2009

This is to certify that the
thesis entitled

Placental Vascular Pathology Findings and Pathways to Preterm Delivery

presented by

Rachel L. Kelly

has been accepted towards fulfillment
of the requirements for the

M.S. degree in Epidemiology

Claudia Holzman
Major Professor's Signature

April 29, 2009
Date

Placental Vascular Pathology Findings and Pathways to Preterm Delivery

By

Rachel L. Kelly

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Epidemiology

2009

ABSTRACT

Placental Vascular Findings and Pathways to Preterm Delivery

By

Rachel L. Kelly

The authors examined the association between groups of placental vascular findings and subtypes of preterm delivery in a subcohort (239 preterm, 814 term) of the Pregnancy Outcomes and Community Health (POUCH) Study. Thirty-nine placental vascular variables from microscopic examinations were grouped into 5 a priori constructs: Maternal-vascular obstructive (MV-O), maternal-vascular disturbance of integrity (MV-I), maternal-vascular developmental (MV-D), fetal-vascular obstructive (FV-O), and fetal-vascular disturbance of integrity (FV-I). Scores were created by adding the number of positive findings in each construct and the distribution of total scores for each construct in term placentas was used to create cutpoints of 'high' (top quartile) and 'not high' (bottom 3 quartiles). Concordance between pairs of constructs was low (-0.01 to 0.17). In polytomous logistic regression models that included all 5 constructs and all maternal characteristics, the PTD risk for 'high' vascular score was compared to that of 'not high'. Strong associations between medically indicated PTD (MI-PTD) at < 35 weeks and high scores for MV-O, MV-I, MV-D, and FV-I were found. A second series of analyses placed all vascular constructs in a single model after excluding MI-PTD. These models showed significant interactions between MV-I, MV-D, and FV-I. MV-O and FV-O were not related to spontaneous PTD. Our results suggest that separating vascular constructs may be informative as we move forward to examine biomarkers and upstream and downstream risk factors in greater depth.

To Ted-Your love and encouragement has brought me to where I am. Thank you.

ACKNOWLEDGMENTS

I would like to thank Claudia Holzman for her support, guidance and everlasting patience during my tenure in the Epidemiology department. Her leadership has meant a tremendous amount to me both personally and academically.

I would also like to thank the other members of my graduate committee. First, Dr. Patricia Senagore for taking the time to teach me about an extraordinary field of medicine and the extraordinary placenta. She has instilled in me the utmost respect for the practice of pathology. Second, I would like to thank Dr. Hwan Chung for his patience and insights during the analytic portion of this endeavor. Last, I would like to thank Jianling Wang and Dr. MH Rahbar for their help with the data analysis.

I would also to thank the entire POUCH team. It has been a true pleasure working with this wonderful group of people over the last 3 years. I appreciate all the help and kindness during this process.

I would like to give a very special thanks to my wonderful husband for his support and love. I could not have done any of this without you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LITERATURE REVIEW

Preterm delivery (PTD), defined by the World Health Organization as delivery occurring before 37 completed weeks of pregnancy, is a major cause of poor maternal and fetal outcomes. With an occurrence rate of 12-13% in the United States, PTD accounts for up to 50% of neonatal mortality (1-4). Furthermore, it is consistently cited as the leading cause of neonatal and African American infant deaths(1, 4). Since 1995, the rate of infant mortality has decreased, most likely due to improvements in neonatal care(4, 5). In contrast, the rate of infant mortality and adverse outcomes attributed to PTD has risen, which parallels an increase in very low birth weight deliveries during this period (6).

Cognitive, educational, and developmental impairments, as well as intracranial hemorrhage are consistently linked to very early PTD (<32 weeks gestation) (1, 5, 7). More recently, mild and moderate PTD (34-36 weeks) have been related to lower cognitive scores and increased risk for ADHD, as well as postneonatal death due to infection, SIDS, and asphyxia when compared to infants delivered at term (5, 8). PTD also accounts for one in five cases of children born with some form of mental retardation(9). The serious often life-threatening morbidities and low birth weight of preterm neonates put an economic strain on the health care system, since they require costly neonatal intensive care unit services and frequent unscheduled acute care visits in the first year of life(10).

Previous studies have shown a relation between low socioeconomic status and PTD (11-14). Women living in disadvantaged areas are more likely to have a myriad of health problems that complicate pregnancy, as well as increased rates of preterm birth

and infant mortality(11-14). These observations have persisted over time, even after controlling for lack of access to health care (15). In addition to socioeconomic status, race is also an important risk factor for PTD. African Americans have higher PTD rates than whites, even after controlling for possible confounders such as differences in social class and Medicaid status(6, 16-19). Furthermore, non-Hispanic blacks are nearly three times more likely to deliver very preterm (<28 weeks) than white women (6). Hispanic women, although underserved, have traditionally had rates similar to whites of PTD and very low birth weight (VLBW)(4). However, Hispanic women have seen an increase in both preterm delivery (11% since 1990) and VLBW (7.4% in 1990 to 8.5% in 2005) in the last 20 years (4, 6).

Previous preterm delivery increases the risk of PTD in subsequent pregnancies (20-23). This pattern is especially evident with each additional preterm delivery at less than 35 weeks (21, 24). Subtype of PTD also appears to be an important factor in determining recurrence. Women with histories of either spontaneous PTD or medically indicated PTD are more likely to subsequently deliver in the same manner(20, 25). This may reflect an ongoing maternal condition, placentation abnormality, or even increased observation by physicians alerted to a patient's complication history.

Recurrence rates are not consistent across social classes and racial groups, and are higher in African Americans than in whites (24, 26). Possible explanations for this finding suggest environmental factors, such as maternal stress and lack of maternal support systems, and biological factors like bacterial vaginosis (27). As stated, previous PTD is an important risk factor for PTD, yet it's prognostic utility is unclear. A study of

15,000 women followed over two or more pregnancies showed that previous PTD could predict only 10% of preterm births in this group (21).

Subtypes of PTD

PTD can be divided into multiple subtypes based on presentation at time of birth. The most common subtypes are: 1) spontaneous labor beginning before rupture of membranes (PTL); 2) premature rupture of membranes before the onset of labor (PROM); and 3) medically-indicated PTD without rupture of membranes or spontaneous labor (MI-PTD). Spontaneous preterm delivery, defined as labor beginning before 37 completed weeks of gestation with or without rupture of membranes, accounts for at least two-thirds of preterm deliveries each year(28). PTL accounts for 40-45%, while PROM accounts for 25-30% of PTD yearly(3). While PTL and PROM are separate clinical scenarios, previous studies suggest that they may share common etiologies and often can be grouped as spontaneous PTD(29, 30). Medically indicated PTD accounts for the rest of PTD cases. This group is primarily comprised of pregnancies complicated with preeclampsia, pregnancy-induced hypertension, poor fetal growth and evidence of fetal distress or hypoxia (31).

PTD can also be divided by gestational age. The majority of preterm deliveries occur at 34-36 weeks gestation, comprising 60-70% of all PTD (3). The nearly 30% increase in PTD in the last 25 years can be attributed to this group (28). PTD occurring before 32 weeks gestation are frequently related to acute infection/inflammation and bleeding (3, 32). Studies using very early PTD (<32 weeks) have shown a strong correlation between acute inflammatory lesions in the placenta and PROM and PTL(20, 32-34). Placental lesions related to decidual hemosiderin (i.e. evidence of bleed), such as

uteroplacental vascular thrombosis, absence of physiologic spiral artery change, and villous fibrosis, have also been linked to preterm delivery at less than 32 weeks(35). In contrast, studies using a PTD cut-off of 37 weeks have shown stronger relationships between spontaneous PTD and specific types of vascular placental pathology (lack of physiologic change of spiral arteries and placental infarcts) (36-38).

Suspected Causes of PTD

The cause of the majority of deliveries before 37 weeks has not been established. PTD is postulated to result from a variety of pathological processes that include ischemia, inflammation/infection, short cervical length, uterine overdistention, and hormonal disorders (2). There have been many studies examining the risk factors for PTD. Despite the medical community's best efforts to reduce the number of preterm births in the United States, PTD rates continue to increase (39). Heretofore, clinical interventions aimed at decreasing individual risk factors have been unsuccessful, primarily because they do not address underlying pathologic processes (39).

The placenta has become a focus of investigation to help us better understand the underlying mechanisms resulting in PTD. Two placental pathways to preterm delivery have been identified, namely vascular and inflammatory (36, 40). Infection is implicated in 25-40% of preterm births (41, 42). Infection and acute inflammation lead to premature rupture of membranes and spontaneous preterm labor, most likely by triggering an inflammatory cascade(3). There are four pathways to intrauterine infection: ascending from the lower genital tract; descending from the upper genital tract; hematogenous spread through the placenta from maternal blood; and introduction during a procedure such as amniocentesis (29). Infections originating in the genital tract are the most

common pathways to intrauterine infection (29) and are most consistently associated with preterm labor and preterm PROM(29, 32, 42).

Much of the research has focused on infectious/inflammatory causes of PTD, although these causes account for less than half of all preterm births (43). An infection/inflammation pathway cannot adequately explain vascular complications leading to PTD such as gestational hypertension, preeclampsia, IUGR, and overt bleeding. Thus, vascular pathways to PROM and PTL have also been proposed. The placenta is the ideal organ to explore vascular function during pregnancy on both the fetal and maternal sides. Abnormal placentation, along with uteroplacental ischemia and hemorrhage, comprise the major proposed mechanisms for the vascular pathway to PTD (2, 3). Specifically, uteroplacental ischemia has been proposed as a possible mechanism for PTL and PROM in the absence of infection and inflammation (2). A number of studies that associate maternal vascular lesions with PROM and PTL, have found abnormal maternal decidual blood vessels changes, including failure of transformation and vasculopathy, to be much more common in these groups than in normal, term deliveries (36-38). The role of fetal vascular lesions in the development of PTL and PROM has not been established and little research has focused solely on the contribution these findings have on delivery outcomes (2).

