classified as “at least low active” did not have a significant effect on predicting tPA activity. There was a statistically significant difference in y intercept in tPA activity after grouping women by step count that was similar in pattern but not significant when grouping women by METmin/wk. In both cases, y intercept was greater in the physically active group versus the sedentary group, implying that tPA activity is higher pre-pregnancy among physically active individuals.

Our findings are inconsistent with the hypothesis that tPA activity would be enhanced in active pregnant women, versus sedentary pregnant women, at any point

during pregnancy. Research has previously been conducted investigating the relationship between physical activity and tPA activity, independent of pregnancy. Among non-pregnant women aged 25-64 years, Eliasson et al. (1996) found that tPA activity was enhanced due to increased volumes of physical activity. Our finding that y intercept was greater among women meeting physical activity recommendations and classified as “at least low active” suggests that women who are active at time of conception have greater fibrinolytic potential than their sedentary counterparts. Though consistent with the idea of increased tPA activity due to physical activity (Eliasson, 1996) and the hypothesis that active women would start pregnancy with higher tPA activity levels than sedentary women, the findings of this study did not determine that physical activity during pregnancy affects tPA activity levels.

Fibrinolytic Inhibition

Trimester-specific values and Patterns during Pregnancy

Our results indicate that PAI-1 and tPA antigen are were statistically significantly for a higher mean 3rd trimester value versus the 2nd trimester mean. Additionally, ANCOVA results suggest that PAI-1 and tPA antigen values are positively affected by gestational age and multiple regression found gestational age to be a statistically significant predictor of PAI-1 and tPA antigen. This heightened state of fibrinolytic inhibition seen with the advancement of pregnancy is consistent with our hypothesis of greatest fibrinolytic inhibition in the 3rd trimester and previous literature suggesting an increase in PAI-1 and tPA antigen as pregnancy progresses (Choi, 2002; Cerneca, 1997).

Fibrinolytic Inhibition and Volume of Physical Activity

ANCOVA indicated no statistical significance for meeting physical activity recommendations or being classified as “at least low active” predicting tPA antigen or PAI-1; however, tPA antigen approached statistical significance under both conditions ($p = 0.073$ and 0.057 , respectively). Further, multiple regression analysis resulted in a statistically significant model in which gestational age and average MET_{min}/wk at the current trimester of pregnancy predicted tPA antigen. The multiple regression equation suggests that tPA antigen increases by an average of 0.096 ng/mL every week during pregnancy but decreases by an average of 0.001 for every additional MET_{min} of physical activity. No statistically significant differences were found in slope or y intercept of tPA antigen or PAI-1 when grouped by meeting physical activity recommendations or being classified as “at least low active.”

Previous research has indicated that as level of physical activity increases, fibrinolytic inhibition, as observed by tPA antigen and PAI-1 levels, decreases in non-pregnant adults (Wanamethee, 1996; 2002). However, in pregnant women, increased fibrinolytic inhibition has been indicated as a consequence of increased gestational age, independent of volume of physical activity (Choi, 2002; Cerneca, 1997). Due to these conflicting relationships, our hypothesis was that tPA antigen and PAI-1 would be lower at the start of pregnancy in active women and the slope of increase would be diminished versus sedentary women as pregnancy progressed. Our multiple regression results support the idea that tPA antigen will be higher at greater gestational ages, but that this increase in tPA antigen will be diminished by increased activity levels. This finding is novel and suggests that physical activity may attenuate the progression of a

hypercoagulant state in pregnancy, which predisposes women to a number of health conditions, such as miscarriage, pre-eclampsia, intrauterine growth restriction, venous thromboembolism, and diabetes. The lack of significant findings for PAI-1 is potentially due to our small sample size. Another potential explanation is that majority of women in this study entered pregnancy meeting ACOG physical activity recommendations. Therefore, the study lacked a true “sedentary” group which would have been beneficial during the ANCOVA analysis. Instead, we possessed a group of women who were active pre-pregnancy and decreased activity during pregnancy.

