SUMMARIZING PLACENTAL VASCULAR PATHOLOGY FINDINGS AND THEIR RELATION TO PRETERM DELIVERY USING EXPLORATORY FACTOR ANALYSIS

By

Jianling Wang

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ABSTRACT

SUMMARIZING PLACENTAL VASCULAR PATHOLOGY FINDINGS
AND THEIR RELATION TO PRETERM DELIVERY
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An empirical approach was used to identify patterns of placental vascular lesions and their relation to preterm delivery (PTD) in the POUCH (Pregnancy Outcomes and Community Health) Study, which enrolled 3019 pregnant women (16-27 weeks' gestation) from 52 clinics among 5 Michigan cities. To date, 1052 subcohort placentas (238 preterm, 814 term) have been fully assessed. Placental pathology exams were performed and items for exploratory factor analysis (EFA) were compiled based on a diagnostic coding instrument. Six 'Factors' were derived from the EFA. They represented vascular lesions in the fetal compartment (Factors 1, 2) and maternal compartment (Factors 3 to 6), which closely paralleled the structure in the pathology-based coding instrument. Multinomial logistic models were performed with the outcome of PTD divided by weeks' gestation and by clinical subtype: spontaneous labor, premature rupture of membranes (PPROM), and medically indicated (MI). Each factor-based score was dichotomized as explanatory variables, using the values that were closest to 75th percentile of the distribution as cutoff points. In the model that included all six Factors, Factor 5 (maternal vessel obstruction) was associated with MI deliveries at <35 weeks (adjusted odds ratio (AOR) = 3.8, 95% CI 1.7, 8.7); Factor 4 (evidence of bleeding) was associated with spontaneous and MI deliveries <35 weeks (AOR =2.4, 95% CI 1.0, 5.8; AOR =2.9, 95% CI 1.2, 7.0); Factor 3 (maternal vasculopathy) was associated with MI and PPROM <35 weeks (AOR = 4.4, 95% CI 2.0, 10; AOR= 2.9, 95% CI 1.2, 6.9).). These results suggest that EFA may be useful in identifying multiple PTD-related vascular pathways for further study.

This thesis is dedicated to my parents who have given me

the opportunity of an education from the best schools.

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KEY TO ABBREVIATION

EFA	exploratory factor analysis
FV-I	fetal vascular lesions - disturbance of integrity
FV-O	fetal vascular lesions - obstructive
FV-OL	fetal vascular lesions - large vessel thrombi
FV-OS	fetal vascular lesions - small vessel thrombi
GA	gestational age at delivery
LMP	last menstrual period
MI	medically indicated preterm delivery
MoM	multiples of the mean
MSAFP	maternal serum alpha-fetoprotein
MV-D	maternal vascular lesions - development
MV-I	maternal vascular lesions - disturbance of integrity
MV-O	maternal vascular lesions - obstructive
POUCH	Pregnancy Outcomes and Community Health
PPROM	preterm premature rupture of membranes
PTD	preterm delivery
SP	spontaneous preterm delivery

BACKGROUND

Preterm delivery (PTD) is defined as delivery of an infant less than 37 completed weeks of gestation. PTD is the single largest factor worldwide in infant mortality (1) and morbidity (2). In the United States, PTD occurred in 12.2% of all births in 2009 and the incidence has increased 15 percent from 10.6% in 1990 (3). Attempts to prevent PTD have included enhanced prenatal care (4), frequent office visits and cervical examinations (5), home monitoring of uterine contractions (6, 7), prophylactic tocolytics (8-10), nutritional supplements (11-13) and social support (14). However, none of the above has been proved to be consistently beneficial.

A variety of risk factors for PTD have been identified by previous studies. Multiple gestations has been associated with increased risk of PTD (15-17). Among singleton births, prior preterm delivery has been consistently reported as a risk factor of PTD (18-24). Equally noteworthy is the racial/ethnical disparity in PTD incidence rates; the rate among African American women has been documented to be higher than other ethnic groups (25-27). Other risk factors include low body mass index and/or certain nutrient deficiencies (28-31), high levels of psychological or social stress (32-34), clinical depression/anxiety (35-37) and tobacco use (38, 39) during pregnancy.

PTD is often divided into subtypes by weeks of gestation or clinical circumstances. When divided by completed weeks of gestation, PTD is often grouped as very preterm (<32 weeks) and moderate preterm (32-36 weeks) (21, 40-44). Some studies have defined very preterm as less than 33 weeks (45) or 34 weeks (46) of gestation and the rest of PTD as moderate preterm. Some studies have also divided infants delivered between 32 and 36 weeks into two subgroups and both 34 weeks (47) and 35 weeks (48) were used as cut-off point.

Based on clinical circumstances, PTD is typically divided into medically-indicated preterm and spontaneous PTD. Medically-indicated preterm refers to those undertaken because of severe medical or obstetrical complications that jeopardize the health of the mother or the fetus. Spontaneous PTD is usually subdivided into two groups: spontaneous preterm labor with intact membranes and preterm premature rupture of the membranes (PPROM) before the onset of contractions. A study of the data assembled by the National Center for Health Statistics showed that in 2000, 10.4% of all the singleton births in the United States were PTD, among which 36% were medically-indicated, 55% were spontaneous preterm labor, and 9% were PPROM (49). Our understandings of the biologic pathways that contribute to these clinically-defined PTD subtypes are limited, and the pathways may be overlapping. Other categorization schemes, which are biologically-based and reflect the heterogeneous etiology of PTD, are needed as research on PTD progresses (50).

