Serum exosomal microRNA pathway activation in placenta accreta spectrum: pathophysiology and detection

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BACKGROUND: Placenta accreta spectrum disorders are a complex range of placental pathologies that are associated with significant maternal morbidity and mortality. A diagnosis of placenta accreta spectrum relies on ultrasonographic findings with modest positive predictive value. Exosomal microRNAs are small RNA molecules that reflect the cellular processes of the origin tissues.

OBJECTIVE: We aimed to explore exosomal microRNA expression to understand placenta accreta spectrum pathology and clinical use for placenta accreta spectrum detection.

STUDY DESIGN: This study was a biomarker analysis of prospectively collected samples at 2 academic institutions from 2011 to 2022. Plasma specimens were collected from patients with suspected placenta accreta spectrum, placenta previa, or repeat cesarean deliveries. Exosomes were quantified and characterized by nanoparticle tracking analysis and western blotting. MicroRNA were assessed by polymerase chain reaction array and targeted single quantification. MicroRNA pathway analysis was performed using the Ingenuity Pathway Analyses software. Placental biopsies were taken from all groups and analyzed by polymerase chain reaction and whole cell enzyme-linked immunosorbent assay. Receiver operating characteristic curve univariate analysis was performed for the use of microRNA in the prediction of placenta accreta spectrum. Clinically relevant outcomes were collected from abstracted medical records.

RESULTS: Plasma specimens were analyzed from a total of 120 subjects (60 placenta accreta spectrum, 30 placenta previa, and 30 control). Isolated plasma exosomes had a mean size of 71.5 nm and were 10 times greater in placenta accreta spectrum specimens (20 vs 2 particles/frame). Protein expression of exosomes was positive for intracellular adhesion molecule 1, flotilin, annexin, and CD9. MicroRNA analysis showed increased detection of 3 microRNAs (mir-92, -103, and -192) in patients with placenta accreta spectrum. Pathway interaction assessment revealed differential regulation of p53 signaling in placenta accreta spectrum and of erythroblastic oncogene B2 or human epidermal growth factor 2 in control specimens. These findings were subsequently confirmed in placental protein analysis. Placental microRNA paralleled plasma exosomal microRNA expression. Biomarker assessment of placenta accreta spectrum signature microRNA had an area under the receiver operating characteristic curve of 0.81 (P<.001; 95% confidence interval, 0.73−0.89) with a sensitivity and specificity of 89.2% and 80%, respectively.

CONCLUSION: In this large cohort, plasma exosomal microRNA assessment revealed differentially expressed pathways in placenta accreta spectrum, and these microRNAs are potential biomarkers for the detection of placenta accreta spectrum.

Key words: abnormal placentation, biomarker, cesarean hysterectomy, exosome, microRNA, placenta accreta

Introduction

Placenta accreta spectrum (PAS) is a complex continuum of placental disorders that are characterized by uterine wall disruption by hypervascular placental tissue, and this leads to significant maternal morbidity and mortality.[1,2] The recommended delivery planning is currently a coordinated delivery at 34 to 36 weeks' gestation by cesarean hysterectomy.[3] Several modifications in delivery management, including uterine-preserving surgery, uterine artery embolization, aortic compression, balloons, and radical hysterectomy, have been reported.[4−7]

Implementation and the use of multidisciplinary teams for the management

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Why was this study conducted?

Placenta accreta spectrum (PAS) disorders are associated with significant morbidity, and preoperative detection is currently dependent on ultrasonography because effective biomarkers have not been identified.

Key findings

Exosomal microRNA from the plasma of patients with PAS enables the identification of underlying pathology and provides a greater understanding of PAS molecular biology.

What does this add to what is known?

Identification of PAS biomarkers remains essential for optimal patient outcomes; this study shows feasibility and efficacy of exosomal microRNA as a potential PAS biomarker.

of PAS has been shown to reduce the associated morbidity.[8–11] The greatest challenge in referral and the concentration of PAS cases remains accurate antenatal detection.[12–14] Current characterization of PAS relies on the combination of historic risk factors (previous uterine surgery) and ultrasonography findings (placenta previa, lacunae, and hypervascularity among others).[15,16] This approach has led to a PAS detection rate varying from 50% to 80% depending on the center and clinical suspicion. Although objective PAS detection through the use of biomarkers would be ideal, this remains elusive at this time. Several biomarkers have been proposed, but none are currently in clinical use.[17,18]

MicroRNAs (miRs) are small (18–22 base pairs) oligonucleotides that regulate protein synthesis. MiRs bind to the 3' or 5 ' untranslated regions (UTR) of target messenger RNA (mRNA), causing suppression or degradation.[19] This process leads to a typical dyssynchronous molecular signature of RNA transcription with protein degradation.[20] MiRs regulate key cellular processes, such as differentiation, malignant transformation, and metastasis, through this mechanism.[21–23] In cases of PAS, several miRs play a role in pathogenesis, including miR-34a, -125a, -193a, and -518b.[24–27] However, miR data for PAS are limited. Chen et al[28] have shown potential benefit in using a 4 miR PAS signature in a small cohort of patients with placenta increta or percreta.[18] The overall stability of plasma miRs remains a concern given the small size, circulatory RNase susceptibility, and impact of collection mechanisms.[29]