Blood Coagulation

Trimester-specific Values and Patterns during Pregnancy

Mean vWF values between 2nd and 3rd trimester were not statistically different and multiple regression results found that gestational age did not predict vWF levels. ANCOVA results approached significance ($p = 0.088$) an effect of gestational age on vWF using the physical activity recommendations model but not the step count classification model. Taken as a whole, these findings do not support the hypothesis that blood coagulation would be highest in the 3rd trimester or previous studies that have established that vWF increases with increasing gestational age (Wickstrom, 2004; Clark, 1998; Sie, 2003). Clark et al. (1998) found a non-linear, direct relationship between vWF and gestational age in a cross sectional of 239 healthy pregnant women. If the progression of vWF during pregnancy is non-linear, as Clark et al. (1998) suggested, having a larger number of participants broken down into smaller ranges of gestation age (e.g. 6-12 weeks gestation, 13-19 weeks gestation, etc.) may help in understanding the

pattern of blood coagulation, as seen through vWF, during pregnancy. ANCOVA results suggest that a pattern of increased vWF with increasing gestation age may occur, though in this study we are likely to have too few participants for this pattern to be evident.

Blood Coagulation and Volume of Physical Activity

The ANCOVA indicates that vWF is not predicted by meeting physical activity recommendations or being classified as “at least low active.” Additionally, no statistical differences in y intercept or slope were found when the women were grouped. This implies that there was no difference in vWF prior to pregnancy or in estimated vWF based on gestational age in “active” and “sedentary” women. The reader should be cautioned that this slope analysis was based off cross-sectional data from a small sample size.

The current findings are in opposition with the hypothesis that women meeting physical activity recommendations and being classified as “at least low active” would have vWF values that were lower at the start of pregnancy and would have a smaller positive slope of increase in comparison their sedentary counterparts. Previous literature has determined an inverse relationship between physical activity and markers of blood coagulation, including vWF, independent of pregnancy (Yarnell, 2000; Lakka, 1993; Abramson, 2002; Wannameethee, 2002; Panagiotakos, 2005). However, blood coagulation potential is known to increase with the progression of pregnancy (Wickstrom, 2004; Clark, 1998; Sie, 2003). This increase in blood coagulation potential is important in late pregnancy, as it may protect pregnant women against the hemostatic challenges of placental separation (Bremme, 2003).

Study Limitations and Importance of Future Research

Our study is limited as a small, cross-sectional study with participants spread throughout pregnancy and postpartum and no control data from age-matched, healthy, non-pregnant women. With this design and small study population it is difficult to determine if there is a relationship between volume of physical activity, during pregnancy and postpartum, on blood coagulation and fibrinolytic potential.

Another limitation of this study and this area of research is that although normal ranges for tPA antigen, tPA activity, PAI-1, vWF, and fibrinogen in women exist, no clinical cut points exist for the many markers of fibrinolysis and blood coagulation for any population. A further assessment of these blood markers, beyond a comparison to values found in previous studies, is needed as pregnant women are predisposed to health related issues related to hypercoagulation including miscarriage, pre-eclampsia, venous thromboembolism, intrauterine growth restriction, and diabetes (Greer, 2003). Determining cut points for these markers may provide a considerable advantage to clinicians in being able to recognize and possibly treat potential problems related to hypercoagulation during pregnancy as well as in the general population.

In addition to physical activity, BMI has the potential to affect hemostasis in the general population and in pregnant women (Stewart, 2007). It is possible that physical activity has an effect on hemostatic variables during pregnancy that we are able to address currently. Findings of this study are limited to the demographics of the participants, who had a pre-pregnancy BMI that would be considered healthy and of which 95.7% of pregnant women were physically active (exceeding METmin/wk physical activity recommendations) pre-pregnancy. Though multiple regression

suggested that volume of physical activity (METmin/wk) helps predict tPA antigen during pregnancy, no effect of volume of physical activity during pregnancy on hemostatic variables was found in the other blood markers in this group of women who were primarily active prior to pregnancy and either maintained or decreased activity during pregnancy; this question should be further studied in larger cross-sectional and longitudinal studies. Specifically, the effect of volume of physical activity on fibrinolytic and blood coagulation markers in a group of women who are sedentary pre-pregnancy and remain inactive, sedentary pre-pregnancy and become active, active pre-pregnancy and decrease physical activity, and active pre-pregnancy and remain active through pregnancy should be evaluated in concert with pre-pregnancy BMI/body fat levels and whether women meet or exceed weight gain recommendations during pregnancy.