There are two pathways that have been linked to PTD. The association between inflammation/infection and PTD has been reported by several studies (51-54). Maternal vascular diseases have also been examined by investigators as a pathway to PTD. Common clinical conditions associated with vascular problems, e.g. pre-eclampsia, gestational hypertension, and chronic hypertension, have been related to PTD in various studies (55-58). These conditions have often been linked to placental vascular lesions in both the placental beds and placentas. The lack of remodeling of spiral arteries is usually seen in pregnancies with pre-eclampsia (59) and sometimes preterm premature rupture of membranes (60). Vascular abnormalities are related to the reduction in the uteroplacental blood flow and subsequently clinical manifestations of pre-eclampsia, intrauterine growth restriction and PTD (61-63).

Placental vascular pathological findings can reveal connections between PTD and its underlying causes and risk factors. Maternal placental vasculopathy was identified as a distinct subgroup among patients with preterm labor (64). PTD is more prevalent in women with systemic lupus erythematosus, which is related to placental vascular and coagulation-related lesions (65, 66). Utero-placental vascular lesions have been found in excess among women with PTD and the percentage of vasculopathy or infarction found among placentas from PTD women were higher than that among women who delivered at term (67). One study of patterns of placental pathology and preterm pre-eclampsia found that features of maternal and fetal compromise were related to placental pathological patterns (68).

However, the understanding of the overlapping of various maternal/fetal vascular abnormalities and their relation to the subtypes of PTD remain limited. Added to this gap is the lack of knowledge about the distributions of vascular abnormalities among the symptom-negative or the "normal" population of pregnant women because most of the prior studies were conducted in women with severe vascular complications as mentioned above. Few studies have empirically investigated the placental vascular pathology findings to identify which ones tend to co-occur and their implications in the vascular pathway to PTD.

Factor analysis is a group of statistical methods used to explain the relationships between a set of correlated variables by reducing them to a smaller number of composite variables, which are conceptually meaningful and called factors. These factors are often used in further analyses in combination with other statistical methods such as regression analysis. Factor analysis is usually divided into two categories: exploratory factor analysis (EFA) that is used to empirically investigate the nature of the underlying unobservable constructs and the confirmatory factor analysis (CFA) that is used to test the validity of a hypothesized set of constructs. Originated

from the field of psychometrics, a typical usage of factor analysis is to determine groups of variables that "hang together" in a questionnaire and develop scales that respond to a single characteristic when the results of the analysis are conceptually meaningful and interpretable (69).

Factor analysis has been applied to a variety of epidemiological studies (70-74). However, studies that have employed factor analysis to investigate morphological data are relatively infrequent. A few studies have utilized factor analysis to investigate the relation between brain MRI and schizophrenia. Tien and colleagues utilized both EFA and CFA to analyze data obtained from MRI brain volume measures (75). Faraone and colleagues used EFA to derive phenotypes using similar brain volume data from MRI (76). MRI data of hippocampal atrophy (hippocampal height and interuncal distance) and the severity of vascular pathology (number of brain infarcts) were studied using EFA to identify the vascular lesion(s) that discriminate demented from non-demented patients better (77). Additionally, a recent study applied EFA to data obtained from pathological examination of bone marrow to classify subtypes of thrombocythemia (78).

Few studies have utilized EFA to analyze placental vascular pathology data. Salafia and colleagues have employed EFA to relate placental lesions to pre-eclampsia (68, 79). However, only less than twenty different types of placental vascular lesions were reported in these studies. Hansen and colleagues studied placentas of very low birth weight infants using a larger number of pathological findings (80). Principal component analysis, a statistical method that is related to EFA, was used by Kramer and colleagues to organize placental pathology findings (81). Studies that apply EFA to a large number and a variety of placental vascular pathology findings might help us better understand the pathway of maternal vascular diseases in PTD.

INTRODUCTION

Preterm delivery (PTD) is defined as delivery of an infant less than 37 completed weeks of gestation and is associated with increased neonatal mortality (25). The association of PTD with physical and neurodevelopmental morbidity of both short-term and long-term was reported by national level studies (82-85). PTD occurred in 12.2% of all births in the United States in 2009 and the prevalence has increased 15 percent since 1990 (3). Attempts to prevent PTD have included enhanced prenatal care (4), frequent office visits and cervical examinations (5), home monitoring of uterine contractions (6, 7), prophylactic tocolytics (8-10), nutritional supplements (11-13) and social support (14). However, none of the above has been proved to be consistently beneficial.

To better understand PTD, it is often divided into subtypes by weeks of gestation or clinical circumstances. When divided by completed weeks of gestation, PTD is often divided as very preterm (<32 weeks) and moderate preterm (32-36 weeks) (21, 40-44). Some studies have defined very preterm as less than 33 weeks (45) or 34 weeks (46) of gestation and the rest of PTD as moderate preterm. Some studies have divided infants delivered between 32 and 36 weeks into two subgroups and both 34 weeks (47) and 35 weeks (48) were used as cut-off point. Based on the presence of severe maternal obstetric and medical complications during pregnancy and the initiation of labor or delivery, PTD is typically categorized as spontaneous labor, preterm premature rupture of membranes (PPROM), and medically indicated PTD. However, we don't have a full understanding of the biologic pathways that contribute to these clinically-defined PTD subtypes, and the pathways may be overlapping. Other categorization schemes, which are biologically-based and reflect the heterogeneous etiology of PTD, are needed as research on PTD progresses (50).