Exosomes are biologic, nano-sized vesicles (<100 nm) that allow effective transportation of biologic material between tissues and regulated cellular communication.[30,31] Exosomes are endosomal in origin and may contain miR, DNA, bioactive lipids, and proteins. Once secreted by a cell of origin, exosomes may travel to target tissues through bodily fluids including the blood, urine, and lymph.[32] This mechanism of action enables the use of exosomes and their cargo for biomarker detection and to better understand the tissue of origin through indirect assessment.

Our primary objective was to uncover PAS exosomal miR signatures for both clinical applicability and to better understand PAS pathophysiology during pregnancy without tissue disruption. Optimization of antenatal PAS detection remains key to enable resource allocation and intervention planning in these complex cases.

Materials and Methods

Patient identification and cohort selection

Patients were enrolled in prospective cohorts at 2 tertiary institutions (University of Texas Health San Antonio and University of Utah Health) between January 2017 and December 2021. Institutional review board (IRB) approval was obtained from both institutions before obtaining written patient consent for data and biospecimen collection. The eligibility criteria were maternal age >18 years with a viable singleton pregnancy and either risk factors or antenatal suspicion for PAS based on ultrasonography or magnetic resonance imaging. Final patient inclusion was dependent on the confirmation of the absence (control groups) or presence of PAS pathology by a board-certified perinatal pathologist. Exclusion criteria were the following: fetal death, gestational age <20 weeks, and multifetal gestation.

Exosome isolation and characterization

Maternal blood was collected in lavender top collection tubes (10 mL) and centrifuged at 3000 g for 5 minutes to achieve plasma separation. The plasma supernatant was then collected and subsequently stored at −80°C until planned analysis. Exosomes were isolated using the Total Exosome Isolation Kit (Thermo Fisher Scientific, Waltham, MA) per manufacturer's protocol. The recovered particle size was verified by nanoparticle tracking analysis (NTA) using a NanoSight NS300 instrument (Amesbury, United Kingdom). Data were analyzed with the NTA software (NanoSight version 2.3) using dilutions with deionized water. A fraction of isolated exosomes was dissolved in T-PER Tissue Protein Extraction Reagent (Thermo Fisher Scientific, Waltham, MA) and total proteins were quantified by colorimetric assay (Biorad, Hercules, CA). Western blot was performed for protein analysis as described below.

Western blot

Protein extracts (10 μg) were analyzed by western blot on 12% sodium dodecylsulfate polyacrylamide gels (Bio-Rad, Hercules, CA). Proteins were transferred onto polyvinylidene fluoride membranes (Perkin Elmer, Boston, MA). The membranes were incubated overnight with primary antibodies at a final dilution of 1/1000. Primary antibodies were detected during a 2-hour incubation period with horse radish peroxidase (HRP)–conjugated immunoglobulin G at 1/2000 final

dilution. HRP activity was detected by chemiluminescence using SuperSignal West Femto Maximum Sensitivity Substrate (Thermo Scientific, Waltham, MA). Membranes were stripped with Restore Stripping Buffer (Thermo Scientific, Waltham, MA) before being reprobed with subsequent antibodies. Primary and secondary antibodies were obtained from the Exosome Marker Antibody Kit (Cell Signaling Technology, Danvers, MA).

MicroRNA isolation and quantitative polymerase chain reaction

Exosomal miR was isolated using Trizol reagent (Thermo Scientific, Waltham, MA). Then, global miR detection was performed using the OncoMir microRNA quantitative polymerase chain reaction (qPCR) Array (SBI, Mountain View, CA) on a representative cohort of 10 patients with and without PAS. In addition, placental miR was isolated in similar fashion and assessed by qPCR using Taqman microRNA reverse transcriptase and Taqman microRNA assay. Because nuclear U6 internal control would not be detected in exosomes, we selected the miRs with absolute changes between PAS and control samples. In this regard, the selected miRs were undetectable in control groups and detectable in cases with PAS. The relative expression was calculated using the 2(-Delta Delta C(T)) or reported as CT when appropriate.

Real-time polymerase chain reaction

RNA was extracted with Trizol reagent (Invitrogen). Reverse transcription of 200 ng of complementary DNA (cDNA) was performed using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Waltham, MA) in accordance with the manufacturer's recommendation. Real-time PCR was performed on a 7300 Real-Time PCR System (Applied Biosystems, Waltham, MA) as follows: an initial incubation of 50°C for 2 minutes, followed by 95°C for 10 minutes. After this, the cycling conditions were as follows: 95°C for 15 seconds and 60°C for 60 seconds repeated for 40 cycles. The primer sequences that were used are presented in Supplemental File 1. Primers were purchased from Sigma (St. Louis, MO). The relative expression was calculated using the 2(-Delta Delta C(T)).