The MAQ has been validated for pregnant women ($r=0.57-0.86$), and though objective data would be preferable over questionnaire data, our objective measure of physical activity involved the utilization of a non-validated pedometer placement and daily step count information was not received from all participants. There was though, a moderate, significant correlation between MAQ and step count data. Still, accelerometer data (to assess volume of physical activity) may be more telling objective measures of physical activity in this population.

In this study, we classified participants by the volume of physical activity they were accruing and then determined whether they were meeting or not meeting physical activity recommendations. Further classifications, such as those proposed by Tudor-Locke and Bassett in terms of 4 classifications of activity level based on average daily step count, may help further answer the question of what level or volume of physical

activity creates differences in the progression of hemostatic variables throughout pregnancy and postpartum, if differences do exist. Accelerometer data or fitness assessment data (VO_{2max} estimations, etc.) could add important information to help further classify level or volume of physical activity during pregnancy and postpartum.

Conclusion

Other than one study by KovalcÅ-kovÅj, published in 1975 (not available in English), it appears as though this is this the first study to explore the relationship between hemostasis and volume of physical activity in pregnant women. The finding that physical activity (METmin/wk) is predictive of tPA antigen in pregnant women is novel and suggests that physical activity may help attenuate the extent of hypercoagulation seen in normal pregnancy. This finding and the current study may help provide an impetus for future studies to continue investigating the relationship and predictive values of physical activity during pregnancy on markers of fibrinolytic and blood coagulation potential. Additional studies are needed as pregnant women are predisposed to a number of thromboembolic complications and other health related issues related to hypercoagulation including miscarriage, pre-eclampsia, venous thromboembolism, intrauterine growth restriction, and diabetes (Greer, 2003).

Chapter V

Conclusion

Healthy pregnancy is characterized by increased plasminogen activator inhibitor-1 (PAI-1), tissue-type plasminogen activator (tPA) antigen, and vonWillebrand factor (vWF) and an decreased tPA activity beyond pre-pregnancy levels. These markers return to pre-pregnancy levels after delivery (Choi & Pai, 2002; Holmes, 2005; Hellgren, 2003; Bellart et al. 1998; Comeglio et al. 1996). The pattern of increased coagulation potential and reduced fibrinolytic capacity during pregnancy may protect pregnant women against the hemostatic challenges of placental separation (Bremme, 2003). However, these changes also present an increased risk for thromboembolic complications and hypercoagulability.

Regular physical activity is known to enhance the fibrinolytic profile and reduce blood coagulation potential (Regensteiner, 1995; Helmrigh, 1991; Dempsey, 2004; Womack, 2003; El-Sayed, 2004). Greater leisure time physical activity (LTPA) and endurance training have been shown to decrease PAI-1 while enhancing tPA activity (Eliasson, 1996; Boman, 1994). Other than one study by KovalcÅ-kovÅj, published in 1975 and not available in English, it appears as though this is this the first study to explore the relationship between hemostasis and volume of LTPA during pregnancy.

The current study had a cross-sectional design and investigated the relationship between blood markers for fibrinolytic and blood coagulation potential and LTPA during pregnancy and postpartum. Twenty three women aged 19-34 living in the Harrisonburg-Rockingham County area and who were currently pregnant enrolled and completed this

study. Women completed one fasted testing session, between 6am and 10am, in which a blood draw was taken for PAI-1, tPA antigen, tPA activity, and vonWillebrand factor.

The Modifiable Activity Questionnaire (MAQ) was used to recall leisure time physical activity over the past 12 months (Kriska, 1990). Results were used to indirectly determine metabolic equivalent (MET) minutes per week of leisure time physical activity (LTPA). Participants were grouped according to whether they met American College of Obstetricians and Gynecologists (ACOG, 2002) and American College of Sports Medicine (Haskell, 2007) physical activity recommendations of 450 METmin/wk (or the equivalent of completed 150 minutes of moderate physical activity each week) at their current state of pregnancy (“active”) or not (“sedentary”). Average METmin/wk for each woman’s current state of pregnancy was also used in multiple regression analysis.