Despite the fact that our understanding about the pathways to PTD remains limited, there are at least two pathways that have been linked to PTD. Firstly, the association between inflammation/infection and PTD has been reported by several studies (51-54). The other pathway that has been examined by researchers is maternal vascular diseases. Common clinical conditions associated with vascular problems, e.g. pre-eclampsia, gestational hypertension, and chronic hypertension, have been related to PTD in various studies (55-58). These conditions have often been linked to placental vascular lesions in both the placental beds and placentas. The lack of remodeling of spiral arteries is usually seen in pregnancies with pre-eclampsia (59) and sometimes preterm premature rupture of membranes (60). Vascular abnormalities are related to the reduction in the uteroplacental blood flow and subsequently clinical manifestations of pre-eclampsia, intrauterine growth restriction and PTD (61-63).

Placental vascular pathological findings can reveal connections between PTD and its underlying causes and risk factors. Maternal placental vasculopathy was identified as a distinct subgroup among patients with preterm labor (64). PTD is more prevalent in women with systemic lupus erythematosus, which is related to placental vascular and coagulation-related lesions (65, 66). Utero-placental vascular lesions have been found in excess among women with PTD and the percentage of vasculopathy or infarction found among placentas from PTD women were higher than that among women who delivered at term (67). One study of patterns of placental pathology and preterm pre-eclampsia found that features of maternal and fetal compromise were related to placental pathological patterns (68).

The Pregnancy Outcomes and Community Health (POUCH) study was conducted to better understand the determinants of PTD and their underlying biological and psychosocial factors with three hypothesized pathways of PTD – one dominated by infection, one by maternal

vascular diseases, and one by premature elevations in corticotrophin releasing hormone in the absence of significant histo-pathological findings in the placenta (86). Analyzing the information of placental vascular pathological findings obtained in the POUCH study might help us to better understand the pathway of maternal vascular diseases in PTD.

This thesis will investigate the placental vascular pathology data from the POUCH study by using exploratory factor analysis (EFA) as a tool for examining how vascular findings are grouped. One aim is to observe how well an empirically-driven EFA structure coincides with a pathology-based structure adapted from the Placental Diagnostic Coding Tool by Redline (87). Additionally, the relation between factors extracted by EFA and PTD subtypes defined by clinical circumstances or gestational ages will be examined. By linking placental vascular findings to subtypes of PTD, we hope to get more information about biologic pathways that may be unique or overlapping in different subtypes.

MATERIALS AND METHODS

Study population

The POUCH Study recruited pregnant women, between September 1998 and June 2004, from 52 clinics in five Michigan communities. Inclusion criteria were maternal age $\geq$ 15 years, singleton pregnancy in the 16-27 week of pregnancy with no known chromosomal abnormality or birth defect, screening of maternal serum alpha-fetoprotein (MSAFP) in the 15-22 week of pregnancy, no pre-pregnancy diabetes mellitus, and proficiency in English. Eligible women were invited to participate at the time of MSAFP screening. The study included all women with MSAFP levels greater than 2 multiples of the mean (MoM), and an ethnicity stratified sample of women with normal MSAFP levels. Of 3,038 women enrolled, 19 were lost to follow-up,

resulting in a final cohort of 3,019 women. The study received approval from institutional review boards at Michigan State University, Michigan Department of Community Health, and nine community hospitals.

At enrollment, cohort women were interviewed and biologic samples were collected and stored. A sub-cohort of 1,371 women was created for in-depth analyses, which included assays of stored biologic samples, abstraction of prenatal and labor/delivery records, and examination of the delivered placentas by the study placental pathologist. The sub-cohort included all women with PTD (< 37 weeks), all women with elevated MSAFP (> 2 MoM), and a stratified sample of women with term deliveries and normal MSAFP levels (72% of African-American and 23% of white/other cohort women in the latter group). The sampling scheme was designed to maximize statistical power for studying at-risk subgroups, namely, African-Americans and women with high MSAFP. Placentas were retrieved for 1,213 (88%) sub-cohort women and this analysis included the 1052 women (238 preterm, 814 term) whose placentas were assessed by the POUCH study pathologist. .

Placenta examination

Placentas were formalin fixed and gross examination was performed using standard protocols. Nine tissue samples were paraffin-embedded for microscopic examination: two samples from extra-placental membrane; two from umbilical cord (one proximal and one distal to disc insertion); and five full-thickness disc samples, one from the cord insertion, one from central tissue that appeared normal on gross exam, two from central tissue and one from the margin, these latter three obtained from grossly visible abnormalities if present. The study pathologist was blinded to gestational age at delivery, all clinical data, and gross findings when performing microscopic examinations.

Placental diagnostic coding instrument

Placental microscopic findings were recorded in a computer-based data collection instrument adapted and expanded from Salafia (88), which is primarily descriptive, not diagnostic, and incorporates a large number of pathological findings with details such as their location, frequency, extent, and proximity to one another. Vascular pathological findings recorded in this instrument were extracted and organized using a scheme adapted from the Placental Diagnostic Coding Tool by Redline (87). This adapted data summary tool was used to categorize 39 findings into five conceptual groups: 1) MV-O (maternal vascular lesions-obstructive); 2) MV-I (maternal vascular-disturbance of integrity); 3) MV-D (maternal vascular-developmental); 4) FV-O (fetal vascular lesion-obstructive); and 5) FV-I (fetal vascular lesion-disturbance of integrity). The detailed findings in each group are listed in Table 1.