Placental Function

The placenta is essential for fetal development and pregnancy success. It is the first fetal organ to develop, it mediates implantation into the uterus and supports fetal development throughout pregnancy(44). Specifically, it regulates the exchange of nutrients and electrolytes, such as amino acids, fatty acids, carbohydrates, and vitamins,

between maternal and fetal circulations (45). It also allows for extraction of oxygen from and the elimination of carbon dioxide and carbon monoxide to the maternal circulation by the fetus(44). It also stimulates both maternal blood cell and blood volume production in order to facilitate increased delivery of oxygen to the fetus (44).

Second, the placenta is the source of hormones necessary for proper fetal development. At the beginning of pregnancy, it produces chorionic gonadotropin (beta hCG), a hormone that induces maternal recognition of the paternal elements of the fetus (46). In mice, this hormone inhibits the development of sepsis (46). Progesterone is produced beginning in the 4th month to help maintain the pregnancy. Estrogenic hormones stimulate uterine growth and development of the mammary glands. Somatomammotropin, a growth hormone-like substance, is made throughout pregnancy to give the fetus priority on maternal blood glucose (45).

The placenta also creates a barrier between mother and fetus, allowing some protection from maternal antibodies, bacteria, and viruses. During pregnancy, the decidua sequesters numerous cells of the innate immune system in an attempt to protect the fetus (46). Macrophages, white blood cells specializing in phagocytosis of necrotic material and invading microorganisms, comprise 20-30% of decidual cells at the site of implantation (47, 48). These cells persist through pregnancy, producing cytotoxic agents that destroy invading pathogens(49).

Structure of the Placenta

The placenta is predominantly a fetal organ suffused by maternal blood. It has two tissue components—maternal and fetal (Figure 2). The fetal-placental tissue consists of a chorionic plate into which the umbilical cord "inserts," and branches into consecutively

smaller blood vessels that serve as stem villi from which numerous small terminal villi project, forming the villous tree (45). The stem and terminal villi are suspended in the maternal intervillous space, where they are bathed in maternal blood (45). Each villus is a fetal vessel surrounded by a thin layer of mesoderm covered by two strata of ectodermal cells derived by the trophoblast (cytotrophoblasts and syncytiotrophoblast) (45).

The maternal-placental tissue consists of a thin layer of decidual tissue derived from the endometrial lining of the uterus that is in continuity with the smooth muscle wall until separation of the placenta at delivery (45). It represents a junctional zone, where trophoblasts anchor the villous tree and invade to transform spiral arteries (45). The maternal intervillous circulation is established when maternal uterine blood flows in a fountain-like fashion through enlarged transformed decidual spiral arteries into the placental intervillous space and returns via endometrial veins (45). This flow allows for oxygen and nutrient transfer to the fetus across chorionic villi bathed in maternal blood.

Normal development of the Placenta

The placenta develops from the trophoblast, the cells of the outer wall of the blastocyst and the embryo from the inner cell mass (45). Shortly after conception, the outer trophoblastic cells proliferate to form an inner layer, called the cytotrophoblast, and an outer layer, called the syncytiotrophoblast (45). These layers later will form the chorionic plate and the chorionic villi at about the second month post-conception (45).

As the blastocyst implants into the uterine endometrium, it stimulates a reactive change in the cells of the endometrial stroma. These stromal cells accumulate lipid and nutrients, thicken, and form the decidua (45). During implantation, trophoblasts

infiltrate spiral artery walls, creating thin-walled large-diameter vessels with low resistance (50). Transformation of these vessels allows large amounts of maternal blood to reach the intervillous space and chorionic villi (50). By 18 weeks, 30% of the vessels are invaded and successfully converted(51). In a normal pregnancy, more than 90% are converted by 40 weeks(51). At about the same time, lacunae form within the trophoblast shell and ultimately connect, forming the intervillous space into which maternal uterine blood will circulate (45).

Abnormal Placental Development- Maternal Side

Placental abnormalities can reflect incomplete vascular development, or obstruction to or disruption (loss of integrity) of blood flow. On the maternal side, vascular lesions likely begin with abnormal remodeling of spiral arteries destined to supply oxygen and other nutrients to the placenta and fetus. In normal development, decidual and myometrial segments of the spiral arteries are infiltrated by trophoblasts, and this process leads to thinned walls and wide-open lumens that result in decreased peripheral vascular resistance. Additionally there is degeneration of muscular contractile elements needed for vasoactive agents to cause constriction (37, 38, 50). In some cases of abnormal development, trophoblastic invasion of the myometrium is incomplete or too superficial, which leads to decreased vessel compliance and a diminished capacity of the placenta to regulate blood flow to the fetus (38, 52). Initially this abnormal development is identified microscopically as a persistence of smooth muscle in the walls of spiral arteries of the decidua basalis (basal plate) (52). Much later, these vessel walls begin to necrose (fibrinoid necrosis), and associated inflammatory and other changes are thought to cause thrombotic or disruptive changes that prevent optimal uterine blood flow to the

intervillous space (obstructive lesions) (51, 53). These changes are similar to those seen in atherosclerosis, since both are related to lipoprotein deposition and the accumulation of foam cells (i.e. lipophilic macrophages) in the walls of the vessels (51).

Histologic placental changes that reflect obstructive lesions in the maternal decidual vasculature of the placenta may result in decreased villous perfusion later in gestation. Lesions associated with maternal under-perfusion/placental ischemia include the diffuse formation of syncytial knots, excess deposition of perivillous fibrin, and villous infarctions. Syncytial knots form when transient hypoxia causes the proliferation of irregularly shaped capillaries in terminal villi, creating a knotted appearance on the surface of the trophoblast (54). Syncytial knotting early in pregnancy (called budding) is a normal process that serves to increase chorionic villi surface area (54, 55). Few of these knots exhibit apoptotic nuclei and cytoplasmic degeneration consistent with normal cell turnover during pregnancy(54, 55). However, extended periods of underperfusion or reduced available oxygen in the villous space will stimulate capillary proliferation and cell turnover, leading to increased numbers of syncytial knots later in pregnancy(54, 56).

The cause of excessive perivillous fibrin deposition during times of underperfusion is unclear. However, increased deposition leads to altered maternal blood flow into the intervillous space (56, 57). When alterations in maternal spiral artery blood flow cause thrombus formation and complete occlusion of one or more maternal vessels, the villous tree in the perfused area is at risk for infarction (56). Spiral arteries running through the myometrium and decidua have no collateral microcirculation, so occlusion at any part of these end-arteries is problematic (58). Since the villous tree "floats"

suspended in maternal intervillous blood, lack of local arterial flow will cause collapse of the space and villous tissue with ischemic necrosis (58).

Disruption of blood flow (loss of integrity) within the maternal vasculature can lead to hemorrhage. Bleeding can be acute or chronic, gross or microscopic, and occur into the decidua or retroplacental space. Hemosiderin pigment in tissues (amnion, chorion, or decidua) may represent evidence of a previous hemorrhage (56).

Abnormal Placental Development- Fetal Side

Normal development of the fetal vasculature is a complicated process involving many maternal, fetal, and environmental factors such as adequate oxygen perfusion, hormones, and growth factors (59). Obstruction of fetal-placental vessels has been related to severe adverse fetal and neonatal outcomes such as preterm delivery, IUGR, neonatal encephalopathy and neurologic impairments (60-62). These lesions are commonly referred to as "fetal thrombotic vasculopathy" and include lesions such as thrombosis of fetal disc or chorionic plate vessels, avascular villi, intimal fibrin cushions, and karyorrhexis of the fetal vessel cells (63). Vasculopathy is thought to result from vascular stasis, hypercoagulability, and tissue damage (64). Redline has shown that chorionic plate and disc thrombosis leads to avascular villi and has also been related to evidence of bleeding(61, 64). Avascular villi are clusters or segments of terminal villi that have become small and atrophic because of a prolonged period of thrombosis with lack of fetal blood flow (63). Intimal fibrin cushions are focal areas of sub-intimal fibroblast proliferation in fetal vessels walls that bulge into the lumen and contain collections of fibrin material (63). Although the etiology of this lesion is not known, it is similar to lesions that develop in the pulmonary vasculature secondary to pulmonary

hypertension (63). It has also been postulated to reflect insudation of plasma through damaged endothelium resulting from increased transmural pressure of an upstream compression (65).

Another group of important lesions are those that represent disruption/loss of fetal vascular integrity such as subchorionic hemorrhage, intervillous thrombus, villous stromal hemorrhage, and villous edema. Subchorionic hemorrhage and intervillous thrombi are considered areas of fetal to maternal bleeding in the intervillous space, in different locations(54). Both likely represent areas where fetal villous blood becomes admixed ("laminated") with maternal blood in the intervillous space (54, 65). The hemorrhage is likely due to an extravasation from the villi into the maternal space from a site of chorionic villous damage (54). Villous stromal hemorrhage is intravillous hemorrhage that often accompanies sudden ischemia and hemodynamic shifts in suspected preterm abruption(65). Villous edema was originally associated with chorioamnionitis and acute inflammation(66); it has since been linked to antenatal hypoxia (67). The functional significance of villous edema is that it may limit blood flow and gas exchange by compressing the intervillous space and increasing the distance that oxygen must diffuse to reach fetal blood (53, 59, 66). As a group, these lesions may represent placental evidence of more generalized circulatory disturbances similarly affecting other body/organ tissues within the fetus, or maternal-placental vascular disturbances that secondarily have damaged fetal vessels.

Although there is lack of consensus on what pathology findings are most appropriate to include in each conceptual grouping outlined above, attempts have been made to create an organizational tool to standardize recording and interpretation of

placental findings. Specifically, Raymond Redline, a leading pathologist in this field, has created a conceptually driven collection of vascular pathology constructs using the same 5 groups discussed here. An abridged version of Dr. Redline's placental pathology tool is used in this study to categorize our 39 placental vascular findings.

Previous Studies of Placental Vascular Pathology and PTD

A number of approaches have been used to evaluate vascular placental pathology in epidemiological studies of preterm delivery. One approach has been to evaluate individual lesions. Table 1 compares four studies that focused on one lesion as an indicator of a pathologic process occurring in the placenta. Three of the four studies focus on maternal vascular findings and draw conclusions between abnormal development and resulting placental hypoxia (37, 38, 68).

