

## IMAGING

# Fetal renal artery impedance as assessed by Doppler ultrasound in pregnancies complicated by intraamniotic inflammation and preterm birth

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**OBJECTIVE:** The objective of the study was to evaluate the fetal renal artery impedance in the context of inflammation-associated preterm birth.

**STUDY DESIGN:** We conducted a prospective Doppler assessment of the fetal renal artery impedance in 70 singleton fetuses. The study group consisted of 56 premature fetuses (median, 28.1 [interquartile range, 25.3–30.6] weeks at enrollment). Gestational age (GA) reference ranges were generated based on fetuses with uncomplicated pregnancies ( $n = 14$ ). Doppler studies included renal artery pulsatility index (PI), resistance index (RI), systolic/diastolic (S/D) ratio, and presence or absence of end-diastolic blood flow. Proteomic profiling (surface-enhanced laser desorption ionization time-of-flight) was used for assessment of intraamniotic inflammation and biomarker peak corresponding to  $\beta 2$ -microglobulin. Data were interpreted in relationship to amniotic fluid index (AFI), cord blood interleukin (IL)-6 and erythropoietin (EPO) levels. The cardiovascular and metabolic profiles of the neonates were investigated in the first 24 hours of life.

**RESULTS:** Fetuses delivered by mothers with intraamniotic inflammation had higher cord blood IL-6 but not EPO levels. Fetal inflammation did not affect either renal artery PI, RI, S/D ratio, or end-diastolic blood flow. Neonates delivered in the context of intraamniotic inflammation had higher serum blood urea nitrogen levels, which correlated significantly with AF IL-6 levels. The renal artery RI and SD ratio were inversely correlated with the AFI independent of GA, cord blood IL-6, and status of the membranes.

**CONCLUSION:** The fetus is capable of sustaining normal renal artery impedance despite inflammation. Resistance in the renal vascular bed affects urine output independent of inflammation.

**Key words:** amniotic fluid, amniotic fluid index, erythropoietin, fetal renal artery impedance, pulsatility index, resistance index, systolic/diastolic ratio

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Preterm birth (PTB) remains one of the leading causes of perinatal morbidity and mortality worldwide.<sup>1,2</sup> Several distinct pathophysiological pathways are proposed to be involved in triggering PTB.<sup>3</sup> Myometrial stretching, oxidative stress, decidual hemorrhage, and infection are thought to play the most significant roles.<sup>4</sup>

Both clinically symptomatic and asymptomatic intrauterine infection induce an intraamniotic inflammatory response that includes the release of multiple cytokines and chemokines, which in turn trigger histological chorioamnionitis, preterm contractions, and/or rupture of the membranes.<sup>5,6</sup> The current working model in prematurity attendant

intraamniotic infection/inflammation is that a systemic fetal inflammatory response is initiated when pathogens gain access to the fetus and stimulate the production of cytokines.<sup>7,8</sup> This inflammatory response is a well-recognized risk factor for increased perinatal morbidity and mortality after adjusting for gestational age (GA) at birth.<sup>9</sup>

There is strong evidence that abnormalities exist in both vascular anatomy and vasomotor regulation of arterial tone under pathological circumstances (ie, chorioamnionitis) and particularly if the process of fetal inflammation is initiated in utero.<sup>10,11,12,13,14</sup> Thus, we postulated that as intrauterine infection/inflammation can affect fetal brain and cardiac vascular function; the vasomotor regulation of the fetal kidney may also become significantly altered prior to birth.<sup>10,15</sup>

Fetal metabolic stress, such as that caused by inflammation, triggers apo-

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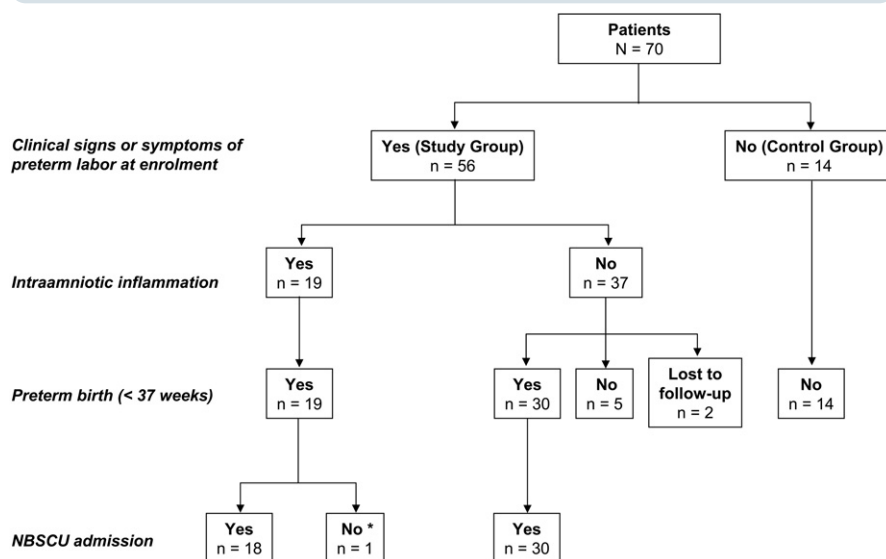
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FIGURE 1

## Enrollment flow chart of patients assigned to the study and control groups



<sup>a</sup>Demise prior to admission in Newborn Special Care Unit (NBSCU).