MicroRNA bioinformatic analysis

Ingenuity Pathway Analysis (IPA) (QIAGEN) was used to evaluate differentially expressed gene pathways (Fold change =1.5) to determine functional significance and upstream regulators of the genes of interest. STRING analysis was performed on differentially expressed genes to determine protein product interactions.

Enzyme-linked immunofluorescence assay

Whole tissue human epidermal growth factor 2 (HER2) and p53 were quantified using human HER2/p53 ELISA Kits (Thermo Scientific, Waltham, MA). All assays were performed according to the manufacturer's specific instructions. The unknown HER2/p53 concentration was calculated from a standard curve composed of serial dilutions of known sample concentrations, measured at an optical density of 450 nm. The background was subtracted from the data obtained at 550 nm. The standard curves were calculated using a linear regression algorithm to provide the best standard curve fit.

Statistical analysis

Normal distribution was determined using the Shapiro-Wilk test based on a P value threshold of >.05. Pearson's chi-square tests, Fisher's exact tests, Mann Whitney U tests, and t tests were applied when appropriate. Categorical factors were summarized using frequencies and percentages, whereas continuous measurement summaries used means±standard deviation (SD) or median and interquartile range as appropriate. P values <.05 were considered significant for 2-tailed analyses. Receiver operating characteristic (ROC) curves were developed for each individual miR and the 3 miRs collectively for PAS detection. Statistical analysis was performed using GraphPad Prism 9 (GraphPad, University of California San Diego, San Diego, CA).

Results

Assessment of the study population

Throughout the recruitment phase of this study, a total of 120 patients provided consent, and the biobanking of their specimens was completed. Of those included, 50% (60/120) had histopathologic confirmation of PAS. The remaining 60 patients, collectively labeled as non-PAS, included 60 patients with a history of cesarean delivery; 30 of these also had placenta previa in the current pregnancy (Table). Patients with PAS were more likely to be older, parous, have a greater number of cesarean deliveries, and deliver at an earlier gestational age. These outcomes were anticipated given the underlying pathology and recommended delivery strategies.

Analysis of plasma exosome isolation

Exosomes were isolated from subjects and described and assessed by nanoparticle tracking. Exosomes were successfully isolated from all patients and the mean particle size was 71.5 nM (Figure 1, A). The overall quantity of exosomes was 10-fold higher among patients with PAS than among those in either control group (Figure 1, B). Subsequently, total proteins were isolated and, through western blot analysis, the exosome markers intracellular adhesion morecule 1, flotilin, annexin, and CD9 were detected in all groups (Figure 1, C). Actin was used as an internal control for these experiments. As cell surface and cytoskeleton markers, variable expression was anticipated in this cellular subcompartment despite protein quantification.

Placenta accreta spectrum microRNA assessment

In an effort to better characterize exosomal miR and its role in PAS, we performed a miR PCR array with

TABLE
Patient demographics

Variable	Non-PAS (n-60)	PAS (n=60)	*P* value
Age (y)	30.5±5.5	33.1±5.1	<.01[a]
Gravidity	5 (3–6)	5 (3–7)	.44
Parity	2 (1–3)	3 (2–4)	<.01[a]
BMI (kg/m^2)	30.1 (26.3–33.2)	32.1 (27.6–37.6)	.07
Placenta previa	30 (50)	56 (93)	<.01[a]
Gestational age at sample collection	32 (25–36)	31 (26–34)	.26[a]
Gestational age at delivery	36 (31–37)	34 (32–35)	<.01[a]
History of CD	60 (100)	57 (95)	1.0
Number of previous CD	2 (1–3)	2 (2–3)	<.01[a]
Emergent delivery	21 (35)	22 (37)	1.0

Values are presented as mean ± standard deviation, median [interquartile range], or number (column percentage).

BMI, body mass index; *CD*, cesarean delivery.

[a] Indicates *P*<.05.

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validated miR targets and compared a small representative cohort of these with a control group of patients with placenta previa, a previous cesarean delivery, and no evidence of PAS. We were able to identify 15 miRs that were exclusively detected in all PAS specimens (n=5). Several key pathways were noted to be regulated by these miRs (Figure 2, A) Review of the literature revealed 3 miRs (miR-92, -103 and -192) with confirmed roles in cellular growth and proliferation.[33–35]