Although these studies illustrate the proposed pathophysiology to some degree, they fail to provide a full explanation of the processes leading to PTD. Due to the restricted scope of each study, there is insufficient information available to determine whether the finding used is the most sensitive and specific indicators of a greater placental pathological processes, or simply circumstantial, and therefore, irrelevant.

A much more common method used to study placental vascular pathology is to employ clusters of lesions that have been grouped using empirical knowledge. Typically, studies utilizing groupings of vascular lesions suggest that vascular pathology is related to PTD(69), PTL (36, 37, 70), preterm PROM (36, 38), preeclampsia(71, 72), and IUGR(33, 73, 74). More generally, previous studies have consistently reported a relationship between PTD and ischemic injury and abnormal development of the placental vasculature (36, 37, 69, 75). This has been extensively studied in preeclamptic

patients in addition to women presenting with premature rupture of membranes (37, 38, 71). Salafia, et al., have also shown that evidence of decidual disease (decidual thrombosis, failure of physiologic change, fibrinoid necrosis of the decidual vessels) is related more to medically indicated PTD than to spontaneous delivery(74). Most recently, Ogunyemi, et al., showed that placental vasculopathy (placental infarcts, villous fibrosis, vascular intimal hypertrophy, and fibrinoid necrosis) was significantly related to medically indicated PTD and was negatively correlated to spontaneous PTD(76).

Table 2 highlights four studies using conceptually created groupings of placental vascular lesions to evaluate the role of placental vascular pathology in preterm delivery. All of these studies use histopathologic diagnoses such as maternal/decidual vasculopathy and uteroplacental vascular changes as vascular pathology constructs (Table 3). Said constructs contain many of the same placental vascular findings such as failure of transformation of decidual vessels, syncytial knots, and fibrinoid necrosis. Each study also contains unique findings, which makes comparison of results challenging.

General limitations of previous studies

Comparison of previous studies is difficult because: 1) there is little consistency in placental vascular findings used to define maternal vascular outcomes such as uteroplacental and decidual vasculopathy; 2) a variety of PTD outcomes and gestational ages are used across studies, 3) study samples and reference groups are variable, and 4) agreement of what constitutes a positive finding in a placenta is lacking. Where the overlap of placental vascular findings is concerned, there is little consensus about what individual pathology findings are necessary to include in empirically created groups.

Table 3 outlines the lesions employed in some studies using groups of vascular pathology findings. The lack of consistency in defining such constructs as uteroplacental ischemia and decidual vasculopathy makes it very challenging to compare the results of multiple studies. In addition, as is illustrated in Table 4, the general lack of consistency in findings has also contributed to low inter-rater reliability in studies that did not agree upon a general definition of these groupings beforehand(77, 78).

As stated previously, a variety of PTD outcomes and gestational ages are used across studies. This fact causes further inconsistency in the evaluation and comparison of findings. Many studies have focused on very early preterm delivery (<32 completed gestational weeks) when evaluating the placenta for vascular changes(20, 73, 75, 76). It has been established that very early PTD is more often related to acute inflammation and infection, whereas later PTD (34-36 weeks) seems to have a more chronic, vascular etiology (20, 33, 34). Also, many studies of vascular pathology focus on preeclamptic women, women requiring c-sections and women presenting in preterm labor; thus limiting the generalizability of the results to more general PTD groupings such as medically indicated or spontaneous preterm delivery (37, 38, 70-72, 77).

The fact that sample composition and reference groups are variable across studies introduces further inconsistency. Many studies of placental vascular pathology are conducted at university-based hospitals, leading to an oversampling of high-risk women delivering after 37 weeks (33, 61, 75, 79). Furthermore, some studies do not even use placentas from term women as controls (34, 75). These methods of comparison diminish each study's ability to establish meaningful relations between vascular pathology findings and PTD groups.

Lastly, there is little consensus among study pathologists as to what constitutes a positive histopathologic placental finding. Only four studies have addressed the problem of lack of normalization in vascular placental pathology (40, 52, 64, 77, 78). Table 4 outlines the intrarater and interrater reliability of each study. Interrater reliability for individual pathological findings tends to be good (> 0.50). However, when using pathology constructs, such as maternal/decidual and fetal vasculopathy, the interrater reliability becomes very poor (<0.30)(77, 78). Two studies used group consensus to define these vague vascular constructs, resulting in improved agreement between pathologists (40, 64). This suggests that the standardization of generally used vascular groupings is needed to improve the reproducibility of pathology tools used to evaluate both term and preterm placentas.

INTRODUCTION

Maternal vascular complications have been most consistently associated with medically indicated preterm delivery (PTD), but they may also contribute to PTDs that result from premature rupture of membranes (PROM) and spontaneous preterm labor (PTL) (36-38, 72, 79). Studies of vascular pathways to PTD have considered clinical signs/symptoms (31, 80), biomarkers (81-88), and placental pathology findings (20, 38, 72), all of which provide clues and unique challenges. Vascular related complications such as preeclampsia, gestational hypertension, intrauterine growth restriction (IUGR), and overt bleeding are defined by extreme signs/symptoms that have potentially multiple causes, some distinct and some overlapping (31, 36-38, 89, 90). In addition, clinically

diagnosed vascular complications most likely under-represent vascular problems associated with PTD, decreased fetal growth, and altered fetal development. Biomarkers such as thrombin(83, 88), flt-1 (85-87), VEG-F (81, 82) and PIGF (86, 87) have been linked to multiple clinically defined vascular complications in pregnancy, which may indicate common underlying etiologies or common sequelae following vascular damage.

Evaluation of placental vascular findings offers another avenue for uncovering vascular pathways. Studies have repeatedly shown that placental evidence of decidual vasculopathy or more basically, uteroplacental vascular lesions, is associated with preeclampsia, gestational hypertension, and fetal intrauterine growth restriction (IUGR) (72, 75, 91). Failed physiologic transformation of maternal spiral arteries and decidual vascular artherosis were found to be more common in PROM and PTL than in normal, term deliveries (38). But incorporating placental vascular findings into epidemiologic studies is also fraught with challenges. There are no 'gold' standards demarcating 'normal' from 'abnormal' along the continuum of pathologic findings, and classification schemes for the different pathologic findings have been quite variable. One approach has been to focus on an individual placental vascular finding, such as failure of physiologic transformation of spiral arteries, and relate it to PTD (37). Another has been to group multiple placental findings to characterize globally-defined vascular complications such as abnormal placentation, uteroplacental ischemia, and hemorrhage, but across studies there are considerable inconsistencies in terminology, definitions, and findings used (Table 3). Few studies have empirically evaluated placental vascular findings to determine how often they co-occur (71, 77) and one of these studies used both term and preterm placentas (77). Finally, studies have primarily concentrated on

maternal-related vascular pathology in relation to PTD; so less is known about the influence of fetal vascular findings, alone or in combination with maternal vascular pathology (40, 61, 92).

The Pregnancy Outcomes and Community Health (POUCH) Study is a prospective cohort study designed to examine the biological and psychosocial factors that determine preterm delivery. Here, a subcohort of these women, including all preterm women, all women with high MSAFP and a subset of term, normal MSAFP women, were used to explore the relationship between vascular placental pathology and preterm delivery. Microscopic vascular findings in term and preterm placentas of these women were divided into five groups, each group representing a pathology-based latent construct. The goals of these analyses were to: 1) examine the extent to which the pathology-based constructs co-occur in the same placenta; 2) evaluate maternal characteristics for each of the five pathology-based constructs; and 3) assess relations between the pathology-based constructs and risk of spontaneous and/or medically indicated PTD.

MATERIALS AND METHODS

Population and study design

The Pregnancy Outcomes and Community Health (POUCH) Study is a prospective cohort study designed to examine pathways to preterm delivery in 3019 pregnant women (93). Between August 1998 and June 2004, pregnant women were recruited from 52 clinics in five Michigan communities. Women were enrolled in the

15^{th} - 27^{th} week of pregnancy. Inclusion criteria included singleton pregnancy with no known congenital anomaly, maternal age of 15 years or greater, prenatal screening of maternal serum alpha-fetoprotein (MSAFP) at the 15^{th} -22^{nd} week of pregnancy, no pre-pregnancy history of diabetes mellitus, and competency in English. Women were recruited at the time of prenatal screening. All women with MSAFP levels greater than 2 MoM (multiples of the mean) were invited to participate (7% of the cohort) because this biomarker had been linked to PTD previously(94) and was of particular interest in the POUCH Study. Women with normal MSAFP levels were stratified by race/ethnicity and sampled into the cohort. Nineteen of the 3,038 women enrolled were lost to follow-up, resulting in a cohort of 3019 women. The study received institutional review board approval at Michigan State University, Michigan Department of Community Health, and nine community hospitals. Race/ethnicity specific comparisons of the study cohort with birth certificate data from women delivering in the study communities showed that cohort participants closely resembled community women on most maternal characteristics measured.

At enrollment, study participants were interviewed and biologic samples were obtained. For in-depth analyses, a sub-cohort (N=1,371) was created which included all women who delivered preterm (<37 weeks gestation), all women who delivered at term with elevated MSAFP (>2 MoM), and a sample of women who delivered at term with normal MSAFP, with an over-sampling of African-American women from this latter category. The sub-cohort sampling scheme was designed to maximize statistical power for studying at-risk subgroups. All sub-cohort analyses use sampling weights to reflect the sampling scheme, and therefore there is no bias introduced by over-sampling certain

subgroups. In the sub-cohort, prenatal and labor/delivery records were abstracted and delivered placentas were examined by a study placental pathologist. Placentas were retrieved for 88% (1,213 women) of the sub-cohort and this analysis includes the first 1,053 (239 preterm, 814 term) placentas assessed in the sub-cohort to-date.

Placental examination protocol

The POUCH Study placental examination protocol has been described elsewhere (93). Briefly, placentas were formalin fixed and grossly examined by the study placental pathologist. Five full thickness samples were taken from the disc: one at the cord insertion, one in grossly normal central tissue, two more from central tissue and one from marginal tissue. The latter three samples were from grossly abnormal tissue if present. Four other samples were also taken: two umbilical cord samples and two extra-placental membrane samples from a membrane roll. Tissue samples were paraffin-embedded, sectioned and H&E stained for microscopic assessment. The study's placental pathologist was blinded to gestational age at delivery, all clinical data, and gross examination findings during the microscopic examination.