Pregnancy outcome

Gestational age at delivery was calculated using last menstrual period (LMP), or the estimate from ultrasound if the two estimates differed by more than two weeks. PTD was defined as birth occurred before 37 completed weeks of gestation. PTD was subdivided into three groups commonly used in clinical settings: 1) Spontaneous PTD, which included spontaneous labor with regular contractions that led to cervical changes ($\geq$2 cm dilatation); 2) PPROM, which is defined as rupture of membranes at the same time or before the onset of labor; and 3) Medically indicated PTD, which included delivery that begins by induction or C-section in the absence of spontaneous labor or rupture of membrane as an initiating event. Within the clinical subtypes, PTD was further divided according to gestational week at delivery, i.e. <35 weeks and 35-36 weeks, since pregnancy complications and clinical interventions vary as pregnancy progresses.

Analytical strategy

Our goals were to 1) use exploratory factor analysis (EFA) to identify patterns of placental vascular pathology findings; 2) compare the EFA results with a pathology-based grouping approach; and 3) categorize women based on EFA results and test the associations between EFA generated factors and risk of PTD by subtype. All analyses were performed with SAS 9.1.3 (89) using the principal axis factoring method (PROC FACTOR). Items used for EFA were compiled based on the adapted placental diagnostic coding instrument mentioned above.

The EFA method is based on the idea to extract (derive) a small number of latent variables from a larger set of observed variables. The latent variables extracted are usually called factors and the observed variables items. Factors were extracted, or derived, in descending order of importance according to the proportion of variance in the observed data set that are explained by each factor. In other words, the first factor is a combination of observed variables ("items") that together accounts for the largest proportion of the total variance of the observed data. The second factor, then, is the combination of observed variables that accounts for the largest proportion of the remaining variance, and so on (90).

In this study, placental vascular pathology findings were used as "items" and subjected to EFA to identify "factors" that reflect the patterns of how these findings relate to each other. The EFAs were conducted using the following criteria: 1) Items with factor loadings $<\pm 0.30$ were dropped and the EFA was repeated until all remaining items loaded on one of the factors extracted; 2) Each factor had to account for at least 5% of the total variance; 3) Scree plots were examined for a "break" indicating a small change in the eigenvalue with an additional factor; and 4) Factors had to be conceptually meaningful. Oblique (promax) rotations were performed to ease the interpretation of the factors.

To detect stability of the factor structure, the sample was first split into two data sets using simple random sampling and EFA were conducted on each data set. Other subsets (term, preterm <37weeks, normal MSAFP, normal MSAFP and term) were also submitted to EFA to see whether the factor structures vary according to timing of delivery and a biomarker of potential complications (i.e. MSAFP levels).

Items had a continuous score representing the number of slides in which the vascular pathology finding was present. The scores ranged from 0 to 2 if the item was in the extraplacental membranes only (2 slides), 0 to 5 if the item was found only within the placental disc slides (5 slides) and 0 to 7 if the item could be found in the disc and the extraplacental membranes (7 slides). Factor-based scores were derived by adding up each item score in a factor with all items given equal weight. For example, if factor X is composed of 4 items (findings) and a woman had finding #1 on 3 slides, finding #2 on 2 slides and no findings #3 and #4, the factor-based score for factor X would equal 5. A factor score for each woman for a given factor was computed by taking the woman's standardized score on each item, multiplying it by the corresponding factor loading of the item for the given factor, and summing these products.

Pearson correlation coefficients between different factors were assessed to check the EFA process and the use of the factor-based scoring approach. Both factor-based scores and factor scores were then dichotomized as normal or high using the distribution of scores in placentas from term deliveries with normal MSAFP. The high cutoff was selected to be at the percentile closest to 75%. To take into account the oversampling of African-Americans, women with high MSAFP, and PTD into the subcohort, the sampling probability was incorporated using weighted analyses. SAS procedure PROC SURVEYLOGISTIC was used to fit multinomial logistic models to test the relations between the dichotomized vascular pathology factors and PTD.

RESULTS

Six factors, composed of the 24 items left from the initial 39 items, were retained in the EFA for the whole sample (Table 1). The items in the table are listed according to the pathology-based groupings to facilitate the comparison between the clinical and EFA approach.

The first factor extracted from the EFA included four items from the pathology-based "Fetal vascular lesion-obstructive" group that were related to thrombi of small vessels, thus named fetal vascular lesion-small vessel thrombi (FV-OS). The second factor was comprised of five items from the same pathology-based grouping, but the items were all related to large vessel thrombi, thus named fetal vascular lesion-large vessel thrombi (FV-OL). Four items from the "maternal vascular lesion-developmental" group and two items from the "maternal vascular lesion-obstructive" loaded onto the third factor and were named maternal vascular lesion-developmental (MV-D). Two items from "maternal vascular lesion-disturbance of integrity" loaded high on the fourth factor, which was named maternal vascular lesion-disturbance of integrity (MV-I). Four items from "maternal vascular lesion-obstructive" comprised the fifth factor which was named maternal vascular lesion-obstructive (MV-O). The last factor was a combination of one item from the pathology-based "maternal vascular lesion-obstructive" and two items from "maternal vascular lesion-disturbance of integrity" (MV-O/MV-I mix). We did not find a factor that contained findings of the "fetal vascular lesion-disturbance of integrity (FV-I)" group. The Pearson correlation coefficient between FV-OS and FV-OL was -0.47. All other inter-factor correlations were weak to moderate in magnitude with absolute values ranging from 0.02 to 0.35.