Plasma microRNA regulated pathways

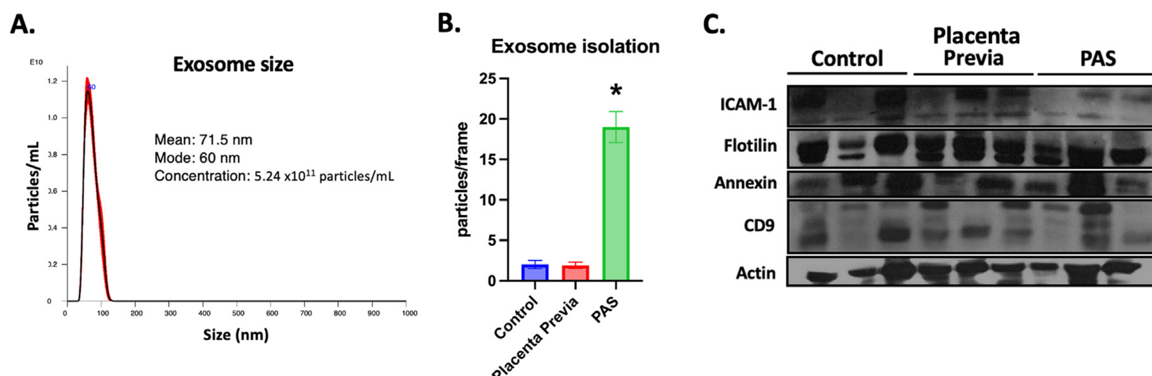
MiR Bioinformatic analysis was performed using Ingenuity software for miR analysis in both the control group with previa and the PAS cohort. This revealed that erythroblastic oncogene B2 (ERBB2) expression was highly regulated by miRs in cases of placenta previa (Figure 3, A), whereas TP53 expression was regulated in the PAS cohort in this analysis (Figure 3, B).

Placental tumor protein P53 and erythroblastic oncogene B2 regulation by microRNA

An advantage of exosomal studies is that exomes reflect expression in the primary tissue. Thus, placental samples were isolated from 40 subjects (10 control, 10 placenta previa, and 20 PAS cases). All cases were identified intraoperatively (Figure 4, A) and confirmed with subsequent histology (Figure 4, B). MiR-92, -103, and -192 were detected by PCR and found to be significantly elevated in PAS specimens when compared with either of the control groups (Figure 4, C).

In addition, placental mRNA and protein expression were assessed by reverse transcriptase–PCR and whole tissue enzyme-linked immunosorbent assay, respectively. *ERBB2* mRNA was noted to be significantly increased in cases of placenta previa, whereas *TP53* mRNA was 2-fold higher in PAS specimens (Figure 5, A–B). Conversely, ERBB2 (HER2) protein was significantly decreased in placenta previa, whereas TP53 (p53) was decreased in cases of PAS (Figure 5, C–D). This inverse relationship between mRNA and protein levels is characteristic of

FIGURE 1
Exosome isolation and characterization



Plasma exosomes were isolated from all groups and analyzed for size (**A**), quantity (**B**), and surface protein expression (**C**).

PAS, placenta accreta spectrum.

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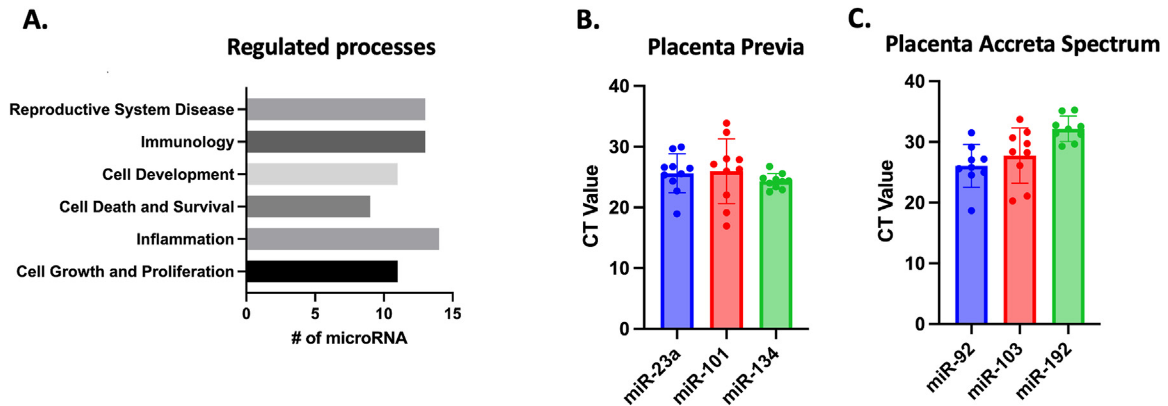
FIGURE 2
MicroRNA array



Several microRNA-regulated pathways were noted (**A**). MicroRNAs were assessed and 3 microRNAs (mir-92, -103, and -192) in placenta previa (**B**) were exclusively expressed in PAS specimens (**C**) in this cohort.

CT, cycle threshold; *PAS*, placenta accreta spectrum.