In addition, average daily step count using a modified placement of Walk (Walk 4 Life) pedometers was used as an objective measure of physical activity (Walk, Walk 4 Life Inc.). Women were categorized as “sedentary” (<5,000 steps/day) or “at least low active” (5,000+ steps/day) as an extension of classifications suggested by Tudor-Locke and Bassett (2004). Average daily step count was also used in multiple regression analysis.

We found that fibrinolytic inhibition (PAI-1, tPA antigen) was higher and fibrinolytic potential (tPA activity) was lower during the 3rd trimester of pregnancy versus 2nd trimester. ANCOVA suggests that while gestational age played a highly significant effect on PAI-1, tPA activity, and tPA antigen when analyzed by physical activity recommendations and classifications, meeting physical activity recommendations did not have a significant effect on predicting any of the fibrinolytic or blood coagulation

variables, though tPA antigen approached significance under both physical activity conditions. Significance was found in the multiple regression analysis as volume of physical activity (METmin/wk) predicted tPA antigen during pregnancy. Using a linear regression model, no significant y intercept or slope differences were seen in blood coagulation in relationship to volume of physical activity. A significant difference in y intercept ($p=0.047$) was found for tPA antigen; “at least low active” women had a larger y intercept than “sedentary” women.

Our study is limited as a small, cross-sectional study with participants spread throughout pregnancy and no control data from age-matched, healthy, non-pregnant women. With this design and numbers, it was difficult to determine the relationship between volume of physical activity during pregnancy on blood coagulation and fibrinolytic potential. Regardless, other than one study by KovalcĀ-kovĀĵ, published in 1975 and not available in English, it appears as though this is this the first study to explore the relationship between hemostasis and volume of physical activity during pregnancy. Future research is needed, due to the predisposition of pregnant woman to a number of thromboembolic complications and other health related issues related to hypercoagulation including miscarriage, pre-eclampsia, venous thromboembolism, intrauterine growth restriction, and diabetes (Greer, 2003) and the potential for physical activity to enhance fibrinolytic and blood coagulation potential, as it has in non-pregnant adults (Eliasson, 1996; Wannamethee, 2002; Womack, 2003; El-Sayed, 2004).

The effect of volume of physical activity on fibrinolytic and blood coagulation markers in a group of women who are sedentary pre-pregnancy and remain inactive, sedentary pre-pregnancy and become active, active pre-pregnancy and decrease physical

activity, and active pre-pregnancy and remain active through pregnancy should be evaluated in concert with BMI or body fat levels. Additional classifications of physical activity level should also be utilized when answering these questions. Accelerometer data or fitness assessment data (VO_{2max} estimations, etc.) could add important information to help further classify level or volume of physical activity during pregnancy and postpartum.

Appendix I

Consent to Participate in Research

Identification of Investigators & Purpose of Study

You are being asked to participate in the Fit-Minded Mamas (Madres Saludables) research study conducted by Dr. Judith A. Flohr, Kelly Mattran, and Christine Nicewonger from James Madison University. The purpose of this study is to look at how volume of physical activity during pregnancy and/or right after child birth changes is related to blood sugar and the blood's ability to form and break down blood clots. This information is important because it helps us provide researchers with information on factors that increase or decrease an individual's risk for diabetes and/or heart disease. This study will contribute to the researchers' completion of their master's theses.

Research Procedures

Should you decide to participate in this research study, you will be asked to sign this consent form once all your questions have been answered to your approval. This study consists of ONE testing session and the completion of a 2-week pedometer log. The testing session involves filling out forms related to physical activity and your feelings toward physical activity; measurements including height, weight, hip/waist circumferences, and blood pressure; and a blood draw. The blood will be tested for the factors/chemicals that help control blood sugar levels and influence your risk for diabetes (the chemicals/factors are blood lipids, hemoglobin A1c (HbA1c), fasted insulin, fasted glucose) and factors that control how quickly your blood clots (the factors are, tPA activity, tPA antigen, PAI-1, von Willebrand factor, and fibrinogen). The 2-week pedometer log is a form where you will record the number of steps you take each day, measured by a small device called a pedometer, which will be provided.