The EFA of the preterm only subset also resulted in six factors (Table 2). The components of FV-OS and FV-OL were same as those of the whole data set. For MV-D, the

results from preterm did not include the two items from the "maternal vascular lesion-obstructive" group, namely fibrinoid necrosis in decidua of basal plate and fibrinoid necrosis in decidua of membranes. The factor of MV-I extracted from preterm women had one more item from the "fetal vascular lesion-obstructive" part as compared with the result from the whole sub-cohort. For MV-O, the result from preterm women included three more items from the "maternal vascular lesion-obstructive" group. The last factor extracted from the preterm-only sample was a combination of two items from MV-I, one item from FV-O and one item from FV-I. This was the factor that had the poorest agreement when comparing results from the whole data set with that from the preterm subset, indicating a lack of stability.

EFA results from both the normal AFP subset and the normal AFP term delivery subset were comparable to that of the whole data set, with six factors and similar items selected within each factor. The two randomly-split samples also yielded similar EFA results, both having six factors with just a few items grouped differently across the data sets (details not shown).

To assess relations between vascular factors and PTD, EFA factor-based scores were dichotomized as normal or high using the percentile closest to 75% in the distribution of normal AFP, term deliveries. Due to the rarity of certain pathology findings, cut-off points for FV-OS and FV-OL were 79.2% and 92.1%, respectively. Dichotomized factor scores (described in methods) were compared to dichotomized factor-based scores for each factor using Pearson correlation coefficients. The correlation coefficients for the corresponding pairs were statistically significant and ranged from 0.72 to 0.95, thus justified the use of the factor-based score as a proxy for the factor score.

In the first set of analyses the dichotomized factor-based score for each vascular factor was entered into a separate model (Table 3). A high MV-D score and a high MV-I score were

significantly associated with PTD <35 weeks with odds ratios of 2.2 and 2.5 respectively. For MV-I the association was even stronger for PTD <32 weeks (OR=3.6). MV-D was significantly related to PPROM and medically indicated PTD at <35 weeks, with ORs of 2.9 and 4.6 respectively. MV-I was significantly related to spontaneous PTD and medically indicated PTD at <35 weeks with OR of 2.5 and 3.4 respectively. Both FV-OL and MV-O had significant odds ratios for medically indicated PTD <35 weeks with ORs of 2.9 and 4.6 respectively. After including all vascular factors into a single model, FV-OL was no longer significant for any of the PTD subtypes (table 4). This is probably caused by the fact that only a small number of women fell into this category, so future studies with larger sample size will be needed to fully explore this association. In addition the magnitude of the relations between MV-I and MV-O with medically indicated PTD at <35 weeks were slightly attenuated but still statistically significant with ORs of 2.9 and 3.8 respectively.

DISCUSSION

In this well-characterized cohort of pregnant women, a large variety of maternal and fetal placental vascular findings were evaluated through EFA. The EFA structure was compared with a grouping scheme that was pathology-based. We found that the factor structure from the EFA was similar to the a priori pathology groupings, which helped to validate the pathology-based approach. In addition, factor-based scores were computed and linked to distinct subtypes of PTD.

The components of MV-O, MV-I, MV-D and FV-O were similar between the EFA results and the pathology-based groupings. The FV-O split into two factors: FV-OS and FV-OL containing obstructive lesions of small fetal vessels and large fetal vessels, respectively. In each grouping, a few items were not retained in the EFA structure. In FV-I, all of the four findings

were eliminated in the EFA process. Additionally, the EFA generated a hybrid of findings from MV-O and MV-I.

Slight differences existed across the EFA results of the whole sample and the sub-sample of preterm only. Most notably the fibrinoid necrosis and non-inflammatory necrosis of the decidua (basal plate and extraplacental membranes) remained together with other findings of the pathology-based MV-O group in the preterm subset, while the former appeared with other MV-D items and the latter fell into the hybrid factor six in the EFA for the whole sample. These results suggest that particular findings can occur within different patterns of lesions, some patterns being stronger indicators of PTD risk. Another difference in EFA across the whole data set and the preterm only was seen in the components of the MV-O/MV-I hybrid factor. This sixth factor was the least stable in the EFA analyses; none of the items grouped in factor six with the preterm subset were the same as those grouped in factor six with the whole sample.

Though factor analysis has been extensively used by researchers from various medical fields, few studies have applied this statistical method to investigate variables derived from a set of histologic findings. A few studies have utilized EFA to link brain MRI findings to schizophrenia (75, 76) and dementia (77). A recent study used EFA of the bone marrow pathology to identify subtypes of thrombocythemia (91). Salafia and colleagues have employed EFA to relate placental lesions to pre-eclampsia (68, 79). However, only less than twenty different types of placental vascular lesions were reported in these studies. Principal component analysis, a statistical method that is related to EFA, was used by Kramer and colleagues to organize placental pathology findings (81). To our knowledge, no previous study has applied EFA to the large number and variety of placental vascular findings as we did in this study.

As in our study several investigators have found associations between maternal placental vascular lesions and risk of PPROM (60, 64, 92, 93). In some studies, placental vascular lesions that were similar to the MV-D (60) or a mixture of items from our MV-D and MV-O categories (64, 93) were found to be linked to PPROM. One study grouped maternal and fetal vascular findings into a single category which was then positively associated with risk of PPROM (92). In our study only the MV-D factor was significantly related to PPROM.

Some studies have reported links between uteroplacental ischemia (67) and failure of physiological change of the spiral arteries (94) and spontaneous preterm labor with intact membranes. However, as in our study, others have noted that placental vasculopathy was related to medically indicated PTD but not spontaneous PTD (95). In our data only maternal disturbances of vascular integrity (MV-I), a finding consistent with bleeding, increased the risk of spontaneous preterm labor with intact membranes. MV-I was also most strongly associated with delivery at <32 weeks, suggesting that maternal decidual bleeding may be an important contributor to the earliest PTDs.

