Published in final edited form as:

Med Hypotheses. 2015 November ; 85(5): 558–564. doi:10.1016/j.mehy.2015.07.026.

A proposed bio-panel to predict risk for spontaneous preterm birth among African American women

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Abstract

Preterm birth (PTB), or birth prior to 37 weeks gestation, impacts 11.5% of U.S. deliveries. PTB results in significant morbidity and mortality among affected children and imposes a large societal financial burden. Racial disparities in PTB are alarming. African American women are at more than 1.5 times the risk for PTB than white women. Unfortunately, the medical community's ability to predict who is at risk for PTB is extremely limited. History of a prior PTB remains the strongest predictor during a singleton gestation. Cervical length and fetal fibronectin measurement are helpful tools. However, usefulness is limited, particularly among the 95% of U.S. women currently pregnant and lacking a history of PTB. Therefore, preventive therapies do not reach a great number of women who may benefit from them. This manuscript, in response to the pressing need for predictors of PTB risk and elimination of racial disparities in PTB, presents a proposed bio-panel for use in predicting risk for spontaneous PTB among African American women. This bio-panel, measured each trimester, includes stimulated production of interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-1 receptor antagonist (Ra), soluble(s) TNF receptor(R) 1, and sTNFR2, and cortisol responsiveness. We hypothesize that greater IL-1 β and TNF- α production, decreased IL-1Ra, sTNFR1, and sTNFR2 production, and decreased cortisol responsiveness at

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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each time point as well as a more expedient alignment with this unfavorable profile over time will be associated with PTB. The choice to focus on inflammatory parameters is supported by data highlighting a crucial role for inflammation in labor. Specific inflammatory mediators have been chosen due to their potential importance in preterm labor among African American women. The bio-panel also focuses on inflammatory regulation (i.e., cytokine production upon *ex vivo* stimulation), which is hypothesized to provide insight into potential *in vivo* leukocyte responses and potential for initiation of a preterm inflammatory cascade. Production of receptors antagonists is also considered, as pro-inflammatory mediator effects can be greatly influenced by their balance with respective antagonists. Finally, leukocyte responsiveness to cortisol is included as a measure of cortisol's ability to convey anti-inflammatory signals. The development of a bio-panel predictive of risk for spontaneous PTB among African American women would represent a significant advancement. Available preventive therapies, namely progesterone supplementation, could be delivered to women deemed at risk. Further, the identification of biological predictors of PTB may uncover novel targets for preventive therapies.

PRETERM BIRTH

Preterm birth (PTB), or birth occurring at less than 37 weeks gestation, accounts for 11.5% of all U.S. deliveries (1). Children born preterm are significantly more prone to serious acute and chronic illness, including bronchopulmonary dysplasia, necrotizing enterocolitis, vision/hearing impairment, and neurodevelopmental disability, as well as death (2). In the U.S., newborn hospital stays average 3.4 days and \$3,200 but reach 14.3 days and \$21,500 for preterm infants (3). Therefore, the acute care of preterm infants alone accounts for about 57% of the \$12.2 billion in total annual newborn hospital costs (3).

Racial disparities in the U.S. are striking, with significantly more African American infants being born preterm than white infants (16.26% vs. 10.17%, respectively) (1). Of additional concern, infant mortality among African Americans is more than twice that of whites (4). Improving birth outcomes and achieving health equity are national priorities (5); however, progress toward these goals has been slow. Our current ability to predict who will experience PTB is remarkably limited. In fact, the American College of Obstetricians and Gynecologists (ACOG) recommends against universal biological screening for PTB risk, as no test has proven sufficiently beneficial (6). In part due to lack of predictive ability, PTB prevention is often not feasible.

PREDICTION AND PREVENTION

The strongest predictor of PTB in a current singleton pregnancy is PTB in a prior pregnancy (2). Women with a history of PTB exhibit 1.5–2 fold higher risk of subsequent PTB compared to women lacking this history, with earlier and greater numbers of previous PTBs conveying greater risk (7). When the first PTB is spontaneous, risk for subsequent spontaneous PTB reaches more than 5 fold (8). Importantly, knowledge of this risk factor allows for early preventive measures. Progesterone supplementation is a proven preventive pharmacotherapy for women with a singleton pregnancy and prior PTB, lowering recurrent PTB risk by as much as 45% compared to women receiving placebo (9).