Time Required

Participation in this study will require a total of approximately 90 minutes of your time. The test session may take up to an hour of your time. Filling out the pedometer logs and turning them in is intended to take less than 30 minutes (spread out over the two week measurement period). We may also contact you, via phone, following this study, to ask you questions about your study experience.

Risks

The investigators do not see more than minimal risks from your involvement in this study. Trained phlebotomists from the JMU Department of Kinesiology and/or JMU Health Center will be utilized for all blood draws in which ~3 Tablespoons of blood will be taken. The blood draws are of no greater risk than any other blood draw which would normally occur during pregnancy. Safety procedures will be followed during the blood draw, including that the researchers will wear non-latex gloves. After use, sharp objects will be placed in a sharps biohazard container and any other biohazard material will go in a biohazard bag to be discarded at Rockingham Memorial Hospital. Following each blood draw, the area where your blood draw was taken will be cleaned and bandaged.

Benefits

Potential benefits from participation in this study include obtaining all blood work results. In addition, participants will be provided with a pedometer (a device that counts the number of steps you take). Participants will also receive pregnancy-related reading materials to keep after the 2-week pedometer log is completed and returned to us.

Confidentiality

The results of this research will be presented at Masters' thesis defenses. The results of this project will be coded in such a way that the respondent's identity will not be attached to the final form of this study. The researcher retains the right to use and publish non-identifiable data. While individual responses are confidential, aggregate data will be presented representing averages or generalizations about the responses as a whole. All data will be stored in locked file cabinets accessible only to the researchers. Personal information will be stored separately from files with data items, and identification numbers will replace participant names on all questionnaires in which signatures are not required. Upon completion of the study, all information that matches up individual respondents with their answers will be destroyed.

Participation & Withdrawal

Your participation is entirely voluntary. You are free to choose not to participate. Should you choose to participate, you can withdraw at any time without consequences of any kind.

Questions about the Study

If you have questions or concerns during the time of your participation in this study, or after its completion or you would like to receive a copy of the final aggregate results of this study, please contact:

Kelly Mattran	Christine Nicewonger	Dr. Judith A. Flohr
Department of Kinesiology Kinesiology James Madison University University 540-568-4348 mattraka@dukes.jmu.edu	Department of Kinesiology James Madison University 540-568-4348 nicewocm@ad.jmu.edu	Department of James Madison 540-568-3448 flohrja@ad.jmu.edu

Questions about Your Rights as a Research Subject

Dr. David Cockley
Chair, Institutional Review Board
James Madison University
(540) 568-2834
cocklede@jmu.edu

Giving of Consent

I have read this consent form and I understand what is being requested of me as a participant in this study. I freely consent to participate. I have been given satisfactory

answers to my questions. The investigator provided me with a copy of this form. I certify that I am at least 18 years of age.

Name of Participant (Printed)

Name of Participant (Signed)

Date

Name of Researcher (Signed)

Date

Appendix II

ID # _____ Date _____

Questionnaire for Blood Draws

1. Have you consumed alcoholic beverages within the last 24 hours? _____
2. Have you used nicotine within the last 10 hours? _____
3. Have you consumed any food or drink, except water, within the last 10 hours? _____
4. Have you had any infection, fever, or illness within the last week? _____
5. Have you taken any medication, vitamins, or other nutritional/herbal supplements within the last 12 hours? _____

If yes to any question, please explain:

Appendix III

Fit-Minded Mamas: Supplemental Participant Characteristics

If you are CURRENTLY PREGNANT:

How far along are you in your current pregnancy? _____ wks

___ 1st Trimester ___ 2nd Trimester ___ 3rd Trimester

When are you due? _____ (m/d/y)