Our strongest findings were for the relation between vascular factors, particularly the MV-D and the MV-O, and risk of medically indicated PTD. At least one previous study has also demonstrated that the magnitude of the association between decidual disease and PTD is greater for medically indicated PTD than for spontaneous PTD (96). Medically indicated PTD often results because of pre-eclampsia, gestational hypertension, and intrauterine growth restriction. One might expect that poor maternal artery conversion (MV-D) alone would not increase the risk of medically indicated PTD unless there were related complications such as infarcts or other obstructive lesions (MV-O). But we found that MV-D was associated with medically indicated PTD even after adjusting for the presence/absence of MV-O. We might hypothesize that

obstructive lesions are more likely to result in fetal indications for interventions and early delivery whereas the MV-D lesions track with maternal indications for intervention such as pre-eclampsia.

A distinctive characteristic of this study was its attempt to empirically validate a pathology-based system for summarizing placental histologic findings. The study had several strengths. The cohort was diverse with respect to race and socioeconomic status and included over 1,000 women. The frequency of vascular findings, organized as factors, was assessed within placentas from normal MSAFP, term deliveries to determine what was typical and atypical. To establish the robustness of our findings we used randomly-split samples and sub-samples based on both gestational age at delivery and MSAFP status. These multiple EFAs yielded parallel structures similar to that of the pathology-based groupings. Also we were able to use the EFA for data reduction, going from the original 39 items down to 24 items. One limitation of this study is that the analyses were performed within a single cohort, thus our approach needs to be replicated among other populations.

Future directions might include attempts to further reduce the number of pathology findings needed to capture relations between the vascular groupings and risk of PTD. This could be accomplished through sensitivity analyses to see which items could be eliminated.

Table 1. EFA results of the sub-cohort with completed placental assessments (N=1052)

Pathology-based groupings	EFA-extracted factors											
	MV-O		MV-I		MV-D		FV-OS		FV-OL		MV-I /MV-O mix	
Maternal vascular lesion-obstructive (MV-O)												
Syncytial knots	37	†	-5		2		1		1		-5	
Villous infarcts	37	†	23		3		10		4		-2	
Perivillous fibrin (not in Redline)	41	†	-9		-4		2		6		3	
X-cell proliferation (not in Redline)	45	†	-4		-2		-6		-2		6	
Fibrinoid necrosis in decidua of basal plate (atherosis)	8		5		35	†	0		-1		-14	
Fibrinoid necrosis in decidua of membranes (atherosis)	11		4		40	†	1		-2		-1	
Non-inflammatory necrosis of decidua in basal plate *												
Non-inflammatory necrosis of decidua in membranes	10		2		-5		0		-2		51	†
Maternal vascular lesion-disturbance of integrity (MV-I)												
Retroplacental blood with disruption/compression	-7		58	†	-2		4		1		4	
Retroplacental blood with fibrin	-5		57	†	-3		-3		7		4	
Retromembranous blood *												
Decidual hemorrhage in basal plate *												
Decidual hemorrhage in membranes	1		10		8		6		-1		36	†
Decidual thrombi in basal plate or membranes	-6		1		1		-2		0		53	†
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)												
Unaltered/abnormal decidual vessels in basal plate	0		-8		39	†	2		-1		2	
Unaltered/abnormal decidual vessels in membranes	-10		-3		53	†	-3		2		9	
Mural hyperplasia of decidual vessels in basal plate	0		-6		34	†	2		0		-4	
Mural hyperplasia of decidual vessels in membranes	-4		4		47	†	-2		2		6	

Table 1 (cont'd).

	EFA-extracted factors											
Pathology-based groupings	MV-O		MV-I		MV-D		FV-OS		FV-OL		MV-I /MV-O mix	
Fetal vascular lesion-obstructive (FV-O)												
Thrombi in small fetal disc vessels												
Luminal septation small fetal vessels	5		-19		-1		44	†	15		10	
Hemorrhagic-mural disruption small fetal vessels	9		7		8		58	†	-5		0	
Fragmented RBC in small fetal vessels	-1		4		0		75	†	-3		-1	
Non-tropho karyorrhexis small fetal vessels	-9		4		-7		73	†	4		-3	
Thrombi in large fetal disc vessels	7		21		-8		-7		33	†	6	
Luminal septation large stem fetal vessels	2		-10		0		14		56	†	5	
Hemorrhagic-mural disruption large stem fetal vessels	4		20		7		1		37	†	-4	
Fragmented RBC in large stem fetal vessels	4		4		0		-9		71	†	-5	
Non-tropho karyorrhexis large stem fetal vessels	-8		-3		1		11		70	†	-3	
Thrombi in chorionic plate fetal vessels												
Sub-intimal cushions (intimal fibrin cushion) in chorionic plate fetal vessels *												
Sub-intimal cushions (intimal fibrin cushion) in large fetal disc vessels *												
Avascular villi *												
Fetal vascular lesion-disturbance of integrity (FV-I)												
Subchorionic hemorrhage (maternal dissecting hemorrhage) *												
Villous stromal hemorrhage *												
Villous edema *												
Intervillous thrombus *												

All values were multiplied by 100 and rounded to the nearest integer.

*: Indicates item dropped where the factor loading score < ±0.30 for all extracted factors.

†: Indicates factor loading score of ±0.30 or higher.