Shorter cervical length (CL) in early- to mid-pregnancy is also associated with earlier labor onset. Among pregnant women with a prior spontaneous PTB, those who subsequently deliver prior to 35 weeks gestation are >10 times more likely to have a short cervix (CL <25mm) in early pregnancy than women who deliver at term (10). Unfortunately, CL is less predictive of PTB among nulliparas and multiparas without a PTB history, among whom short cervix is associated with 14% probability of delivering prior to 35 weeks (11). Further, prevalence of the more conservative < 15mm CL cut-off is so low that evaluation of an estimated 238 nulliparas or 1075 multiparas without previous PTB would be required to prevent one PTB (12). Adding measurement of cervicovaginal fetal fibronectin, a glycoprotein typically limited to the maternal-fetal interface, to CL improves PTB prediction; however, a positive test is still only associated with a 50% probability of PTB (11). Nevertheless, prophylactic progesterone and cervical cerclage benefit women with a short cervix (13–15), highlighting the usefulness of even an imperfect measure of risk in directing clinical decision-making.

Although history of PTB and short cervix are useful predictors, the ability to identify women at risk for PTB is incomplete. For example, only ~5% of U.S. births are to multiparous women with singleton gestation and a history of PTB (16), a key clinical population for which PTB prevention is considered. If all women falling into this category received prophylactic progesterone, the national PTB rate would drop by only 0.3% (16). Approximately 40% of U.S. births occur to nulliparous women (1), among whom about 8% deliver preterm (17). In addition, approximately 6% of multiparous women with no history of PTB will deliver preterm (17). As both groups lack a history of PTB, the likelihood of preventive action is greatly reduced. Here, an incidental finding of short CL may be the only indicator of altered prenatal physiology. Similarly, women known to be at higher risk, such as African Americans (1), the socioeconomically disadvantaged (18), or women with high psychosocial stress exposure (19), cannot routinely be provided with such preventive therapies since the clinical value for these groups has not been established.

Early identification of women at risk for PTB and who may benefit from preventive strategies is key. Current intervention strategies prompted by signs and symptoms of preterm labor, such as regular uterine contractions and/or ruptured membranes, are of limited clinical value. Anti-contraction agents, such as nifedipine and terbutaline, delay birth by only several days (20). Similar delays result from the administration of antibiotics to women experiencing preterm premature rupture of membranes (PPROM) (21). While these approaches may provide time for the administration of glucocorticoids, which do reduce risk for respiratory distress, intraventricular hemorrhage, and necrotizing enterocolitis (22), they are ultimately not effective strategies to prevent PTB.

There is a clear need for accurate and reliable identification of women at greatest risk for PTB, ideally well in advance of symptom onset. Identifying early deviations from healthy gestational physiology is crucial in achieving this goal. Here, as part of a line of work aiming to close this critical gap in obstetric knowledge, we present a biological panel potentially predictive of impending PTB among African American women. Novel components of this inflammatory bio-panel include biomarkers hypothesized to play the most important role in preterm labor among African American women specifically,

assessment of inflammatory regulation as opposed to inflammation, and analysis of change over time.

THE HYPOTHESIS

We hypothesize that a biological panel measured each trimester consisting of stimulated interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , IL-1 receptor antagonist (Ra), soluble(s) TNF receptor(R) 1, and sTNFR2 production, and cortisol responsiveness will predict risk for spontaneous PTB among African American women (see Figure 1). Specifically, we posit that greater IL-1 β and TNF- α production, decreased IL-1Ra, sTNFR1, and sTNFR2 production, and decreased cortisol responsiveness at each time point as well as a more expedient alignment with this unfavorable profile over time will be associated with PTB.

We suggest prospective testing of the proposed bio-panel in a lower risk cohort of African American women, excluding those who are likely candidates for preventive therapies (e.g., women with a history of PTB) or to undergo early induction or cesarean section (e.g., women with gestational hypertension or diabetes). This approach better enables evaluation of the natural progression of pregnancy and labor. IL-1 β , TNF- α , IL-1Ra, sTNFR1, and sTNFR2 production will be quantified using a minimally invasive *ex vivo* assay in which whole blood is incubated with lipopolysaccharide (LPS), a non-specific innate immune stimulant, and levels compared to control values (see Table 1). Leukocyte responsiveness to cortisol can be quantified as the correlation between plasma cortisol levels and the neutrophil:lymphocyte ratio.

WHY AN INFLAMMATORY PROFILE?

