Vascular Changes In The Placentas Of Buprenorphine-Exposed Pregnancies

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INTRODUCTION

- Prenatal opioid use is an issue of significant concern in the United States and has links to neonatal opioid withdrawal syndrome and other adverse outcomes.
- Medications for opioid use disorder (MOUD) are considered vital to the treatment of OUD in pregnancy.
- Chronic opioid exposure is associated with pathologic changes to placental vasculature that can have potential health consequences for mothers and their babies.
- We aimed to characterize levels of potential markers of abnormal vascular remodeling and impaired exchange in the vessels of MOUD exposed pregnancies.

METHODS

- Our pilot study included pregnant women with and without a diagnosis of OUD at Carilion Roanoke Memorial Hospital in Roanoke, VA.
- We included four MOUD-exposed and four MOUD-unexposed singleton pregnancies in our analysis. Pregnancies with a diagnosis of gestational hypertension, preeclampsia, gestational diabetes, placenta abruption, or chorioamnionitis were excluded. Placentas with known amphetamine or cocaine exposure were also not used for this analysis.
- Biopsies were collected from four distinct quadrants of each placenta after delivery and fixed, then subsequently immunostained, imaged using confocal microscopy, and analyzed for multiple components of the microvasculature using ImageJ.
- Samples were matched on age, gestational age, and smoking status.

Primary Antibody	Dilution	Secondary Antibody	Dilution	Specificity
Goat anti-COLIV	1:300	Donkey anti-goat 568	1:600	Collage type IV (COLIV)
Sheep anti-PECAM-1	1:300	Donkey anti-sheep 647	1:600	Endothelial cells
Mouse anti-alpha-SMA, FITC conjugated	1:500	None		Smooth muscle cells (alpha isoform) (α-SMA)
DAPI	1:1000	None		Nuclei

Table 1: Summary of antibody solutions and their specificities.

RESULTS

- Study participants were non-Hispanic white with an average age of 31.4 years. Mean gestational age at delivery was 40 weeks and 0 days.
- 100% of the opioid-exposed participants were taking buprenorphine.
- We examined a total of 50 vessels across 27 terminal villi from the 8 placentas: 18 from opioid-exposed pregnancies and 32 from control pregnancies.
- We observed no significant differences in COLIV or α-SMA content between our opioid-exposed and control placentas.

Immunostaining	Exposed (n = 4)		Control (n = 4)		
	Mean	SD	Mean	SD	p-value
Ratio of COLIV positive area (μm²) to lumenal area of vessel (μm²)	6.72	2.89	6.67	3.98	0.91
Percentage COLIV positivity across all vessels (%)	30.50	18.90	28.60	9.70	0.74
Ratio of α-SMA positive area (μm²) to lumenal area of vessel (μm²)	5.60	2.90	5.50	2.20	0.97
Percentage α-SMA positivity across all vessels (%)	25.90	16.60	25.40	14.60	0.91
Ratio of COLIV to PECAM-1†	0.87	0.49	0.73	0.20	0.97
Ratio of α-SMA to PECAM-1†	0.71	0.28	0.72	0.49	0.91

Table 2: Estimated means from linear mixed models comparing several features of COLIV and α-SMA positivity across the four exposed and four control placentas, including the ratios of each stain to their respective vessel lumen cross-sectional area and the percentage positivity of each stain around their vessels. †Represents the percentage COLIV and α-SMA positivity normalized to the percentage of PECAM-1 positivity.

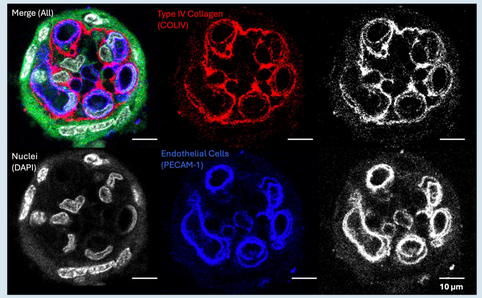


Figure 1: Immunofluorescence of vessels from a villus in a placenta with unknown exposure disaggregated into COLIV (red), PECAM-1 (blue), and DAPI (white). COLIV tended to encircle regions of PECAM-1 signal as well as displayed a reticular pattern in the villus highlighting the presence of vascular remodeling and potential damage.

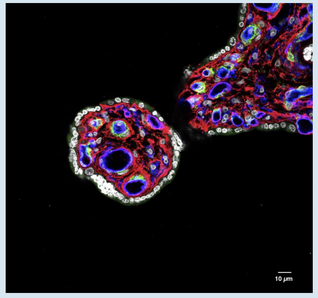
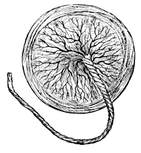


Figure 2: Immunofluorescence of a villus from a control placenta showing vessels of variable sizes. COLIV (red), PECAM-1 (blue), and DAPI (white) are visualized. We also noted the presence of cells known as pericytes (green) encircling vessel walls.

CONCLUSION

- To our knowledge, this is the first study to examine the microvasculature of MOUD-exposed placentas using confocal microscopy.
- No significant differences in collagen and smooth muscle content were seen between MOUD-exposed and control placentas.
- These results may be reassuring given that buprenorphine is a first-line addiction treatment during pregnancy.
- Various factors may account for a lack of effect. Whether an opioid is a partial or full agonist such as methadone may determine the degree of change seen in the placenta. Dosing, timing of treatment during pregnancy, and medication consistency may also influence any potential changes.
- Future studies may examine opioid characteristics such as dose and agonism.



AUTHORS & DISCLOSURES

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The authors have no disclosures.

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