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posttranscriptional modifications such as miR regulation.[36]

Prospective plasma microRNA assessment

Following miR screening of the initial cohort (n=120), exosomal miR detection was performed using a specific, targeting Taqman qPCR assay (n=120) (Figure 6, A−C). MiR-92a, -103, and -192 were all significantly elevated in the peripheral plasma of patients with PAS when compared with either of the control groups (P<.05).

Placenta accreta spectrum microRNA profile as a biomarker

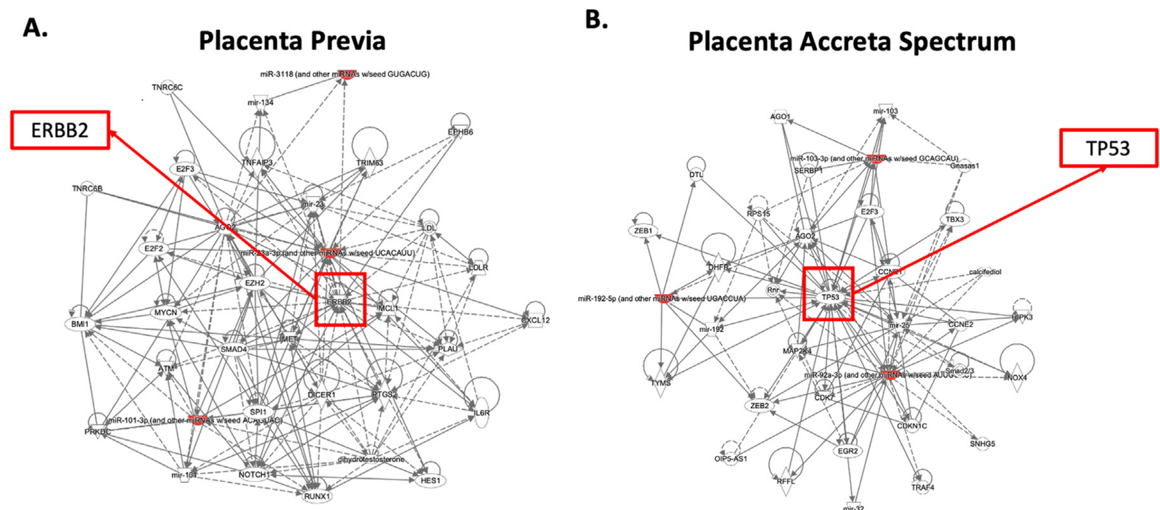
ROC curves were created for individual plasma exosomal miRs as biomarkers for PAS detection and for collective assessment of all 3 (Figure 7). Each individual miR had excellent discrimination with an area under the ROC curve (AUC) of 0.82, 0.83, and 0.82, respectively (P<.0001). As a collective panel, the AUC was 0.81 (P<.0001).

Comment

Principal findings

Exosomal miR isolation and characterization are feasible and reproducible in both controls and patients with PAS. A

FIGURE 3
Bioinformatic analysis



Ingenuity analysis of expressed microRNA shows pathways central to both placenta previa and PAS specimens.

PAS, placenta accreta spectrum.

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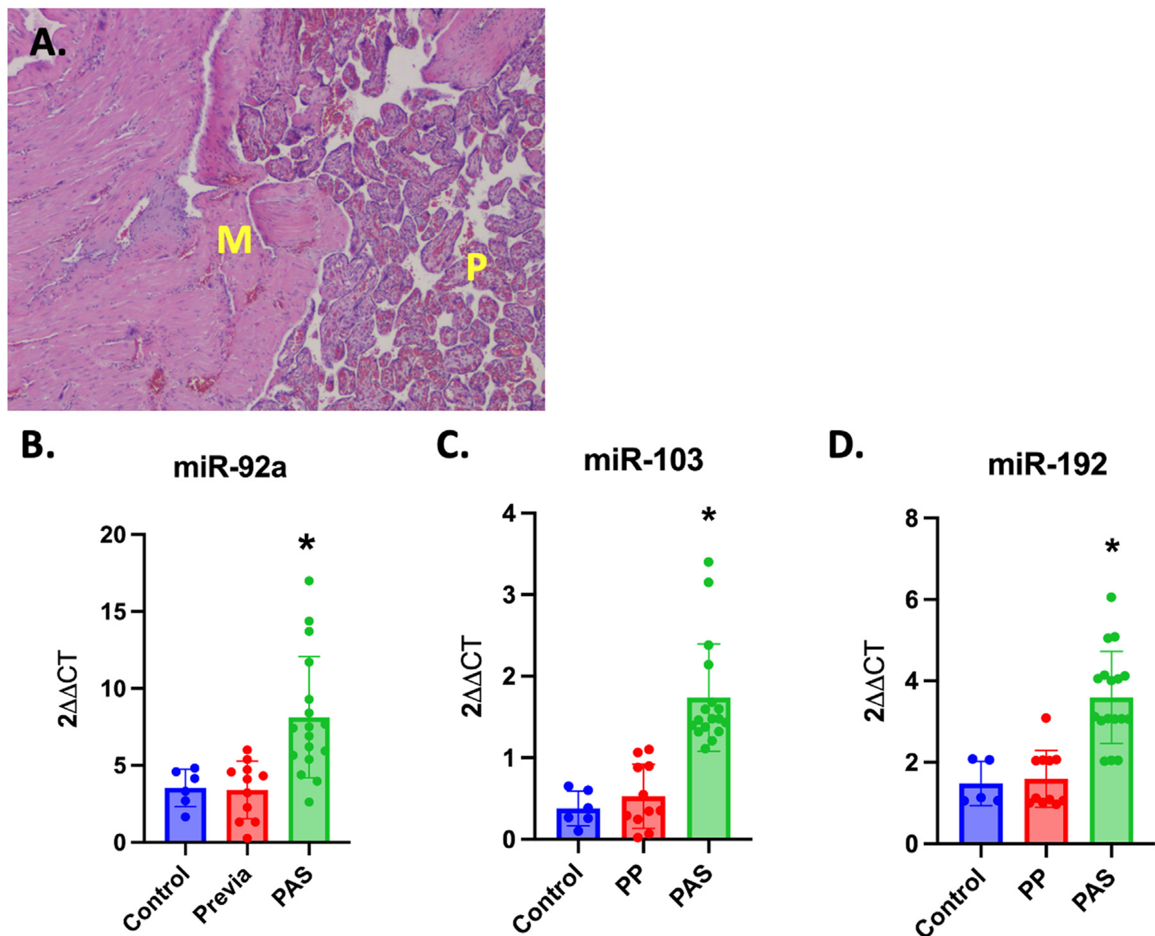
FIGURE 4
Placenta accreta assessment