**Please fill in ONE
of these two boxes****If you are NOT CURRENTLY PREGNANT (postpartum):**

How old is your most recent child? _____ months

How old were you when you last gave birth? _____ yrs

How much weight did you gain while you were pregnant? _____ lbs

How much did you weigh before you became pregnant? _____ lbs

Have you had previous births? ___ yes ___ no

a. If yes, how many? _____

**EVERYONE
ANSWER THESE
QUESTIONS**

1. What country were you born in? _____
2. What is your race/ethnicity? (check all that apply)
 - ___ White (non-Hispanic)
 - ___ Black (non-Hispanic)
 - ___ Am Indian/Alaskan Native
 - ___ Hispanic
 - ___ Asian or Pacific Islander
 - ___ Other: _____
3. Which of the following best describes where you live? (Please check one)
 - ___ City of Harrisonburg
 - ___ Rockingham County
4. Do you feel like there are safe and easily accessible walking routes to and from your house?
 - ___ Yes ___ No
5. Which of the following best describes your current work status? (Please check one)
 - ___ I am **NOT** employed outside the home
 - ___ I am employed part time (less than 35 hours a week)
 - ___ I am employed fulltime outside the home (35 hours or more a week)
 - ___ I operate a home based business
6. Which of the following best describes your average household income? (Please check one)
 - ___ < \$20,000 ___ \$20,000-49,999
 - ___ \$50,000-79,999 ___ \$80,000+
7. Which of the following best describes your highest educational status? (Please check one)
 - ___ I have **NOT** received a high school diploma or a GED.
 - ___ I have a high school degree or a GED
 - ___ I have a two-year associate degree.
 - ___ I have education training beyond high school, but I **DO NOT** have a college degree.
 - ___ I have received at least one, four-year college degree (ie. Bachelors degree)
 - ___ I have received at least one graduate degree (ie. Masters degree, PhD, MD, etc.)
8. Which of the following best describes your current marital status? (Please check one)
 - ___ Never married ___ Widowed
 - ___ Divorced/separated ___ Married or living with partner

Appendix IV

Health History Questionnaire

Instructions: Complete each question accurately. All information provided is **confidential**.

Part I: Demographic Information

1. _____
Subject ID Number
2. _____
Date
3. _____
Local Phone
4. Email: _____
5. Sex (circle one) Male Female
6. Date of Birth _____
Month/ Day/ Year

Part II: Medical History

7. Circle any that died of heart attack before age 50: Father Mother Brother Sister Grandparent
8. Date of last medical exam: _____ Last physical fitness test: _____
9. Circle operations you have had: Back Heart Kidney Eyes Joint Neck Ears Hernia Lung Other _____
10. Please circle any of the following for which you have been diagnosed or treated by a physician or health professional:

Alcoholism	Diabetes	Kidney Problems
Anemia (sickle cell)	Emphysema	Mental Illness
Anemia (other)	Epilepsy	Muscular Injury
Asthma	Eye Problems	Neck Strain
Back Strain	Gout	Obesity
Bleeding trait	Hearing Loss	Orthopedic Injuries
Bronchitis, chronic	Heart Problem	Phlebitis
Cancer	High Blood Pressure	Rheumatoid arthritis
Cirrhosis, liver	Hypoglycemia	Stroke
Concussion	Hyperglycemia	Thyroid problem
Congenital defect	Infectious Mononucleosis	Ulcer
Other _____		

11. Circle all medications taken in the last six months:

Blood thinner	Epilepsy medication	Nitroglycerin
Diabetic pill	Heart-rhythm medication	Other _____
Digitalis	High-blood pressure medication	
Diuretic	Insulin	
ID # _____	Date _____	

12. Any of these health symptoms that occur frequently is the basis for medical attention. Circle the number indicating how often you have each of the following:

5 = Very often 4 = Fairly often 3 = Sometimes 2 = Infrequently 1 = Practically never

a. cough up blood

1 2 3 4 5

f. chest pain

1 2 3 4 5

b. abdominal pain

1 2 3 4 5

g. swollen joints

1 2 3 4 5

c. low back pain

1 2 3 4 5

h. feel faint

1 2 3 4 5

d. leg pain

1 2 3 4 5

i. dizziness

1 2 3 4 5

e. arm or shoulder pain

1 2 3 4 5

j. breathless on slight exertion

1 2 3 4 5

Part III: Health Related Behavior

13. Do you smoke? Yes No

14. If you are a smoker, indicate the number smoked per day:

Cigarettes: 40 or more 20-39 10-19 1-9

Cigars or pipes only: 5 or more or any inhaled less than 5, none inhaled

15. Do you exercise regularly? Yes No

16. How many times in a week do you spend at least 30 minutes in moderate to strenuous/vigorous exercise?

1 2 3 4 5 6 7 days per week

17. Can you walk 4 miles briskly without fatigue? Yes No

18. Can you jog 3 miles continuously at a moderate pace without discomfort? Yes No

Appendix V

MODIFIABLE ACTIVITY QUESTIONNAIRE ID# _____ Date _____

1. Please check the box of all activities that you have done more than 10 times in the last 12 months from _____ to _____.