Placental diagnostic coding tool

Placental microscopic findings were recorded in a computer-based data collection instrument that was adapted from Carolyn Salafia. The instrument is primarily descriptive, not diagnostic, and captures a large number of pathologic changes, their location, frequency, extent, and proximity to one another. Maternal vascular findings recorded in this instrument were organized using a scheme adapted from Raymond Redline in his Placental Diagnostic Coding Tool. This adapted data summary tool was

used to categorize 39 findings into five conceptual groups, or pathology-based latent constructs: 1) Maternal Vascular-Obstructive (MV-O) captures evidence of obstruction as in major placental disc infarcts and decidual vessel atherosis; 2) Maternal Vascular-Disturbance of Integrity (MV-I) includes findings associated with retroplacental hemorrhage and bleeding in the decidua; 3) Maternal Vascular- Developmental (MV-D) incorporates findings consistent with abnormal or incomplete trophoblast remodeling of maternal spiral arteries; 4) Fetal Vascular-Obstructive (FV-O) represents findings related to large and small fetal vessel obstruction; and 5) Fetal Vascular-Disturbance of Integrity (FV-I) includes findings that suggest abnormalities of fetal villous blood flow such as fetal to maternal hemorrhage. A complete list of findings included in each pathology-based vascular construct appears in Table 8.

Pregnancy outcome

Gestational age at delivery was calculated from the date of the last menstrual period (LMP). If the LMP estimate differed from an early ultrasound estimate by more than two weeks ultrasound dates were given preference. PTD (<37 weeks' gestation) was subdivided into two commonly used clinical groupings: 1) Spontaneous PTD, which included women with spontaneous regular contractions that led to cervical changes (≥2 cm dilatation) or women with rupture of membranes prior to or at the onset of labor; and 2) Medically indicated PTD, which included women who delivered after induction of labor or by Caesarian section before the onset of spontaneous regular contractions or membrane rupture. Within the clinical subtypes, PTD was further divided according to gestational week at delivery, i.e. <35 weeks and 35-36 weeks, because pregnancy complications and clinical decisions to intervene vary as pregnancy progresses.

Maternal characteristics

Information on maternal education level, Medicaid insurance status, parity, pre-pregnancy weight, height, and race/ethnicity were obtained through self-report at enrollment. Pre-pregnancy body mass index (BMI) was calculated (weight in kilograms divided by height in meters squared) and divided into three groups, normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese ($\geq$30 kg/m^2). Due to small numbers, underweight women (N= 47) were excluded from analyses involving BMI and the 82 women who were not African-American or White were grouped with Whites (White/other) who shared more similar risks of PTD.

ANALYTIC APPROACH

Development of the Pathology-based Vascular Construct Scores

Each of the 39 vascular findings had a continuous score representing the number of samples per placenta in which the vascular pathology finding was present. Scores ranged from 0 to 2 if relevant to the extra-placental membrane samples only, 0 to 5 if relevant to the placental disc samples only, and 0 to 7 if relevant to the disc and the extra-placental membrane samples. Data from women who delivered at term with normal MSAFP levels were used to determine the typical frequency distribution (number of positive samples per placenta) of each of the 39 vascular findings. The top quartile (or approximately) was considered 'high' and accordingly a vascular finding was scored as either '0' (normal) or '1' (high) for each placenta. The dichotomous vascular finding scores were then summed to give a pathology-based construct score. For example, the

eight findings in the MV-O construct were added to create a construct-specific score ranging from 0-8 for each placenta. Again data from women who delivered at term with normal MSAFP were used to represent the typical frequency distributions of construct scores. Due to clumping in the distributions, the most uniform cut-points for 'high' across the constructs were the top 14^{th} -17^{th} percentiles. One construct (FV-I) had to be cut at the top 36^{th} percentile. A dichotomous variable was created for each of the five pathology-based vascular constructs; 'high' was at or above the cut-point and 'normal' was below.

Analyses Using Pathology-based Vascular Construct Scores

Correlations between pathology-based vascular construct scores were determined in two ways. First, the score was modeled as a continuous variable and Spearman's Rank Correlation Coefficients were obtained using SAS Proc Corr (SAS Institute Inc., Cary, NC). Second, the scores were modeled as a dichotomous variable (high and normal as defined above) and co-occurrence was assessed using the Kappa statistic.

Each pathology-based vascular construct (modeled as high/normal) was evaluated in relation to maternal characteristics (Chi-square test), and in relation to risk of PTD by using a polytomous logistic regression model (SAS Surveylogistic) with a five level outcome variable: term (referent), 35-36 weeks spontaneous PTD, 35-36 weeks medically-indicated PTD, <35 weeks spontaneous PTD, and <35 weeks medically-indicated PTD. In these analyses data were weighted to reflect over-sampling of preterm, high MSAFP and African-American women into the sub-cohort. Because of the low to moderate correlations between the pathology-based vascular constructs, all vascular constructs were also included in a single polytomous logistic regression model to test

their associations with PTD after accounting for the presence of other constructs. Significant (P< .05) construct interactions were observed for spontaneous PTD but not medically indicated PTD. To clarify these interactions two separate polytomous regression models were used: one excluded spontaneous PTD and had a three level outcome of term (referent), < 35 weeks medically indicated PTD, 35-36 weeks medically indicated PTD; the other excluded medically indicated PTD and had a three level outcome of term (referent), < 35 weeks spontaneous PTD, and 35-36 weeks spontaneous PTD. In a second version of these models, maternal characteristics related to PTD in previous studies (race/ethnicity, parity, age, Medicaid insurance status, and BMI) were added as potential confounders.

RESULTS

The first column in Table 5 shows the distributions of demographic and pregnancy-related factors in this sub-cohort sample. The second column includes sampling weights to show the distributions of these same maternal characteristics in the POUCH Study cohort. Weighted and un-weighted distributions were similar except in the characteristics used for sub-cohort sampling, i.e., race/ethnicity and pregnancy outcome. In the sub-cohort sample approximately 28% were over 29 years of age, 51% had more than 12 years of education, 38% were African-American, 54% were insured by Medicaid, and 22.7% delivered preterm.

Correlations between pathology-based vascular construct scores measured on a continuous scale were generally weak to moderate in magnitude with Spearman's Rank

Correlation Coefficients ranging from 0.03 to 0.30 (Table 6a). Co-occurrence of vascular constructs was also tested using dichotomous variables (normal/ high) and a Kappa statistic, which has a range of -1 to 1 (complete concordance). The Kappa coefficients for the vascular constructs were all low, -0.01 to 0.17 (Table 6b)

Maternal and fetal vascular obstructions, evidenced by a high MV-O or FV-O score, were more common in primiparous women (Table 7). High MV-I and FV-O scores, indicative of maternal bleeding and fetal vessel thrombosis, were observed more often in whites/others than in African-Americans. A high MV-D score, consistent with poor conversion of spiral arteries, was associated with being African-American, < 20 years of age, insured by Medicaid, overweight, and obese. When all maternal characteristics were included in a single logistic regression model, a high MV-D score continued to be more prevalent in African-American women (adjusted odds ratio-AOR=2.1, 95% CI 1.3, 3.2), women <20 years of age (AOR=3.4, 95% CI 1.6, 7.2), overweight women (AOR= 2.7, 95% CI 1.6, 4.6), and obese women (AOR= 3.3, 95% CI 2.0, 5.4).

High scores for MV-O, MV-I, MV-D, FV-O and FV-I were each associated with medically indicated PTD at < 35 weeks with unadjusted ORs ranging from 2.3 to 4.8 (Table 8). MV-I and MV-D were also related to spontaneous PTD at <35 weeks (unadjusted ORs 2.0 and 2.1 respectively) and FVI was associated with spontaneous PTD at 35-36 weeks (unadjusted OR=1.8). All pathology-based vascular constructs were placed in a single model after excluding spontaneous PTDs. The AORs for medically indicated PTD < 35 weeks were attenuated but remained statistically significant with the exception of FV-O (Table 9). Following additional adjustment for maternal variables, i.e.,

parity, Medicaid status, race/ethnicity, age, and BMI there continued to be strong associations between medically indicated PTD at < 35 weeks and high scores for MV-O (OR= 3.5, 95% CI 1.6, 7.8), MV-I (OR= 2.5, 95% CI 1.1, 5.9), MV-D (OR= 3.7, 95% CI 1.6, 8.8), and FV-I (OR= 2.8, 95% CI 1.2, 6.5). There were no statistically significant interactions (P<0.5) among the vascular constructs in this model and no significant associations with medically indicated PTD at 3-36 weeks.

A second series of analyses placed all vascular constructs in a single model after excluding medically indicated PTD. These models showed significant interactions between MV-I, MV-D, and FV-I (Table 10). After adjusting for maternal characteristics, the presence of a high score in any one of these three vascular constructs significantly increased the risk of spontaneous PTD at 35-36 weeks with AORs ranging from 2.9 to 4.4. The presence of two or more high scores increased the risk of spontaneous PTD at < 35 weeks with AOR ranging from 4.0 to 7.5; only the combination of MV-I and MV-D did not reach statistical significance. MV-O and FV-O were unrelated to spontaneous PTD.

DISCUSSION

We found that a pathology-based system of grouping placental vascular findings into constructs offers insights into preterm delivery pathways. Separate consideration of the various vascular constructs was supported by three observations. First, the correlations between the pathology-based vascular construct scores were weak to moderate, suggesting co-occurrence of these latent processes is not common. Second,

there was considerable variation in the maternal characteristics associated with each of the vascular constructs. And third, some but not all constructs were related to spontaneous PTD.

The maternal vascular-developmental construct was most closely linked to multiple maternal characteristics including high BMI, whereas the maternal vascular obstructive construct was associated only with primiparity. While inadequate maternal vessel remodeling can lead to placental obstructive lesions(52), our results suggest there may be value in exploring upstream and downstream factors related to each of these constructs. The higher prevalence of maternal vascular disturbance of integrity (bleeding), and fetal vascular obstruction (thrombosis) in Whites/others compared with that in African-Americans may reflect differential predispositions such as thrombophilias (95). Some acute placental abruptions, which are most evident by clinical presentation and/or gross pathology findings and may have a different epidemiology, are probably not sufficiently captured in this construct defined only by microscopic placental findings.