PAS was confirmed by histopathology (**B**). MicroRNAs identified in previous array were detected in PAS placental specimens (**B-D**).

M, myometrium; *P*, placenta.

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significantly increased quantity of exosomes was encountered in the plasma of patients with. MiR profiles identified in PAS placentas were confirmed in the serum of patients with PAS. In addition, the molecular pathways regulated by these miRs seemed to impact the overall cellular survival and proliferation. Understanding exosomal miRs enables the uncovering of the molecular pathways involved in PAS pathology and may improve antenatal detection of PAS.

Results in the context of what is known

Current PAS detection and subsequent referral for multidisciplinary management remains dependent on antenatal suspicion and risk stratification in the absence of available biomarkers. Our data suggest that exosomal miR merits further study as biomarkers for antenatal detection of PAS. This is attractive because it is noninvasive and requires only a small sample of peripheral blood.

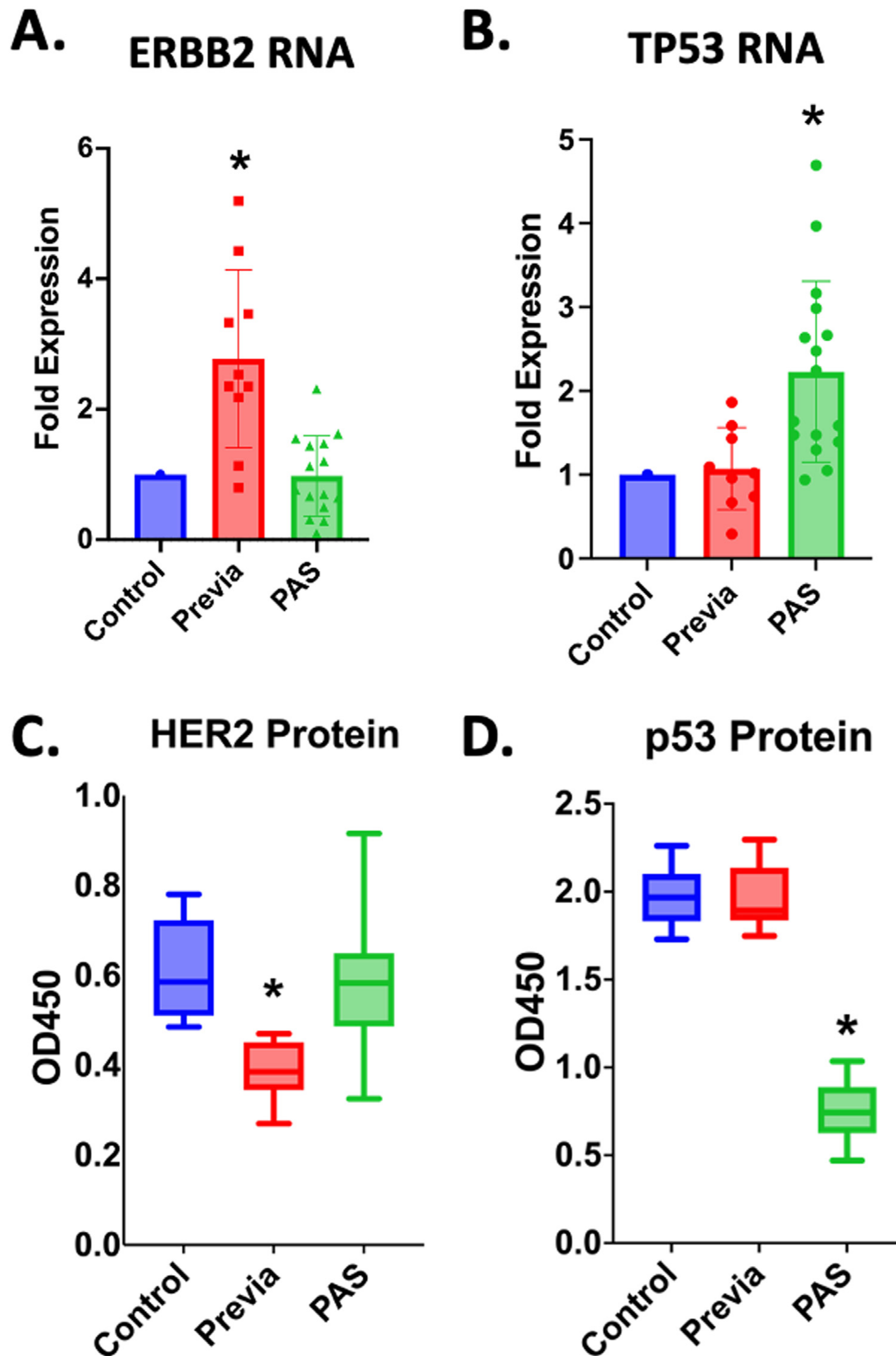
Clinical implications

