American Journal of Obstetrics and Gynecology (2006) **195**, 1011–4

ELSEVIER

American Journal of Obstetrics & Gynecology

www.ajog.org

17-hydroxyprogesterone caproate reverses induced vasoconstriction of the fetoplacental arteries by the thromboxane mimetic U46619

Damian J. Paonessa, MD,[a,*] Andrea D. Shields, MD,[a] Bobby C. Howard, MD,[a] Jennifer L. Gotkin, DO,[a] Shad H. Deering, MD,[a] Nathan J. Hoeldtke, MD,[b] Peter G. Napolitano, MD[a]

Division of Maternal-Fetal Medicine, Madigan Army Medical Center,[a] Tacoma, WA; Division of Maternal-Fetal Medicine, Tripler Army Medical Center,[b] Honolulu, HI

Received for publication March 10, 2006; revised June 2, 2006; accepted June 10, 2006

KEY WORDS
Pregnancy
Progesterone
Placenta
Placental vessels

Objective: This study was undertaken to determine whether 17-hydroxyprogesterone caproate (17P) has a vasoactive effect on fetoplacental vasculature.

Study design: Two cotyledons were obtained from each of 5 placentas. Baseline perfusion was established with Hanks-based solution. One cotyledon from each pair was then infused with perfusate to which U46619 a thromboxane sympathomimetic had been added. After 30 minutes, a dose of 17P was then administered to each cotyledon. Finally, a vasoconstricting dose of angiotensin II was administered to each cotyledon. Perfusion pressures were recorded throughout. Statistical analysis of pressure change for a single cotyledon was performed by using a paired *t* test. Statistical analysis of mean perfusion pressure difference between U46619 exposed and nonexposed cotyledons was analyzed by using a students *t* test.

Results: 17P did not significantly alter the perfusion pressure of the control cotyledon. (30.6 $\pm$ 8.3 mm Hg vs 30.1 $\pm$ 7.8 mm Hg $P = .48$). 17P administration significantly lowered the perfusion pressure of the U46619 preconstricted vessels in comparison with preadministration. (60.1 $\pm$ 13 mm Hg vs 27.3 $\pm$ 7.1 mm Hg $P = .03$). Both groups of cotyledons responded with vasoconstriction to angiotension II with no difference in response between groups (38.3 $\pm$ 12 mm Hg vs 45.8 $\pm$ 8.2 mm Hg $P = .63$).

Conclusion: 17P reverses induced vasoconstriction by U46619 in fetoplacental arteries.

Supported by a research grant provided by the Air Force Institute of Technology.

Presented at the 26th Annual Meeting of the Society for Maternal Fetal Medicine, January 30-February 4, 2006, Miami, FL.

The opinions expressed herein are those of the author and do not reflect the official policy or position of the Department of the Air Force, the Department of the Army, the Department of Defense, or the United States Government.

* Reprint requests: Damian Paonessa, MD, Madigan Army Medical Center, 9040 Fitzsimmons Ave, Tacoma, WA 98431-1100.
E-mail: dmpaonessa2000@yahoo.com

0002-9378/$ - see front matter © 2006 Mosby, Inc. All rights reserved.
doi:10.1016/j.ajog.2006.06.041

In recent years, progesterone has become an accepted therapy for the prevention of preterm labor.[1,2] Attempts to elucidate potential mechanisms by which progesterone may provide this beneficial effect have focused on the inflammatory cascade and progesterone's effect on the production of various cytokines.[3,4] Although progesterone is a known direct smooth muscle relaxant, little has been done in the evaluation of its direct effects on the myometrium and smooth muscle of the placental vasculature. One study examined the effects of progesterone administration on uterine activity in the setting of preterm labor and reported a reduction in uterine activity in comparison with placebo.[5] Progesterone also has an effect on vasculature. For instance, progesterone-induced vasorelaxation of preconstricted porcine coronary artery specimens has been demonstrated.[6] This led to our question what effect does progesterone have on fetoplacental vascular tone?

The ex vivo placental cotyledon model has been previously used to determine the effects of different agents on fetoplacental vasculature tone. U46619, a thromboxane sympathomimetic is a known potent vasoconstricting agent that produces a predictable response in the fetoplacental arteries. We undertook this study to examine the effects of progesterone on baseline fetoplacental vascular tone and fetoplacental vasculature preconstricted with U46619.