Inflammation is a consistently noted component of labor, whether preterm or term (23). This includes labors without evidence of infectious etiology (e.g., uterine overdistension) (24). Production of pro-inflammatory cytokines, namely IL-1 β , TNF- α , IL-6, and IL-8, is enhanced among laboring women. For example, levels of leukocyte IL-1 β and IL-8 mRNA in the maternal circulation are higher among term laboring versus non-laboring women (25). Serum IL-1 β and IL-6 levels are elevated during preterm labor versus quiescent pregnancy (26). Elevated serum IL-1 β and IL-6 has been reported among women with PPRM who birth within two days versus those who do not (27). Further, TNF- α , IL-6, and IL-8 levels are elevated in the uterus, cervix, and fetal membranes at term cesarean following trial of labor versus quiescent pregnancy (28,29). Such findings support a role for inflammation in labor.

Inflammation is known to beget greater inflammation. For example, infusion of IL-1 β into the amniotic compartment of rhesus monkeys results in rapid release of TNF- α (30). Likewise, culturing of human uterine cells with IL-1 β or TNF- α further propagates inflammation. For instance, a 6-hour incubation with 1ng/ml IL-1 β or TNF- α induces dramatic increases in IL-8 (31). An 8-hour incubation with 5ng/ml IL-1 β results in a 50,000-fold increase in IL-6 (32). Therefore, subtle changes in the inflammatory profile may indicate that an inflammatory cascade is poised to ensue.

A progressing inflammatory cascade is certainly capable of promoting labor-associated cellular and molecular processes (33,34). For example, culturing human uterine cells with IL-1 β or TNF- α induces production of cyclooxygenase-2 and prostaglandins (35,36), and increases in oxytocin (32), oxytocin receptor mRNA expression, and oxytocin receptor binding potential (37). Similarly, culturing human decidual cells with TNF- α induces changes in progesterone receptor (PR) ratios consistent with labor-associated functional progesterone withdrawal (35). PR-A, an inhibitive receptor, rises in a dose dependent manner, while PR-B, the active receptor responsible for communicating anti-contractile signals, remains unaffected (36). Intracervical application of IL-1 β , TNF- α , and IL-8 among guinea pigs results in marked dissolution of the fibrous cervical tissue (38). Exposure to IL-1 β and TNF- α (through amniotic infusion among rhesus monkeys or human fetal membrane culture) induces matrix metalloproteinase (MMP) production and caspase activity, thereby promoting collagen remodeling and apoptosis (39–41). Once such processes are underway, uterine contraction, cervical ripening, dilation, and effacement, rupture of fetal membranes, and likely birth are soon to follow (38,39,41–43). Each of these critical events of labor can be theoretically and temporally tied back to enhanced inflammation.

Inflammatory markers have been evaluated as predictors of PTB among asymptomatic women. Recently, Conde-Agudelo and colleagues (44) and Hee (45) systematically reviewed the prediction of PTB by various biomarkers, including peripheral, cervicovaginal, and amniotic fluid levels of C-reactive protein (CRP), IL-6, IL-8, TNF- α , IL-2, IL-10, and MMP-8. Only elevated amniotic fluid MMP-8 (likelihood ratio [LR]+ 40) (44) and serum TNF- α (LR+ 10) (45) were associated with substantial increases in the likelihood of PTB. While these findings lend support to the theory that an inflammatory cascade is involved in the initiation of spontaneous preterm labor, several factors prohibit the use of these biomarkers among general clinical populations. First, these findings must be replicated. Second, biomarkers indicating a substantial increase in likelihood of PTB following a positive result failed to indicate more than a minimal decrease in likelihood of PTB following a negative result. Third, the testing conditions make widespread use difficult. MMP-8 levels were determined through invasive amniocentesis (46) serum TNF- α was predictive among women with a history of PTB, a group already known to be at high risk (47). There is much work to be done in learning how to transform this knowledge into the development of clinically meaningful screening tools.

WHY THESE BIOMARKERS AMONG AFRICAN AMERICAN WOMEN?