Activity	Month												Frequency Average # of times per month	Duration Average # of minutes each time
	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC		
<input type="checkbox"/> Aerobic Dance/Step Aerobics	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Badminton	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Basketball	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Bicycling (indoor, outdoor)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Bowling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Calisthenics/Toning Exercises	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Canoeing/Rowing/Kayaking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Dancing (square, line, ballroom)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Elliptical Trainer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Fencing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Fishing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Football/Soccer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Gardening or Yardwork	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Golf	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Hiking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Horseback Riding	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Hunting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Jogging (outdoor, indoor)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Jumping Rope	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Martial Arts (karate, judo)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Pilates	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Racquetball/Handball/Squash	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Rock Climbing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Scuba Diving	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Skating (roller, ice, blading)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Snow Shoeing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Snow Skiing (downhill)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Snow Skiing (x-country, Nordic Track)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Softball/Baseball	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Stairmaster	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Strength/Weight Training	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Swimming (laps, snorkeling)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Tai Chi	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Tennis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

<input type="checkbox"/> Volleyball	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Walking for Exercise (outdoor, indoor, treadmill)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Water Aerobics	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Yoga	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<input type="checkbox"/> Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

2. Excluding time at work, in general how many HOURS per DAY do you usually spend watching television or working on the computer? _____ hours

3. Over this past year, have you spent more than one week confined to a bed or chair as a result of an injury, illness, or surgery? Yes _____ No _____

If yes, how many weeks over the past year were you confined to a bed or chair? _____ weeks.

4. Do you have difficulty doing any of the following activities?

a. getting in or out of a bed or chair? Yes _____ No _____

b. walking across a small room without resting? Yes _____ No _____

c. walking for 10 minutes without resting? Yes _____ No _____

5. Did you ever compete in an individual or team sport (not including any time spent in sports performed during school physical education classes)? Yes _____ No _____

If yes, how many total years did you participate in competitive sports? _____ years

6. Have you had a job for more than one month over the past year, from last _____ to this _____?

List all JOBS that the individual held over the past 12 months for more than one month. Account for all 12 months of the past year. IF unemployed/disabled/homemaker/student during all or part of the past 12 months, list as such and probe for job activities of a normal 8 hour day, 5 day week.

Job Name	Job Code	Walk or bicycle to/from work Min/Day	Average Job Schedule			Hrs. spent sitting at work	Out of the total # of "hrs/day" the individual reported working at this "job", how much of this time was usually spent sitting? Enter this # in "hrs sitting" column, then place a check in the category that best describes their job activities when they are not sitting.		
							Check the category that best describes job activities when not sitting		
			Mos/Yr	Days/Wk	Hrs/Day	Hrs Sitting	A	B	C

Category A (Includes all sitting activities)	Category B (Includes most indoor activities)	Category C (heavy industrial work, outdoor construction, farming)
Sitting	Carrying light loads	Carrying moderate to heavy loads
Standing still w/o heavy lifting	Continuous walking	Heavy construction
Light cleaning	Heavy cleaning	Farming
Driving a bus, taxi, tractor	Gardening	Digging ditches, shoveling
Jewelry making/weaving	Painting/Plastering	Chopping (ax), sawing wood
General Office Work	Plumbing/Welding	Tree/pole climbing
Occasional/short distance walking		Water/Coal/Wood Hauling

JOB CODES	
<u>Not employed outside of the home:</u>	<u>Employed (or volunteer):</u>
1. Student	6. Armed Services
2. Home Maker	7. Office Worker
3. Retired	8. Non-Office Worker
4. Disabled	
5. Unemployed	

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