Azpuruu. Fetal renal artery impedance in pregnancies with intraamniotic inflammation and preterm birth. *Am J Obstet Gynecol* 2009.

ptosis in a variety of tissues, including the nervous system and the kidney.<sup>16</sup> The purpose of this study was to test the hypothesis that disturbances in renal artery blood flow resistance occur in utero as part of a complex adaptive fetal response to inflammation.

## MATERIALS AND METHODS

### Study population and research design

We evaluated fetal renal artery blood flow hemodynamics in 70 fetuses. A flow diagram of our study population is presented in Figure 1. Fifty-six fetuses (study group) were delivered by mothers who had a clinically indicated amniocentesis to rule out intraamniotic infection/inflammation. Gestational age renal artery blood flow velocity reference ranges were generated based on fetuses with uncomplicated pregnancies (n = 14) (control group). All our control fetuses were carried by asymptomatic healthy women undergoing ultrasound as part of their routine prenatal care. We enrolled our study subjects consecutively based on the availability of 3 investigators (H.A., M.O.B., C.S.B.). The Yale University Human Investigation Committee approved our research protocol, and writ-

ten informed consent was obtained from all the participants.

Women in the study group presented to Yale New Haven Hospital between October 2004 and February 2008, with 1 or several symptoms including advanced cervical dilation (> 3 cm; n = 17), preterm labor symptoms (n = 29), or preterm premature rupture of the membranes (PPROM) (n = 27). Gestational age was established based on either the last menstrual period or a first- or second-trimester ultrasound evaluation. Eligible women had a singleton fetus of at least 22 weeks and of less than 34 weeks' completed GA without evidence of structural abnormalities at the time of assessment or birth. Women with maternal medical complications (ie, hypertension, preeclampsia, diabetes, thyroid disease), viral infections (human immunodeficiency virus, hepatitis B or C), anhydramnios, fetal intrauterine growth restriction (estimated fetal weight less than the 10th percentile for GA), and fetuses with abnormal karyotypes and/or congenital anomalies were excluded.

Preterm labor was defined as presence of regular uterine contractions associated with advanced cervical dilatation or

effacement at less than 37 weeks of gestation. We confirmed rupture of the membranes by either pooling on speculum examination, positive nitrazine, and ferning tests or by a positive amnio-dye test. Clinical chorioamnionitis was diagnosed in the presence of maternal fever (> 37.8°C), maternal leukocytosis (> 15,000 cells/mm<sup>3</sup>), uterine tenderness, foul-smelling amniotic fluid (AF), or visualization of pus at the time of the speculum examination, and/or maternal or fetal tachycardia.<sup>17</sup>

In all study cases, assessment of the renal artery Doppler velocity was performed immediately prior to the amniocentesis procedure. Following amniocentesis and fetal renal artery Doppler assessment, each patient was followed up prospectively to delivery. Clinical care of the patients was left to the discretion of the clinical team. In PPRM patients, digital examinations were not allowed. Women with PPRM received corticosteroids for lung maturity if less than 32 weeks, and antibiotic therapy (ampicillin/erythromycin or clindamycin) if less than 34 weeks' GA.<sup>18</sup>

Per our institutional protocol, women were monitored with vital sign assessment (temperature, blood pressure, pulse) every 4 hours and by cardiotocography at least twice daily for the presence of fetal heart abnormalities and/or uterine contractions. Induction of labor or a surgical delivery was recommended for clinical indications such as clinical chorioamnionitis, AF laboratory results suggestive of intraamniotic infection/inflammation, breech presentation, prolapsed umbilical cord, presence of fetal heart rate abnormalities (fetal bradycardia, recurrent, late, severe and prolonged variable deceleration), and/or GA 34 weeks or greater.

Amniotic fluid was retrieved by ultrasound-guided amniocentesis under sterile conditions. Following retrieval, AF was cultured for aerobic and anaerobic bacteria and *Ureaplasma* and *Mycoplasma* species. The clinical laboratory performed the glucose and lactate dehydrogenase (LDH) measurements, the Gram stain, and the AF white blood cell count (WBC). An AF glucose cutoff of 15 mg/dL or less and LDH levels 419 U/L or

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