From a clinical perspective, preeclampsia, fetal distress, poor fetal growth, and placental abruption account for the majority of medically-indicated PTDs (31). It has been unclear if all or only certain types of vascular pathology 'drive the association with medically indicated PTD'. By building models that included all five pathology-based vascular constructs we were able to show that, with the exception of fetal vascular obstructive, each construct increased the risk of medically indicated PTD at < 35 weeks. The continued importance of the maternal vascular-developmental construct after adjusting for maternal obstructive lesions (e.g. infarcts and atherosis) suggests that developmental findings alone (abnormal or incomplete remodeling of maternal vessels)

may be sufficient to trigger maternal complications (high blood pressure) that result in medically indicated PTD.

Other studies have reported an increased risk of spontaneous PTD in association with placental findings such as uteroplacental vascular thrombosis, infarcts, absence of physiologic spiral artery change, and villous fibrosis (36-38). We found that among three of the five vascular constructs (MV-D, MV-I, and FV-I) there was an inverse 'dose response' between the number of high construct scores and timing of spontaneous PTD, a clear indication that vascular constructs are important to both late and early spontaneous PTD. The reason for the presence of a three-way interaction in the spontaneous PTD group only is unclear. This finding could reflect a number of different scenarios. First, the placental injury resulting from the combination of two or more of these three groups could result in clinical findings that only present after PROM or PTL have occurred. Second, the severity of placental injury incurred from these three lesion groups could result in sudden progression to preterm labor or rupture of membranes. However, the underlying reason for this finding is ultimately unknown since we are still not able to clearly understand the clinical and pathophysiological scenarios leading to spontaneous and indicated PTD. The lack of association between maternal vascular-obstruction and spontaneous PTD may be because in severe cases medically indicated PTD supersedes. Fetal vessel obstruction was not linked to spontaneous or medically indicated PTD once other vascular constructs were included in the models. The FV-O construct included the largest number of items (findings). Future sensitivity analyses may help to pare down the item list and strengthen the importance of this construct.

Comparisons across studies of PTD-related vascular placental pathology are made difficult by: 1) the variability in definitions and groupings of pathology findings, and 2) geographical and secular trends in medically indicated PTD, influenced both by prevalence of indications and variation in medical practices. In addition, previous studies have showed that inter-rater reliability for diagnosing histologic evidence of vascular-related pathology is not high (40, 64, 77), perhaps because there is a lack of agreement as to what constitutes a critical mass of findings for the designation of 'positive'.

Strengths of the Study

Major strengths of this study include the sample, which was recruited from multiple community clinics and shown to be highly comparable to community women delivering during this period. The pathologist was blinded to all clinical information, which is not typical with referred placental examinations in perinatal medicine. We examined the distributions of placental vascular findings and constructs in term placentas as a means of determining what might be considered 'normal.' It is often the case that studies of placental vascular pathology comparing subgroups of preterm (20, 73, 75, 76) use high- risk term placentas as the reference group (79), or are conducted in teaching hospitals where patient populations over-represent high-risk pregnancy conditions, even among term deliveries. By using term women recruited from communities around Michigan, we were able to illustrate what constitutes a normal threshold of placental vascular change in pregnancies not complicated by preterm delivery or adverse birth outcomes.

The placental evaluation tool in this study was one of the most detailed of those used in vascular placental pathology research. Previous studies have suggested that commonly used conceptual groupings (uteroplacental ischemia, maternal vasculopathy) are vague and result in low agreement between pathologists in what constitutes a positive finding (Table 3). Our tool identifies what individual findings represent each conceptual grouping. This strongly suggests our results will be reproducible assuming the same study protocol. In addition, we tested the correlations between conceptual groupings to identify any collinearity. This suggests that each pathology grouping could potentially represent a unique pathway to preterm delivery. Although not reported here, our investigation employed factor analysis in our analysis to determine the patterns of relationships between the placental pathology variables used. The factors created were extremely similar to the empirical constructs used in this study. The results of this analysis were reassuring in that it added validity to our five constructs.

Limitations of the Study

A limitation is that our approach required extensive effort to evaluate and score each placenta. But our intent was not to supplant the hospital-based pathologists' diagnostic process, which is less time consuming, encompasses pattern recognition, makes use of clinical information, and allows for expert interpretation of placental findings. Rather we view our approach as a research tool that can aid in uncovering similarities and distinctions between the various vascular-related pathways that affect pregnancy outcomes. In future analyses we plan to assess the importance of individual placenta vascular findings within each vascular construct, and through sensitivity analyses determine which if any can be excluded.

Another limitation to our approach is that we were unable to test either interrater or intrarater reliability of our placental tool. Because it is extensive and time-consuming, it could be difficult to reproduce. Future work will include testing the reliability of the tool and determining if the tool can be collapsed to a more usable size.

CONCLUSION

Despite evidence that the vascular pathways leading to PTD have some overlapping features (90), we have found with our results that separating vascular constructs may be informative as we move forward to examine biomarkers and upstream and downstream risk factors in greater depth. This approach is a more in depth look at vascular pathology than has been previously attempted. It is unique in that it related placental vascular pathology to both preterm delivery subtypes and gestational age.

This study provides new insights into the relationship between maternal and fetal placental vascular changes and preterm delivery. More importantly, it provides evidence that vascular findings on the fetal and maternal sides of the placenta are independently related to PTD. Because these conceptual groupings have little overlap, we can conclude that multiple vascular pathways exist to preterm delivery. Since some of these vascular groupings have previously been related to a myriad of clinical circumstances, maternal disorders and birth outcomes, there could also be some common vascular pathways to PTD.

Future research should focus on clarifying the relations found here and identifying possible biomarkers reflective of the underlying pathologic processes leading to PTD. A

larger cohort study could provide enough power to further divide birth outcomes and gestational age in an attempt to clarify the relations found here. A larger study would also make it possible to further investigate the importance of other risk factors (race, age, SES, parity) in this association. Ultimately, conclusions developed here could help decipher the complicated relationship between the placenta and preterm delivery, leading to the early identification of those pathways leading to PTD.

Appendix A: Tables

Table 1: Studies using individual lesions

	Study	Population	Vasc lesion used	Results	Conclusions
Kim, 2002 (38)	Blinded, cross-sectional	59 term, 113 preterm: all c-section	Failure of physiologic transformation of vessels in myometrium	Failure of transformation was greater in preterm PROM and preeclampsia than in term	Defective placentation is present in PTD
Kim, 2003 (37)	Blinded, cross-sectional	103 term, 27 PTL, 43 preeclampsia	Failure of transformation of spiral vessels in myometrium and decidua	Failure was greater in myometrium and decidua of placental bed in PTD. Failure was the same in decidual plate of term and PTD.	Defective placentation in placental bed and myometrium is frequent in PTL and PE.
Stanek, 2005 (68)	Case control	52 cases with laminar necrosis	Laminar necrosis (LN)	LN is associated with hypertensive disorders and markers of utero hypoxia. LN is not associated with gestational age	LN could be a marker of hypoxic placental lesions
Redline, 1995 (61)	Case control-matched on gestational age	29 cases, 58 controls	Avascular villi	AV associated with IUGR, oligohydrmnios, late decelerations. AV more likely to be found with throboembolic disease.	AV is the most sensitive, specific, and quantifiable indicator of fetal thrombotic vasculopathy

Table 2: Studies using grouped lesions

	Study	Population	Inclusion Criteria	PTD outcome	Results	Grouped lesions used
Arias, 1993 AJOG (36)	Case cohort	Community hospital- 105 term, 63 PROM, 42 PTL	?	PTL PROM	1. Infection and maternal vasculopathy is higher in PTL and PROM than term 2. Abruptio is higher in PTL only	1. Maternal vasculopathy- failure of transformation of vessels, thrombi, syncytial knots, placental infarcts
Beebe, 1996 (79)	Case series	University hospital- 1252 preterm deliveries	All PTL< 37 wks, middle class, at least high school educated	PTL	1. Most common findings=ischemic change, meconium and chorioamnionitis 2. Clustering showed that the majority of placentas had only 1 major group of pathologic entity. 3. SGA related to infarction	1. Ischemic changes- villous agglutination, atrophic villi, syncytial knots, perivillous fibrin, infarcts, avascular villi, fibrinoid necrosis, x-cell proliferation
Ghidini, 1997 (75)	cohort	University hospital- 465 preterm	Liver births <32 weeks	All PTD	1. Vascular lesion score correlated with preeclampsia when compared to all PTD.	Uteroplacental vascular lesion score: 1. Absence of physiologic change of vessels 2. Fibrinoid necrosis 3. Abruptio 4. Villous infarcts 5. terminal villous fibrosis 6. Syncytial knots 7. X-cell proliferation 8. Villous hypovascularity 9. Intervillous thrombus, and 10. Nucleated RBCs
Ogunyemi, 2003 (76)	chart review	Community hospital- 774 preterm	All PTD 24-32 weeks	All PTD	1. Vascular placental pathology related to medically-indicated, preeclampsia, vaginal bleeding	1. placental vascular pathology- infarction, abruption, villous fibrosis, sclerosis, intimal hypertrophy, fibrinoid necrosis
Salafia, 1995 AJP (33)		University hospital- 214 term, 249 preterm	All preterm weighing less than 1500g at 24-34 weeks	VLBW PTD	1. Decidual vasculopathy more common in VLBW than term	1. decidual vasculopathy- absence of conversion of vessels, decidual vasculitis, fibrinoid necrosis