Our data introduce the feasibility of exploring exosomal and miR biology into the clinical atmosphere for the detection of complex pathologies, such as PAS, for which accurate and timely diagnosis are essential. In addition, molecular pathways that provide insights into PAS pathophysiology were identified, which may lead to the development of future therapeutic approaches.

Research implications

Exosomal biology in the setting of pregnancy remains limited. Although peripheral circulating RNA enable a technically easier assessment, the overall reproducibility, secondary to degradation, continues to limit clinical use. Because of the highly regulated synthesis, packaging, and secretion of exosomes, they have emerged as an attractive potential clinical biomarker.[37] In our study, TP53 was a central target for miR regulation in PAS placentas as detected in the plasma of these patients.

FIGURE 5
Placental transcription and translation of central pathways



RNA was analyzed for both HER2 (**A**) and TP53 (**B**) in all specimens. In addition, protein assessment by ELISA was performed for both HER2 (**C**) and p53 (**D**).

ELISA, enzyme-linked immunosorbent assay; *HER2*, human epidermal growth factor receptor 2; *TP53*, tumor protein 53.

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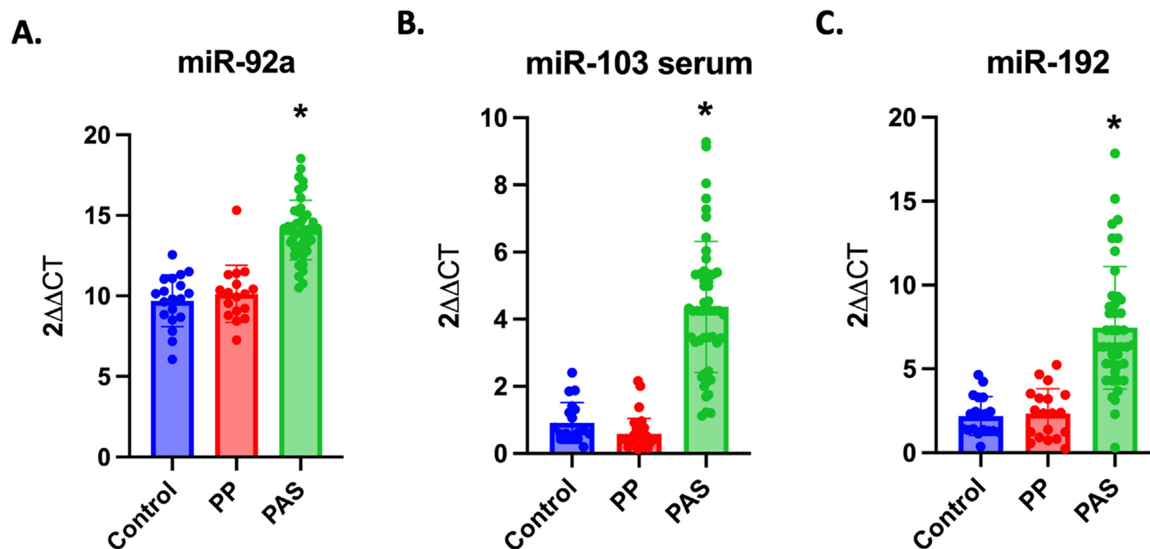
FIGURE 6
Maternal plasma exosomal microRNA expression



Expression of PAS-associated microRNA in the plasma of all subjects was performed (**A**—**C**).