There is a growing body of evidence that meaningful differences may exist between races in the predictive value of given biomarkers. In a multivariate adaptive regression splines (MARS) analysis, maternal race influenced which amniotic fluid and plasma mediators differentiated between women in term versus preterm labor (48). Here, predictive mediators among African American women included IL-1 β , TNF- α , IL-1Ra, sTNFR1, and sTNFR2 (48). Predictive mediators among white women included IL-1Ra and sTNFR1 but not IL-1 β , TNF- α , or sTNFR2 (48). Additional reports provide the levels of these biological mediators among African American and white women (see Table 2). For example, African American women experiencing preterm labor exhibited increased amniotic fluid and plasma IL-1 β and TNF- α as compared to African American women experiencing term labor (49–51). This

pattern was not present among white women, who were more likely to display differing IL-6 and IL-8 profiles (49,52). Culture media from 16 LPS-stimulated fetal membranes collected during elective repeat cesarean contained significantly greater IL-1 among African American women versus white and significantly greater IL-6 among white women versus African American (53).

Brou et al. found that African American women (n = 191) in preterm labor did not display elevated amniotic fluid or plasma IL-1Ra versus those in term labor, which could help balance increases in IL-1 β (50). Among white women, plasma IL-1Ra did significantly rise during preterm versus term labor (50). Considering the TNF receptors, comparisons of amniotic fluid/maternal plasma levels during preterm and term labor revealed rather unpredictable patterns (50). However, *ex vivo* LPS stimulation of fetal membranes uncovered an imbalance among African American women similar to that of IL-1 β :IL-1Ra. Here, stimulation of fetal membranes collected during term cesarean resulted in significant TNF- α production among both African American (n = 9) and white (n = 14) women; however, sTNFR1 and 2 did not rise among African American women as was witnessed among white (54).

These data suggest that biological pathways to PTB may, at least partially, differ according to maternal race. Therefore, we propose that bio-panel development be tailored to inflammatory alterations most salient within racially specified cohorts. This is a critical consideration when attempting to narrow the racial gap in PTB. Indeed, personalized medicine has offered the promise of improved prevention, diagnosis, and treatment of a number of diseases and a more personalized approach to PTB bio-panel development may also play a large role in moving the work forward.

WHY INFLAMMATORY REGULATION?

Regulation of the production and activity of potentially labor-stimulating inflammatory mediators, or lack thereof, may be fundamentally different between women who deliver at term versus preterm. The first component of our proposed regulatory profile includes IL-1 β and TNF- α production upon *ex vivo* LPS immune challenge. As described, researchers have focused on steady state peripheral or localized levels of inflammatory markers in the prediction of PTB. Several limitations to these approaches decrease their clinical usefulness. First, cytokines are rapidly degraded and quantities often approach or exceed the lower limit of detection (55). Therefore, significant elevations may not be appreciable until rising levels are actively propagating labor events. Second, elevations may be an artifact of acute (e.g., exercise) or chronic (e.g., adipose) non-immune influences (56,57). As a result, serum or plasma cytokine levels may not reliably reflect immune activation or impaired ability to regulate excessive inflammation.

During labor, circulating leukocytes release cytokines peripherally (25), rapidly influx the maternal tissues (28,58), and are the primary source of cytokines within the cervix, myometrium, and fetal membranes (29). As such, there may be opportunity to gain critical insights into a woman's ability to regulate pro-inflammatory activity by examining how peripherally obtained lymphocytes respond to *ex vivo* immune challenge during quiescent pregnancy. Peripherally obtained leukocytes that respond to *ex vivo* challenge by producing

large quantities of pro-inflammatory cytokines may very well respond equally robustly to an *in vivo* challenge, instigate an inflammatory cascade, and initiate labor. It may also be that even a seemingly mild challenge, such as subclinical choriodecidual infection, results in labor among women whose immune systems respond particularly vigorously. An increased propensity for peripheral leukocytes to produce pro-inflammatory cytokines may be detected prior to notable steady state elevations of the peripheral or localized levels of cytokines themselves; i.e., *ex vivo* immune challenge may allow a glimpse into future events.

As the second component of the regulatory profile, we suggest quantification of naturally occurring pro-inflammatory receptor antagonists, specifically IL-1Ra, sTNFR1, and sTNFR2, following LPS immune challenge. An important means by which IL-1 β and TNF- α carry out their action is by binding with their respective receptors and triggering transcription of additional pro-inflammatory mediators. Their ability to promote this feed-forward loop appears to be crucial to propagating labor events. For example, double knock-out of IL-1 and TNF receptors decreased the incidence of PTB from 69% to 8% among mice undergoing intrauterine inoculation with killed *Escherichia coli* (59). Ultimately, in the context of inflammatory health conditions, the effects of pro-inflammatory mediators can be greatly influenced by the balance with their respective receptor antagonists (60).