Table 3: Comparison of Groupings of Placental Vascular Pathology

Author	Placental Vascular Pathology
Arias et al, 1993 (36)	1)**Maternal vascular pathology:** unaltered spiral arteries containing recent or old organized thrombi, mural or occlusive, presence of uneven accelerated maturation of the chorionic villi, large numbers of multinucleated syncytial knots, and multiple placental infarcts.
Salafia et al, 1995 (33)	1) **Decidual vasculopathy**: aberrant conversion of spiral arteries, decidual vasculitis, and fibrinoid necrosis or atherosis 2) **Uterine vascular insufficiency**: villous infarcts, intervillous thrombi, gross or microscopic evidence of abruption and villous lesions ...Gross evidence of abruption was frank retroplacental clots with placental compression. Microscopically, abruption was diagnosed if retroplacental hemorrhage and basal plate destruction was accompanied by villous necrosis, trophoblast basophilia and villous crowding.
Beebe et al, 1996 (79)	1) **Histopathologic ischemic changes**: villous agglutination, shrinkage of villi, numerically increased syncytiotrophoblastic knots, increased perivillous fibrin, infarcts, sclerotic or avascular villi and fibrinoid material with abundant X cells. 2) **Placental infarcts**: ischemic villous necrosis, diffuse fibrinoid material with abundant X cells and, sometimes, ghost-like villi.
Ghidini et al, 1997 (75)	1) **Uteroplacental vascular and related villous lesions**: unaltered spiral arteries, fibrinoid necrosis and atheroma, abruptio placentae, villous infarcts, terminal villous fibrosis, increased syncytiotrophoblastic knotting, cytotrophoblast proliferation, villous hypovascularity, villous thrombus, circulating fetal nucleated erythrocytes.
Kim et al, 2002 (38)	1) **Aggregated vascular lesion**: atherosis, fibrinoid necrosis of the decidual vessels, decidual vessel thrombosis, and fetal thrombotic vasculopathy (fibrin thrombi in chorionic or stem vessels
Ogunyemi et al, 2003 (76)	1) **Placental vascular pathology**: placental infarction, placental abruption, villous fibrosis and sclerosis, vascular intimal hypertrophy and decidual fibrinoid necrosis. 2) **Coagulation-related lesions**: uteroplacental thrombosis, hemorrhagic endovasculitis, intervillous thrombosis and intervillous fibrin deposit.

Table 4: Studies testing intra/interobserver reliability

	placental findings used	Intraobserver reliability	Interobserver reliability
Kramer, 2006 (77)	A. Chorioamnitis B. Syncytial knots C. Infarction D. Villitis **E. Decidual Vasculopathy** **F. Fetal Vasculopathy**	A. 0.51 B. 0.38 C. 0.78 D. 0.58 E. 0.62 F. -0.02	A. 0.58 B. NC C. 0.79 D. 0.28 **E. -0.02** F. **-0.02**
Redline 2004 (40)	A. syncytial knots B. intervillous fibrin C. villous hypoplasia D. Acute atherosis E. Mural hypertrophy F. maternal underperfusion	None	A. 0.42 B. 0.25 C. 0.57 D. 0.50 E. 0.43 F. 0.54
Redline 2004 (64)	A. Avascular villi B. Fetal thrombosis C. Intimal fibrin cushion-recent, remote D. Fetal Vascular obstruction	None	A. 0.49 B. 0.34 C. 0.47, 0.78 D. 0.63
Grether 1999 (78)	A. Acute chorioamnionitis B. Chorionic Vasculitis C. syncytial knots D. **Maternal vasculopathy** E. Chronic chorioamnionitis		A. 0.66 B. 0.51 C. 0.25 **D. 0.23** E. 0.51

Table 5. Maternal characteristics and pregnancy outcome in the sub-cohort with completed placental assessments (N= 1053)

Maternal Characteristics	N	%	Weighted %†
Maternal Age (years)			
< 20	167	15.9	13.8
20 - < 30	592	56.2	56.5
>= 30	294	27.9	29.7
Maternal Education (years)			
< 12	213	20.2	16.9
= 12	301	28.6	27.4
> 12	539	51.2	55.7
Race/Ethnicity			
Non-Hispanic Whites	568	53.9	65.9
African Americans	403	38.3	24.6
Others	82	7.8	9.5
Medicaid Insured			
Yes	567	53.9	48.0
No	485	46.1	52.0
Parity			
No previous live birth	433	41.1	41.0
Previous live birth w/ PTD	59	5.6	4.4
Previous live birth w/o PTD	561	53.3	54.6
Week of Pregnancy at Enrollment			
15- < 20	154	14.6	13.8
20- < 25	748	71.0	72.0
25- < 27	151	14.4	14.2
Pregnancy Outcome			
Term	814	77.3	89.3
Spontaneous PTD	163	15.5	7.4
Medically-indicated PTD	76	7.2	3.3

† weighted for the sub-cohort sampling scheme; percentages reflect distribution in original cohort.

Table 6a. Spearman's rank correlations (p value) between pathology-based vascular construct scores*

	MV-O	MV-I	MV-D	FV-O	FV-I
MV-O	1				
MV-I	0.30 (<.0001)	1			
MV-D	0.04 (0.23)	0.08 (0.01)	1		
FV-O	0.25 (<.0001)	0.12 (<.0001)	0.03 (0.39)	1	
FV-I	0.07 (0.03)	0.19 (<.0001)	0.05 (0.09)	0.04 (0.25)	1

* continuous scores

Table 6b. Kappa coefficients for co-occurrence of high pathology-based vascular construct scores*

	MV-O	MV-I	MV-D	FV-O	FV-I
MV-O	1				
MV-I	0.17	1			
MV-D	0.09	0.03	1		
FV-O	0.18	0.08	0.07	1	
FV-I	-0.01	0.10	0.05	0.02	1

* dichotomous scores

Table 7. Maternal characteristics in relation to pathology-based vascular constructs (weighted percentages†, N= 1053)

	Maternal Vascular Obstructive		Maternal Vascular Disturbance of Integrity		Maternal Vascular Developmental		Fetal Vascular Obstructive		Fetal Vascular Disturbance of Integrity	
	MV-O		MV-I		MV-D		FV-O		FV-I	
	Normal %	High %	Normal %	High %	Normal %	High %	Normal %	High %	Normal %	High %
Race/Ethnicity										
White/Others	86	14	81	19*	90	10	84	16*	60	40
African American	86	14	88	12	77	23*	89	11	66	34
Maternal age (years)										
< 20	83	17	82	18	74	26*	82	18	64	36
20 - 29	88	12	84	16	87	13	88	12	62	38
>= 30	82	18	83	17	90	10	83	17	57	43
Medicaid insured										
Yes	85	15	85	15	83	17*	87	13	62	38
No	86	14	82	18	90	10	84	16	60	40
Parity										
0	81	19*	84	16	88	12	81	19*	63	37
Previous live birth w/ PTD	92	8	78	22	92	8	85	15	62	38
Previous live birth w/o PTD	88	12	83	17	85	15	89	11	59	41
BMI**										
Normal	83	17	82	18	92	8	87	13	64	36
Overweight	87	13	86	14	82	18	84	16	59	41
Obese	88	12	81	19	79	21*	85	15	56	44

† weighted for the sub-cohort sampling scheme; percentages reflect distribution in original cohort.
* P<0.05

Table 8. Associations between vascular constructs and preterm delivery (N= 1053); unadjusted odds ratios (95%CI)*

Pathology-based groupings	Medically-indicated PTD		Spontaneous PTD	
	< 35	35-36	< 35	35-36
Maternal vascular lesion-obstructive (MV-O)	**4.8 (2.2, 11)**	1.6 (0.7, 3.4)	0.4 (0.1, 1.3)	0.8 (0.4, 1.5)
Syncytial knots				
Villous infarcts				
Perivillous fibrin (not in Redline)				
X-cell proliferation (not in Redline)				
Fibrinoid necrosis/ atherosis in decidual vessels- basal plate				
Fibrinoid necrosis/ atherosis in decidual vessels- membranes				
Non-inflammatory necrosis of decidua in basal plate				
Non-inflammatory necrosis of decidua in membranes				
Maternal vascular lesion-disturbance of integrity (MV-I)	**3.6 (1.6, 8.1)**	1.0 (0.4, 2.3)	**2.0 (1.0, 4.0)**	1.1 (0.6, 1.9)
Retroplacental blood with disruption/compression				
Retroplacental blood with fibrin				
Retromembranous blood				
Decidual hemorrhage in basal plate				
Decidual hemorrhage in membranes				
Decidual thrombi in basal plate or membranes				

Table 8 continued.

Pathology- based groupings	Medically-indicated PTD		Spontaneous PTD	
	<35	35-36	<35	35-36
Pigment/hemosiderin in amnion/chorion				
Pigment/hemosiderin-like in deciduas of membranes				
Pigment/hemosiderin-like in deciduas of basal plate				
Maternal vascular lesion-developmental (MV-D)	**4.8 (2.2, 11)**	1.9 (0.9, 4.1)	**2.1 (1.0, 4.5)**	1.7 (1.0, 2.9)
Unaltered/abnormal decidual vessels in basal plate				
Unaltered/abnormal decidual vessels in membranes				
Mural hyperplasia of decidual vessel in basal plate				
Mural hyperplasia of decidual vessels in membranes				
Fetal vascular lesion-obstructive (FV-O)	2.3 (1.0, 5.5)	1.0 (0.4, 2.4)	0.5 (0.2, 1.5)	0.7 (0.3, 1.3)
Thrombi in small fetal disc vessels				
Luminal septation small fetal vessels				
Hemorrhagic-mural disruption small fetal vessels				
Fragmented RBC in small fetal vessels				
Non-tropho karyorrhexis small fetal vessels				
Thrombi in large fetal disc vessels				
Luminal septation large stem fetal vessels				
Hemorrhagic-mural disruption large stem fetal vessels				

Table 8 continued.

Pathology-based groupings	Medically-indicated PTD		Spontaneous PTD	
	<35	35-36	<35	35-36
Fragmented RBC in large stem fetal vessels				
Non-tropho karyorrhexis large stem fetal vessels				
Thrombi in chorionic plate fetal vessels				
Sub-intimal cushions in chorionic plate fetal vessels				
Sub-intimal cushions in large fetal disc vessels				
Avascular villi				
Fetal vascular lesion-disturbance of integrity (FV-I)	**3.1 (1.4, 6.8)**	1.7 (0.9, 3.1)	1.8 (1.0, 3.3)	**1.8 (1.2, 2.7)**
Subchorionic hemorrhage (maternal dissecting hemorrhage)				
Villous stromal hemorrhage				
Villous edema				
Intervillous thrombus				

* Weighted polytomous logit models.