Table 2. Comparison of EFA results between whole sample (N=1052) and preterm women only (N=238)

Pathology-based groupings	EFA-extracted factors											
	MV-O		MV-I		MV-D		FV-OS		FV-OL		MV-I /MV-O mix	
	w	p	w	p	w	p	w	p	w	p	w	p
Maternal vascular lesion-obstructive (MV-O)												
Syncytial knots	†	†										
Villous infarcts	†	†										
Perivillous fibrin (not in Redline)	†	†										
X-cell proliferation (not in Redline)	†	†										
Fibrinoid necrosis in decidua of basal plate (atherosis)		†			†							
Fibrinoid necrosis in decidua of membranes (atherosis)		†			†							
Non-inflammatory necrosis of decidua in basal plate *		†										
Non-inflammatory necrosis of decidua in membranes											†	
Maternal vascular lesion-disturbance of integrity (MV-I)												
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											†	
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)												
Unaltered/abnormal decidual vessels in basal plate					†	†						
Unaltered/abnormal decidual vessels in membranes					†	†						
Mural hyperplasia of decidual vessels in basal plate					†	†						
Mural hyperplasia of decidual vessels in membranes					†	†						

Table 2 (cont'd).

Pathology-based groupings	EFA-extracted factors											
	MV-O		MV-I		MV-D		FV-OS		FV-OL		MV-I /MV-O mix	
	w	p	w	p	w	p	w	p	w	p	w	p
Fetal vascular lesion-obstructive (FV-O)												
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									†	†		
Fragmented RBC in large stem fetal vessels									†	†		
Non-tropho karyorrhexis large stem fetal vessels									†			
Thrombi in chorionic plate fetal vessels												†
Sub-intimal cushions (intimal fibrin cushion) in chorionic plate fetal vessels *												
Sub-intimal cushions (intimal fibrin cushion) in large fetal disc vessels *												
Avascular villi *												
Fetal vascular lesion-disturbance of integrity (FV-I)												
Subchorionic hemorrhage (maternal dissecting hemorrhage) *												†
Villous stromal hemorrhage *												
Villous edema *												
Intervillous thrombus *												

"w"denotes whole sample and "p" denotes preterm sample.

*: Indicates item dropped where the factor loading score < ±0.30 for all extracted factors in one or both of the analyses.

†: Indicates factor loading score of ±0.30 or higher.

Table 3. Association between PTD and dichotomized vascular factors derived from factor-based scores (unadjusted, each vascular factor modeled separately)

	Four-level PTD (defined by weeks of delivery)					
Percentile of factor-based scores	**35 ≤ GA< 37**		**32 ≤ GA < 35**		**GA < 32**	
	OR	95% CI	OR	95% CI	OR	95% CI
MV-O (Factor 5)						
≤ 72.1%	1.0		1.0		1.0	
> 72.1%	0.8	(0.5, 1.2)	1.2	(0.6, 2.2)	1.0	(0.4, 2.5)
MV-I (Factor 4)						
≤ 77.5%	1.0		1.0		1.0	
> 77.5%	1.2	(0.8, 1.8)	**2.2**	**(1.2, 4.0)**	**3.6**	**(1.6, 8.0)**
MV-D (Factor 3)						
≤ 74.2%	1.0		1.0		1.0	
> 74.2%	1.2	(0.8, 1.8)	**2.5**	**(1.4, 4.6)**	**2.7**	**(1.2, 6.1)**
FV-OS (Factor 1)						
≤ 79.2%	1.0		1.0		1.0	
> 79.2%	0.8	(0.5, 1.2)	1.0	(0.5, 2.0)	1.0	(0.4, 2.6)
FV-OL (Factor 2)						
≤ 92.1%	1.0		1.0		1.0	
> 92.1%	0.8	(0.4, 1.6)	2.1	(0.9, 4.9)	1.5	(0.5, 4.6)
MV-O/MV-I mix (Factor 6)						
≤ 70.5%	1.0		1.0		1.0	
> 70.5%	1.4	(1.0, 2.0)	0.9	(0.5, 1.7)	1.8	(0.8, 3.9)

Table 3 (cont'd).

Percentile of factor-based scores	Seven-level PTD (defined by weeks of delivery and clinical circumstances)											
	SP, 35 ≤ GA< 37		**PPROM, 35 ≤ GA< 37**		**MI, 35 ≤ GA< 37**		**SP, GA< 35**		**PPROM, GA< 35**		**MI, GA< 35**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MV-O (Factor 5)												
≤ 72.1%	1.0		1.0		1.0		1.0		1.0		1.0	
> 72.1%	0.6	(0.3, 1.1)	0.9	(0.4, 1.9)	1.1	(0.6, 2.2)	0.2	(0.1, 1.1)	0.4	(0.1, 1.4)	**4.6**	**(2.1, 10)**
MV-I (Factor 4)												
≤ 77.5%	1.0		1.0		1.0		1.0		1.0		1.0	
> 77.5%	0.9	(0.5, 1.7)	1.9	(0.9, 3.9)	1.3	(0.7, 2.7)	**2.5**	**(1.1, 5.8)**	2.0	(0.8, 4.7)	**3.4**	**(1.6, 7.5)**
MV-D (Factor 3)												
≤ 74.2%	1.0		1.0		1.0		1.0		1.0		1.0	
> 74.2%	1.2	(0.7, 2.1)	1.0	(0.5, 2.3)	1.3	(0.7, 2.6)	1.2	(0.5, 3.1)	**2.9**	**(1.2, 6.7)**	**4.6**	**(2.1, 9.9)**
FV-OS (Factor 1)												
≤ 79.2%	1.0		1.0		1.0		1.0		1.0		1.0	
> 79.2%	0.6	(0.3, 1.2)	0.5	(0.2, 1.4)	1.3	(0.6, 2.6)	**0.0**	**(0.0, 0.0)**	1.3	(0.5, 3.4)	2.1	(0.9, 4.8)
FV-OL (Factor 2)												
≤ 92.1%	1.0		1.0		1.0		1.0		1.0		1.0	
> 92.1%	0.5	(0.2, 1.6)	1.5	(0.5, 4.4)	0.6	(0.1, 2.7)	1.0	(0.2, 4.4)	1.8	(0.5, 6.5)	**2.9**	**(1.1, 7.5)**
MV-O/MV-I mix (Factor 6)												
≤ 70.5%	1.0		1.0		1.0		1.0		1.0		1.0	
> 70.5%	1.5	(0.9, 2.5)	1.5	(0.7, 3.0)	1.2	(0.6, 2.3)	2.2	(1.0, 5.2)	1.1	(0.4, 2.6)	0.6	(0.2, 1.5)