Another novel component of the proposed bio-panel includes measurement of maternal leukocyte responsiveness to the anti-inflammatory actions of the glucocorticoid cortisol. Cortisol carries out multiple biological functions, including dampening leukocyte pro-inflammatory responses and controlling leukocyte trafficking, and synthetic forms have been widely used as immunosuppressive drugs (61). Cortisol's ability to serve as an endogenous anti-inflammatory agent depends upon both bioavailability and responsiveness of leukocytes to conveyed anti-inflammatory signals. Decreased cortisol responsiveness may be particularly detrimental to pregnant women, among whom careful regulation of inflammatory activity is important.

There are multiple ways to assess leukocyte responsiveness to cortisol, including completing rather involved mRNA transcriptional analyses or *ex vivo* multi-condition cultures. In otherwise healthy individuals, high cortisol levels induce neutrophil leukocytosis as well as lymphocytopenia in an attempt to control leukocyte influx into sites of inflammation (62). Therefore, we propose that the correlation between plasma cortisol levels and the neutrophil:lymphocyte ratio be measured, with high or low correlations serving as indicators of high or low cortisol responsiveness, respectively. This approach, which requires only two common laboratory procedures, has greater potential for widespread use and has been applied successfully to psychoneuroimmunologic studies of stress-induced impaired cortisol responsiveness (63–65). In sum, this continuous variable is hypothesized to provide important additional information regarding a woman's ability to regulate pro-inflammatory activity during the course of pregnancy.

WHY LONGITUDINAL ASSESSMENT?

It is plausible that the extent to which a woman's functional profile deviates from that seen during healthy gestation over time will offer improved prediction over cross-sectional data. At the time of labor, specific subsets of leukocytes appear to be attracted to the maternal-

fetal interface. When challenged *ex vivo*, these leukocytes produce significant amounts of cytokines such as IL-1 β and TNF- α (66). This ‘activated’ cellular state speculatively propagates labor events. Whether leukocytes are primed in the maternal peripheral blood leading up to the events of labor remains unclear. Cytokine production upon innate immune challenge is attenuated during quiescent pregnancy versus non-pregnancy (67,68). Also, while Denney and colleagues found that *ex vivo* LPS stimulated IL-1 β and TNF- α production remained relatively constant during healthy gestation, as measured in each trimester (69), Daher et al. report progressive increases in LPS-stimulated TNF- α production in normal pregnancy, with the highest values at the time of labor (70). If leukocytes are primed in the peripheral circulation in preparation for labor prior to recruitment to maternal tissues, subtle phenotypic changes may be best appreciated through examination of their rate of change over time as opposed to a snapshot of their function in a given trimester. Further, it may be that the balance between the propensity to produce pro-inflammatory cytokines, produce their respective receptor antagonists, and communicate the signals of critical anti-inflammatory agents such as cortisol is what is altered in preparation for labor. The answer to this question is certainly worth exploring.

SIGNIFICANCE OF THE HYPOTHESIS

There is much work to be done if birth outcomes in the U.S. and worldwide are to be optimized. An important focus of this work is eliminating racial disparities in PTB. In the current manuscript, we have presented a bio-panel proposed to predict risk for spontaneous PTB among African American women. Our hypothesis is predicated on recent advancements in reproductive immunology and our approach aims to traverse some of the hurdles encountered during previous efforts to biologically predict PTB. Achieving the goal of accurate, reliable, and sufficiently early prediction would represent a major advancement in the field of obstetrics. Women deemed at risk could be provided with progesterone, the most promising preventive approach available to date, or other future preventive therapies. Further, the identification of biological predictors of PTB may uncover novel targets for preventive therapies.

Acknowledgments

Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under Award Number F31NR014605.

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Figure 1.

Theoretical Framework of bio-panel proposed to predict risk for spontaneous PTB among African American women. Three components of inflammatory regulation are measured during the first, second, and third trimesters of pregnancy. We hypothesize that this bio-panel will identify women at risk for PTB by their tendency to produce higher levels of IL-1 β and TNF- α , and lower levels of IL-1Ra, sTNFR1, and TNFR2, and exhibit a diminished response to cortisol earlier in pregnancy. As such, a threshold will be reached which allows for a feed-forward inflammatory cascade, labor-associated cellular and molecular processes, the signs and symptoms of labor, and, ultimately, preterm delivery of the neonate.