Table 9. Associations between vascular constructs and medically-indicated PTD (N= 890†)

	Medically-indicated PTD, adjusted odds ratios (95%CI)			
	* Model includes all five vascular		** Model includes all five vascular constructs, race, Medicaid, parity, maternal age and BMI (pre-pregnancy/at screening, continuous).	
	< 35*	**35-36***	**< 35****	**35-36****
MV-O	**3.5 (1.6, 7.7)**	1.5 (0.7, 3.3)	**3.5 (1.6, 7.8)**	1.5 (0.7, 3.5)
MV-I	**2.4 (1.0, 5.6)**	0.8 (0.3, 2.0)	**2.5 (1.1, 5.9)**	0.9 (0.4, 2.3)
MV-D	**3.6 (1.6, 8.2)**	1.8 (0.8, 4.0)	**3.7 (1.6, 8.8)**	1.5 (0.6, 3.7)
FV-O	1.3 (0.5, 3.4)	0.9 (0.4, 2.1)	1.4 (0.5, 3.6)	0.9 (0.4, 2.0)
FV-I	**2.8 (1.2, 6.5)**	1.6 (0.8, 3.1)	**2.8 (1.2, 6.5)**	1.6 (0.8, 3.2)

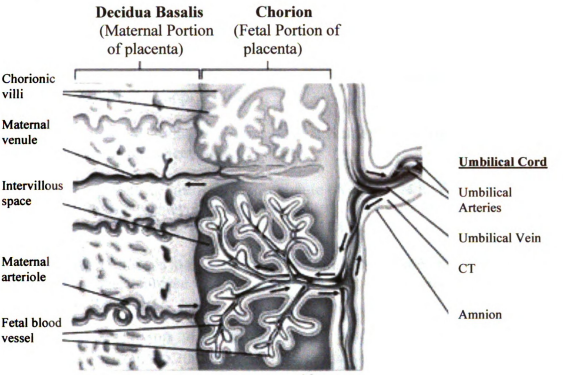
† Term and medically-indicated PTD only

Table 10. Associations between vascular constructs and spontaneous PTD (N= 977†)

	Spontaneous PTD, adjusted odds ratios (95%CI)			
	* Model includes all five vascular constructs.		** Model includes all five vascular constructs, race, Medicaid, parity, maternal age and BMI (pre-pregnancy/at screening, continuous).	
	< 35*	**35-36***	**< 35****	**35-36****
MV-I, MV-D, FV-I				
(+, −, −)	0.5 (0.1, 2.0)	**2.8 (1.3, 6.3)**	0.6 (0.1, 2.4)	**2.9 (1.3, 6.6)**
(−, +, −)	1.3 (0.3, 5.8)	**4.6 (2.2, 9.6)**	1.3 (0.3, 6.0)	**4.4 (2.0, 9.6)**
(−, −, +)	0.8 (0.3, 1.9)	**3.0 (1.8, 4.9)**	1.0 (0.4, 2.3)	**3.0 (1.8, 5.2)**
(+, +, −)	2.3 (0.3, 21)	**0.0 (0.0, 0.0)**	4.0 (0.4, 36)	**0.0 (0.0, 0.0)**
(+, −, +)	**4.2 (1.7, 11)**	2.2 (0.9, 5.2)	**5.6 (2.2, 14)**	2.3 (1.0, 5.5)
(−, +, +)	**3.7 (1.2, 11)**	2.5 (0.9, 6.5)	**3.6 (1.2, 11)**	2.6 (1.0, 7.2)
(+, +, +)	4.3 (0.8, 23)	1.4 (0.2, 12)	**7.5 (1.3, 42)**	1.4 (0.2, 13)
MV-O	0.3 (0.1, 1.3)	0.8 (0.4, 1.5)	0.3 (0.1, 1.1)	0.8 (0.4, 1.5)
FV-O	0.5 (0.2, 1.7)	0.6 (0.3, 1.2)	0.5 (0.2, 1.7)	0.6 (0.3, 1.3)

Appendix B: Figures

Figure 1: Structure of the Placenta



References

1. Anderson P, Doyle LW. Neurobehavioral outcomes of school-age children born extremely low birth weight or very preterm in the 1990s. JAMA 2003;289:3264-72.

2. Romero R, Espinoza J, Kusanovic JP, et al. The preterm parturition syndrome. BJOG 2006;113 Suppl 3:17-42.

3. Goldenberg RL, Culhane JF, Iams JD, et al. Epidemiology and causes of preterm birth. Lancet 2008;371:75-84.

4. Martin JAH, B. E.; Sutton P. D. ; Stephanie J. Ventura, M.A.; Fay Menacker, Dr. P.H.;, Sharon Kirmeyer PDaMLM, M.S. Birth: Final Data for 2005. National Vital Statistics Reports- CDC 2007;56:1-104.

5. Bhutta AT, Cleves MA, Casey PH, et al. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 2002;288:728-37.

6. Mathews TJMMFM, Ph.D., Division of Vital Statistics. Infant Mortality Statistics from the 2005 Period Linked Birth/Infant Death Data Set. National Vital Statistics Reports- CDC 2008;57:1-32.

7. Gupta SN, Kechli AM, Kanamalla US. Intracranial hemorrhage in term newborns: management and outcomes. Pediatr Neurol 2009;40:1-12.

8. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284:843-9.

9. Rich-Edwards JW, Gillman MW. Commentary: a hypothesis challenged. BMJ 1997;315:1348-9.

10. Cuevas KD, Silver DR, Brooten D, et al. The cost of prematurity: hospital charges at birth and frequency of rehospitalizations and acute care visits over the first year of life: a comparison by gestational age and birth weight. Am J Nurs 2005;105:56-64; quiz 5.

11. Peacock JL, Bland JM, Anderson HR. Preterm delivery: effects of socioeconomic factors, psychological stress, smoking, alcohol, and caffeine. BMJ 1995;311:531-5.

12. Parker JD, Schoendorf KC, Kiely JL. Associations between measures of socioeconomic status and low birth weight, small for gestational age, and premature delivery in the United States. Ann Epidemiol 1994;4:271-8.

13. Basso O, Olsen J, Christensen K. Study of environmental, social, and paternal factors in preterm delivery using sibs and half sibs. A population-based study in Denmark. J Epidemiol Community Health 1999;53:20-3.

14. Thompson JM, Irgens LM, Rasmussen S, et al. Secular trends in socio-economic status and the implications for preterm birth. Paediatr Perinat Epidemiol 2006;20:182-7.

15. Luo ZC, Kierans WJ, Wilkins R, et al. Disparities in birth outcomes by neighborhood income: temporal trends in rural and urban areas, british columbia. Epidemiology 2004;15:679-86.

16. Branum AM, Schoendorf KC. Changing patterns of low birthweight and preterm birth in the United States, 1981-98. Paediatr Perinat Epidemiol 2002;16:8-15.

17. Schoendorf KC, Hogue CJ, Kleinman JC, et al. Mortality among infants of black as compared with white college-educated parents. N Engl J Med 1992;326:1522-6.

18. McGrady GA, Sung JF, Rowley DL, et al. Preterm delivery and low birth weight among first-born infants of black and white college graduates. Am J Epidemiol 1992;136:266-76.

19. Collins JW, Jr., Hammond NA. Relation of maternal race to the risk of preterm, non-low birth weight infants: a population study. Am J Epidemiol 1996;143:333-7.

20. Goldenberg RL, Andrews WW, Faye-Petersen O, et al. The Alabama Preterm Birth Project: placental histology in recurrent spontaneous and indicated preterm birth. Am J Obstet Gynecol 2006;195:792-6.

21. Bloom SL, Yost NP, McIntire DD, et al. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001;98:379-85.

22. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92:921-8.

23. Kristensen J, Langhoff-Roos J, Kristensen FB. Implications of idiopathic preterm delivery for previous and subsequent pregnancies. Obstet Gynecol 1995;86:800-4.

24. Adams MM, Elam-Evans LD, Wilson HG, et al. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283:1591-6.

25. Ananth CV, Getahun D, Peltier MR, et al. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195:643-50.

26. Demissie K, Rhoads GG, Ananth CV, et al. Trends in preterm birth and neonatal mortality among blacks and whites in the United States from 1989 to 1997. Am J Epidemiol 2001;154:307-15.

27. Goldenberg RL, Iams JD, Mercer BM, et al. The preterm prediction study: the value of new vs standard risk factors in predicting early and all spontaneous preterm births. NICHD MFMU Network. Am J Public Health 1998;88:233-8.

28. Faye-Petersen OM. The placenta in preterm birth. J Clin Pathol 2008;61:1261-75.

29. Romero R, Gomez R, Chaiworapongsa T, et al. The role of infection in preterm labour and delivery. Paediatr Perinat Epidemiol 2001;15 Suppl 2:41-56.

30. Pickett KE, Abrams B, Selvin S. Defining preterm delivery--the epidemiology of clinical presentation. Paediatr Perinat Epidemiol 2000;14:305-8.

31. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol 2006;195:1557-63.

32. Shim SS, Romero R, Hong JS, et al. Clinical significance of intra-amniotic inflammation in patients with preterm premature rupture of membranes. Am J Obstet Gynecol 2004;191:1339-45.

33. Salafia CM, Ernst LM, Pezzullo JC, et al. The very low birthweight infant: maternal complications leading to preterm birth, placental lesions, and intrauterine growth. Am J Perinatol 1995;12:106-10.

34. Mehta R, Nanjundaswamy S, Shen-Schwarz S, et al. Neonatal morbidity and placental pathology. Indian J Pediatr 2006;73:25-8.

35. Salafia CM, Lopez-Zeno JA, Sherer DM, et al. Histologic evidence of old intrauterine bleeding is more frequent in prematurity. Am J Obstet Gynecol 1995;173:1065-70.

36. Arias F, Rodriquez L, Rayne SC, et al. Maternal placental vasculopathy and infection: two distinct subgroups among patients with preterm labor and preterm ruptured membranes. Am J Obstet Gynecol 1993;168:585-91.