Bold face denotes p-value < 0.05, referent for all models is term delivery (≥ 37 weeks).

Table 4. Association between PTD and dichotomized vascular factors derived from factor-based scores (adjusted, all vascular factors combined in a single model)

	Four-level PTD (defined by weeks of delivery)					
Percentile of factor-based scores	**35 ≤ GA< 37**		**32 ≤ GA < 35**		**GA < 32**	
	OR	95% CI	OR	95% CI	OR	95% CI
MV-O (Factor 5)						
≤ 72.1%	1.0		1.0		1.0	
> 72.1%	0.8	(0.5, 1.2)	1.1	(0.5, 2.0)	0.9	(0.4, 2.3)
MV-I (Factor 4)						
≤ 77.5%	1.0		1.0		1.0	
> 77.5%	1.2	(0.8, 1.9)	**2.1**	**(1.1, 3.9)**	**3.4**	**(1.5, 7.9)**
MV-D (Factor 3)						
≤ 74.2%	1.0		1.0		1.0	
> 74.2%	1.2	(0.8, 1.8)	**2.5**	**(1.4, 4.6)**	**2.7**	**(1.2, 6.0)**
FV-OS (Factor 1)						
≤ 79.2%	1.0		1.0		1.0	
> 79.2%	0.8	(0.5, 1.3)	0.8	(0.4, 1.7)	0.8	(0.3, 2.1)
FV-OL (Factor 2)						
≤ 92.1%	1.0		1.0		1.0	
> 92.1%	0.8	(0.4, 1.7)	2.0	(0.8, 4.8)	1.3	(0.4, 3.9)
MV-O/MV-I mix (Factor 6)						
≤ 70.5%	1.0		1.0		1.0	
> 70.5%	1.4	(0.9, 2.0)	0.8	(0.4, 1.6)	1.5	(0.7, 3.5)

Table 4 (cont'd).

Percentile of factor-based scores	Seven-level PTD (defined by weeks of delivery and clinical circumstances)											
	SP, 35 ≤ GA< 37		**PPROM, 35 ≤ GA< 37**		**MI, 35 ≤ GA< 37**		**SP, GA< 35**		**PPROM, GA< 35**		**MI, GA< 35**	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
MV-O (Factor 5)												
≤ 72.1%	1.0		1.0		1.0		1.0		1.0		1.0	
> 72.1%	0.7	(0.4, 1.2)	0.9	(0.4, 1.9)	1.1	(0.5, 2.1)	0.3	(0.1, 1.3)	0.3	(0.1, 1.4)	**3.8**	**(1.7, 8.7)**
MV-I (Factor 4)												
≤ 77.5%	1.0		1.0		1.0		1.0		1.0		1.0	
> 77.5%	0.9	(0.5, 1.7)	1.8	(0.9, 3.8)	1.3	(0.6, 2.7)	**2.4**	**(1.0, 5.8)**	2.0	(0.8, 4.9)	**2.9**	**(1.2, 7.0)**
MV-D (Factor 3)												
≤ 74.2%	1.0		1.0		1.0		1.0		1.0		1.0	
> 74.2%	1.2	(0.7, 2.1)	1.0	(0.5, 2.3)	1.3	(0.7, 2.6)	1.2	(0.5, 3.0)	**2.9**	**(1.2, 6.9)**	**4.4**	**(2.0, 10)**
FV-OS (Factor 1)												
≤ 79.2%	1.0		1.0		1.0		1.0		1.0		1.0	
> 79.2%	0.7	(0.3, 1.4)	0.5	(0.2, 1.2)	1.3	(0.6, 2.8)	**0.0**	**(0.0, 0.0)**	1.3	(0.5, 3.9)	1.2	(0.5, 2.8)
FV-OL (Factor 2)												
≤ 92.1%	1.0		1.0		1.0		1.0		1.0		1.0	
> 92.1%	0.6	(0.2, 1.9)	1.6	(0.6, 4.4)	0.5	(0.1, 2.6)	1.5	(0.3, 7.0)	1.6	(0.4, 6.3)	1.9	(0.7, 5.2)
MV-O/MV-I mix (Factor 6)												
≤ 70.5%	1.0		1.0		1.0		1.0		1.0		1.0	
> 70.5%	1.5	(0.9, 2.5)	1.4	(0.7, 2.9)	1.2	(0.6, 2.2)	2.1	(0.9, 4.9)	1.0	(0.4, 2.5)	0.5	(0.2, 1.4)

Bold face denotes p-value < 0.05, referent for all models is term delivery (≥ 37 weeks).

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