Table 1

Proposed bio-panel components

Variable	Measurement Approach	Information Gained
IL-1 β Production TNF- α Production	• Whole blood production following <i>ex vivo</i> LPS stimulation	• Production of the pro-inflammatory cytokine upon innate immune challenge
IL-1Ra Production sTNFR1 Production sTNFR2 Production	• Whole blood production following <i>ex vivo</i> LPS stimulation	• Availability of endogenous receptor antagonists to counteract pro-inflammatory cytokine activity
Cortisol Responsiveness	• Correlation between plasma cortisol levels and neutrophil:lymphocyte ratio	• Ability of cortisol to convey anti-inflammatory signals to leukocytes

Table 2

Labor-associated profiles among African American and white women

Comparison (Race)	Analyte (Medians pg/ml)	p Value	Reference
<i>Amniotic Fluid Concentrations</i>			
Preterm Laboring v. Term Laboring Women (African American)	IL-1 β (80.0 v. 23.7)	<0.001	Menon et al. (49)
	TNF- α (1009.34 v. 67.91)	<0.001	Velez et al. (51)
	IL-6 (2042 v. 2366)	0.60	Menon et al. (52)
	IL-8 (237.7 v. 23.74)	0.90	Menon et al. (49)
	IL-1Ra (2399.1 v. 2243.6)	0.20	Brou et al. (50)
	TNFR1 (285 v. 690)	0.01	Brou et al. (50)
	TNFR2 (2824 v. 2099)	0.92	Brou et al. (50)
Preterm Laboring v. Term Laboring Women (white)	IL-1 β (25.5 v. 21.3)	0.20	Menon et al. (49)
	TNF- α (138.39 v. 67.62)	0.075	Velez et al. (51)
	IL-6 (3773 v. 1682)	0.0003	Menon et al. (52)
	IL-8 (25.64 v. 22.64)	<0.001	Menon et al. (49)
	IL-1Ra (1132.1 v. 1526.2)	0.97	Brou et al. (50)
	TNFR1 (448 v. 233.8)	0.11	Brou et al. (50)
	TNFR2 (2070 v. 1622.5)	0.25	Brou et al. (50)
<i>Maternal Plasma Concentrations</i>			
Preterm Laboring v. Term Laboring Women (African American)	IL-1 β (119.5 v. 52)	0.03	Brou et al. (50)
	TNF- α (50.4 v. 18)	0.03	Brou et al. (50)
	IL-8 (435 v. 178.7)	0.15	Brou et al. (50)
	IL-1Ra (81.6 v. 91.2)	0.71	Brou et al. (50)
	TNFR1 (1462.6 v. 777)	0.03	Brou et al. (50)
	TNFR2 (27153.5 v. 24252.4)	0.21	Brou et al. (50)
Preterm Laboring v. Term Laboring Women (white)	IL-1 β (51.2 v. 44.1)	0.79	Brou et al. (50)
	TNF- α (18.6 v. 10)	0.79	Brou et al. (50)
	IL-8 (311.5 v. 104)	0.18	Brou et al. (50)
	IL-1Ra (152.6 v. 89.9)	0.02	Brou et al. (50)
	TNFR1 (1729.7 v. 873)	0.02	Brou et al. (50)
	TNFR2 (26679 v. 26993)	0.98	Brou et al. (50)
<i>Fetal Membrane Cultures</i>			
Unstimulated v. LPS-Stimulated at Term Elective Cesarean (African American)	IL-1 (21.6 v. 179.8)	0.0002	Menon et al. (53)
	TNF- α (51.3 v. 1062.4)	0.001	Menon et al. (54)
	IL-6 (270 v. 343.5)	0.2	Menon et al. (53)
	sTNFR1 (132.5 v. 93.4)	0.006	Menon et al. (54)
	sTNFR2 (331 v. 174.2)	0.01	Menon et al. (54)
Unstimulated v. LPS-Stimulated at Term Elective Cesarean (white)	IL-1 (13.1 v. 23.05)	0.1	Menon et al. (53)
	TNF- α (28 v. 531.8)	<0.0001	Menon et al. (54)

Comparison (Race)	Analyte (Medians pg/ml)	<i>p</i> Value	Reference
	IL-6 (200 v. 867)	0.0002	Menon et al. (53)
	sTNFR1 (92.1 v. 165.7)	0.002	Menon et al. (54)
	sTNFR2 (168.1 v. 223.7)	0.05	Menon et al. (54)

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