37. Kim YM, Bujold E, Chaiworapongsa T, et al. Failure of physiologic transformation of the spiral arteries in patients with preterm labor and intact membranes. Am J Obstet Gynecol 2003;189:1063-9.

38. Kim YM, Chaiworapongsa T, Gomez R, et al. Failure of physiologic transformation of the spiral arteries in the placental bed in preterm premature rupture of membranes. Am J Obstet Gynecol 2002;187:1137-42.

39. Iams JD, Romero R, Culhane JF, et al. Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008;371:164-75.

40. Redline RW, Boyd T, Campbell V, et al. Maternal vascular underperfusion: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004;7:237-49.

41. Andrews WW, Hauth JC, Goldenberg RL. Infection and preterm birth. Am J Perinatol 2000;17:357-65.

42. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500-7.

43. Goncalves LF, Chaiworapongsa T, Romero R. Intrauterine infection and prematurity. Ment Retard Dev Disabil Res Rev 2002;8:3-13.

44. Cross JC. Placental function in development and disease. Reprod Fertil Dev 2006;18:71-6.

45. Sadler TW, Langman J. Langman's medical embryology, Chapter 7: Fetal Membranes and Placenta, Lippincott Williams & Wilkins (Philadelphia), 2000.

46. Wan H, Versnel MA, Cheung WY, et al. Chorionic gonadotropin can enhance innate immunity by stimulating macrophage function. J Leukoc Biol 2007;82:926-33.

47. Lessin DL, Hunt JS, King CR, et al. Antigen expression by cells near the maternal-fetal interface. Am J Reprod Immunol Microbiol 1988;16:1-7.

48. Khong TY. Immunohistologic study of the leukocytic infiltrate in maternal uterine tissues in normal and preeclamptic pregnancies at term. Am J Reprod Immunol Microbiol 1987;15:1-8.

49. Singh U, Nicholson G, Urban BC, et al. Immunological properties of human decidual macrophages--a possible role in intrauterine immunity. Reproduction 2005;129:631-7.

50. Hirano H, Imai Y, Ito H. Spiral artery of placenta: development and pathology-immunohistochemical, microscopical, and electron-microscopic study. Kobe J Med Sci 2002;48:13-23.

51. Salafia CM, Pijnenborg R, ED: Lewis SH, et al. Pathology of the placenta Ch 8: Disorders of the Decidua and Maternal Vasculature, Churchill Livingstone (New York), 1999.

52. Redline RW. Placental pathology: a systematic approach with clinical correlations. Placenta 2008;29 Suppl A:S86-91.

53. Benirschke K, Kaufmann P, Baergen RN, et al. Pathology of the human placenta: Ch 9- Nonvillous Parts and Trophoblast Invasion, Springer (New York), 2006. (Access to the SpringerLink online version restricted; authentication may be required;

54. Faye-Petersen OM, Heller DS, Joshi VV. Handbook of placental pathology. London ; New York: Taylor & Francis, 2006.

55. Popek EJ, Lewis SH, Perrin EVDK. Pathology of the placenta- Ch 3: Normal Anatomy and Histology of the Placenta, Churchill Livingstone (New York), 1999.

56. Baergen RN, Benirschke K. Manual of Benirschke and Kaufmann's Pathology of the human placenta: Ch 19- Miscellaneous Placental Lesions. New York: Springer, 2005.

57. Benirschke K, Kaufmann P, Baergen RN, et al. Pathology of the human placenta: Ch 14- Histopathologic Approach to Villous Alterations, Springer (New York), 2006. (Access to the SpringerLink online version restricted; authentication may be required;

58. Benirschke K, Kaufmann P, Baergen RN, et al. Pathology of the human placenta: Ch 12- Anatomy and Pathology of the Umbilical Cord, Springer (New York), 2006. (Access to the SpringerLink online version restricted; authentication may be required;

59. Benirschke K, Kaufmann P, Baergen RN, et al. Pathology of the human placenta: Ch 7-Architecture of Normal Villous Trees, Springer (New York), 2006. (Access to the SpringerLink online version restricted; authentication may be required;

60. McDonald DG, Kelehan P, McMenamin JB, et al. Placental fetal thrombotic vasculopathy is associated with neonatal encephalopathy. Hum Pathol 2004;35:875-80.

61. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol 1995;26:80-5.

62. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. Am J Obstet Gynecol 2005;192:452-7.

63. Baergen RN, Benirschke K. Manual of Benirschke and Kaufmann's Pathology of the human placenta: Ch 21- Fetal Thrombotic Vaculopathy. New York: Springer, 2005.

64. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol 2004;7:443-52.

65. Redline R, Ed.: Lewis SH, Ed: Perrin EVDK. Pathology of the placenta- Chapter 7: Disorders of the Placental Parenchyma, Churchill Livingstone (New York), 1999.

66. Naeye RL, Maisels MJ, Lorenz RP, et al. The clinical significance of placental villous edema. Pediatrics 1983;71:588-94.

67. Kliman HJ, Perrotta PL, Jones DC. The efficacy of the placental biopsy. Am J Obstet Gynecol 1995;173:1084-8.

68. Stanek J, Al-Ahmadie HA. Laminar necrosis of placental membranes: a histologic sign of uteroplacental hypoxia. Pediatr Dev Pathol 2005;8:34-42.

69. Salafia CM, Vogel CA, Vintzileos AM, et al. Placental pathologic findings in preterm birth. Am J Obstet Gynecol 1991;165:934-8.

70. Germain AM, Carvajal J, Sanchez M, et al. Preterm labor: placental pathology and clinical correlation. Obstet Gynecol 1999;94:284-9.

71. Salafia CM, Pezzullo JC, Ghidini A, et al. Clinical correlations of patterns of placental pathology in preterm pre-eclampsia. Placenta 1998;19:67-72.

72. Salafia CM, Pezzullo JC, Lopez-Zeno JA, et al. Placental pathologic features of preterm preeclampsia. Am J Obstet Gynecol 1995;173:1097-105.

73. Salafia CM, Minior VK, Pezzullo JC, et al. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. Am J Obstet Gynecol 1995;173:1049-57.

74. Salafia CM, Vogel CA, Bantham KF, et al. Preterm delivery: correlations of fetal growth and placental pathology. Am J Perinatol 1992;9:190-3.

75. Ghidini A, Salafia CM, Pezzullo JC. Placental vascular lesions and likelihood of diagnosis of preeclampsia. Obstet Gynecol 1997;90:542-5.

76. Ogunyemi D, Murillo M, Jackson U, et al. The relationship between placental histopathology findings and perinatal outcome in preterm infants. J Matern Fetal Neonatal Med 2003;13:102-9.

77. Kramer MS, Chen MF, Roy I, et al. Intra- and interobserver agreement and statistical clustering of placental histopathologic features relevant to preterm birth. American journal of obstetrics and gynecology 2006;195:1674-9.

78. Grether JK, Eaton A, Redline R, et al. Reliability of placental histology using archived specimens. Paediatr Perinat Epidemiol 1999;13:489-95.

79. Beebe LA, Cowan LD, Altshuler G. The epidemiology of placental features: associations with gestational age and neonatal outcome. Obstet Gynecol 1996;87:771-8.

80. Ananth CV, Savitz DA, Luther ER, et al. Preeclampsia and preterm birth subtypes in Nova Scotia, 1986 to 1992. American journal of perinatology 1997;14:17-23.

81. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. The New England journal of medicine 2004;350:672-83.

82. Chaiworapongsa T, Espinoza J, Gotsch F, et al. The maternal plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated in SGA and the magnitude of the increase relates to Doppler abnormalities in the maternal and fetal circulation. J Matern Fetal Neonatal Med 2008;21:25-40.

83. Chaiworapongsa T, Yoshimatsu J, Espinoza J, et al. Evidence of in vivo generation of thrombin in patients with small-for-gestational-age fetuses and pre-eclampsia. J Matern Fetal Neonatal Med 2002;11:362-7.

84. Romero R, Nien JK, Espinoza J, et al. A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate. J Matern Fetal Neonatal Med 2008;21:9-23.

85. Shibata E, Rajakumar A, Powers RW, et al. Soluble fms-like tyrosine kinase 1 is increased in preeclampsia but not in normotensive pregnancies with small-for-gestational-age neonates: relationship to circulating placental growth factor. The Journal of clinical endocrinology and metabolism 2005;90:4895-903.

86. Signore C, Mills JL, Qian C, et al. Circulating angiogenic factors and placental abruption. Obstet Gynecol 2006;108:338-44.

87. Thadhani R, Mutter WP, Wolf M, et al. First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia. The Journal of clinical endocrinology and metabolism 2004;89:770-5.

88. Elovitz MA, Baron J, Phillippe M. The role of thrombin in preterm parturition. American journal of obstetrics and gynecology 2001;185:1059-63.

89. Ananth CV, Getahun D, Peltier MR, et al. Placental abruption in term and preterm gestations: evidence for heterogeneity in clinical pathways. Obstet Gynecol 2006;107:785-92.

90. Villar J, Carroli G, Wojdyla D, et al. Preeclampsia, gestational hypertension, and intrauterine growth restriction, related or independent conditions? American journal of obstetrics and gynecology 2006;194:921-31.

91. Correa RR, Gilio DB, Cavellani CL, et al. Placental morphometrical and histopathology changes in the different clinical presentations of hypertensive syndromes in pregnancy. Arch Gynecol Obstet 2008;277:201-6.

92. Sander CM, Gilliland D, Akers C, et al. Livebirths with placental hemorrhagic endovasculitis: interlesional relationships and perinatal outcomes. Archives of pathology & laboratory medicine 2002;126:157-64.

93. Holzman C, Bullen B, Fisher R, et al. Pregnancy outcomes and community health: the POUCH study of preterm delivery. Paediatric and perinatal epidemiology 2001;15 Suppl 2:136-58.

94. Waller DK, Lustig LS, Cunningham GC, et al. The association between maternal serum alpha-fetoprotein and preterm birth, small for gestational age infants, preeclampsia, and placental complications. Obstet Gynecol 1996;88:816-22.

95. Dowling NF, Austin H, Dilley A, et al. The epidemiology of venous thromboembolism in Caucasians and African-Americans: the GATE Study. J Thromb Haemost 2003;1:80-7.