CT, cycle threshold; *PAS*, placenta accreta spectrum.

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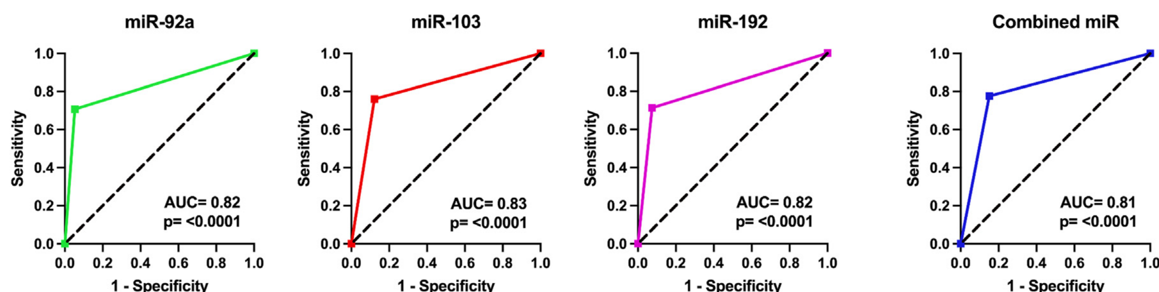
In addition, survival pathways (MAP-kinase), cell-cycling regulation (CCNE1, CCNE2 and CDK7), and cellular development (SMAD2/3, E2F3) were also found to be regulated by these miRs. Further research on the importance and potential roles of these pathways in PAS pathology remains essential for a comprehensive understanding of PAS. For research efficacy, we focused on a small subset of miRs previously validated to impact cellular migration and invasion, and future studies could be expanded in terms of transcriptomics and metabolomics but were beyond the scope of this study.

Although our study focused on exosomal miR, several other mechanisms remain unexplored. In the field of oncology, long mRNA-like, noncoding RNA, GAS5, SNORD50, telomerase RNA, and Y RNA, have been shown to regulate cellular processes.[38,39] With respect to extracellular circulatory vesicles, microvesicles, microparticle, apoptotic bodies, large oncosomes, and migrasomes are alternatives to cellular communication that may be exploited for clinical detection of PAS.[40–42]

Clinical research on the identification of PAS biomarkers remains essential for coordinated patient care. Based on our data, prospective evaluation of exosomal miR for the detection of PAS is warranted. In addition, several miRs

FIGURE 7
ROC curve analysis



Individual PAS-associated microRNA expression (**A**—**C**) and collective microRNA expression (**D**) were assessed in terms of predictive capabilities using ROC curves.

PAS, placenta accreta spectrum; *ROC*, receiver operating characteristic.

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(miR-101, -23a, -3118) were found to regulate pathways within placenta previa without evidence of PAS, and the underlying importance of these miRs and regulated pathways (MYC-N, ATM, and MCL-1) have not been explored.

Strengths and limitations

Our study has several strength and limitations. Samples were collected at 2 institutions in different states with varying population ethnic distributions using the same standardized operating protocols, thereby allowing for a large biologic repository for PAS patients. Both centers were high-volume PAS referral centers with standardized antenatal assessment and management. Clinically, no difference was noted between second-trimester and third-trimester detection of PAS by plasma miRs. This would allow for potentially earlier detection before the third trimester.

The greatest limitation remains the overall technical aspects of exosome isolation and miR detection. In contrast with free circulatory RNA, exosomal RNA requires specialized isolation and confirmation of nano-sized particles. Furthermore, total exosomes were collected without distinction for placental-derived exosomes. This was done to facilitate translational capabilities in biomarker development. Clinical application of exosomes and miR are currently not part of clinical care, however, studies have shown that a large number of exosomes in plasma circulation are placental in origin during pregnancy.[43] In addition, all cases of PAS that were enrolled in our study were identified using ultrasonographic evaluation prenatally, thus precluding a direct comparison of ultrasonographic PAS evaluation with exosomal miR detection without prospective blinded analysis. Finally, the sample size was not large enough to permit validation. The use of these biomarkers for clinical prediction of PAS should be assessed and validated in prospective external cohorts.

Conclusion

Biomarkers of PAS remain elusive and essential for the coordination and optimization of patient care with complex pathology. Exosome-derived miR provides an excellent tool for obtaining a greater understanding of PAS pathology and the development of PAS biomarkers. ■

CRediT authorship contribution statement

Jessian L. Munoz: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Brett D. Einerson:** Writing – review & editing, Resources, Methodology, Conceptualization. **Sureshkumar Mulampurath:** Writing – review & editing, Investigation, Data curation. **Lauren S. Sherman:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Pranela Rameshwar:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Egle Bytautiene Prewit:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Patrick S. Ramsey:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2024.100319.

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