Material and methods

This protocol was approved by the Investigational Review Board of Madigan Army Medical Center. Five placentas from normal parturients were obtained within 15 minutes of delivery. All patients were between 37 and 42 weeks' gestation. Hypertensive disease, diabetes, tobacco use and significant maternal medical disease were exclusion criteria. Placentas from pregnancies complicated by growth restriction, fetal anomalies or abnormal fetal heart rate tracing were also excluded.

After transport to the laboratory, the placenta was visually inspected for lacerations, evidence of infarction or color changes suggestive of hypoperfusion. The fetal surface of the placenta was then inspected for a peripherally located matched chorionic artery and vein pair that were presumed to perfuse a single cotyledon. The artery and the vein selected were cannulated with 22-gauge intravenous catheters. Perfusate, as described later in this article was then slowly injected into the chorionic artery cannula of the cotyledon and a functional circuit was confirmed by a return of effluent from the paired chorionic vein. A circular section of the placenta approximately 8 cm in diameter, which included the selected cotyledon, was excised. This portion of the placenta was clamped into a holder specifically designed to prevent leakage from the cut edges of the placenta as described and illustrated in a prior study published by our institution.[7] Two 21-gauge butterfly needles were inserted through the chorionic surface into the villous tissue to mimic the maternal uteroplacental circulation. Perfusate passing through the butterfly needles actually entered the intervillous space through diffusion as has been described in prior studies that used this model.[8]

A perfusate consisting of Hanks' balanced salt solution (Sigma Aldrich, St. Louis, MO) gentamicin 5 mg/L, bovine albumin 2.0 gm/L (Sigma Aldrich), and sodium heparin 2000 U/L (Elkins-Sinn Inc, Cherry Hill, NJ) was prepared in a sterile fashion before placental collection. At the time of the experiment, the perfusate was warmed to 37°C. A 95% oxygen and 5% carbon dioxide mixture was bubbled into the perfusate, and the pH was maintained between 7.35 and 7.45 throughout the experiment.

Perfusion to the intervillous space was maintained at a rate of 10 mL/min. Perfusion of the fetal artery was run at a rate of 4 mL/min. These rates were obtained from multiple other studies utilizing this model.[7-9] The cotyledon was then transferred to a temperature-controlled chamber maintained at 37°C. A second cotyledon from the same placenta was prepared in a similar manner. All perfusions were established within 30 minutes after delivery of the placenta.

All perfusion circuits used standard commercial intravenous tubing. IMED (IMED, San Diego, CA) pumps controlled the intervillous perfusion. Corpak 300D Enteral (Corpak, Wheeling, IL) roller-type pumps controlled the fetal circulation perfusion. The fetoplacental arterial perfusion pressure was measured with an in-line transducer connected to a fetal monitor. Perfusion rates were maintained at a constant rate and volume during the experiment and changes in pressure were attributed to changes in the fetoplacental artery tone.

The fetoplacental vascular perfusate to the cotyledons was unaltered for 30 minutes to reach a baseline arterial pressure. After this period the fetoplacental arterial vascular perfusate to 1 cotyledon remained unaltered and the fetoplacental arterial perfusate of the other cotyledon was switched to perfusate that contained U46619 (1 nmol/L). This arterial perfusate was maintained in this cotyledon for the remainder of the study. This cotyledon was selected from the obtained cotyledons by random number table assignment. Arterial perfusion pressures were then recorded every 5 minutes for 30 minutes.

After this 30 minutes a bolus dose of 17-hydroxyprogesterone caproate (17P) (0.5 mL of 200 nmol/L) was administered into the vascular circuit of each cotyledon. Response pressures were recorded every 5 minutes over the subsequent 30 minutes. In 2 of the 5 series, oxygen content of the precotyledon perfusate was measured by blood gas analysis by using the AVL Omni 9 blood gas analyzer (AVL Scientific Corp, Roswell, GA). The oxygen content of the venous effluent was also measured in the same manner to demonstrate continued oxygen use by the cotyledon post constriction and 17P administration.