Maternal mortality from systemic illness: unraveling the contribution of the immune response

Juan M. Gonzalez, MD; Ella Ofori, BS; Irina Burd, MD, PhD; Jinghua Chai, MD; Nathalie Scholler, MD, PhD; Michal A. Elovitz, MD

OBJECTIVE: Maternal morbidity and/or mortality (MM) is increased in pyelonephritis and influenza. Alterations in the immune response could account for the increase MM. We sought to determine whether the immune response is functionally different during pregnant and nonpregnant (NP) states.

STUDY DESIGN: Mouse model of systemic and localized inflammation was used. Maternal serum was assessed for expression of T-helper cell type 1 and 2 cytokines. Maternal spleens were harvested for immunohistochemistry.

RESULTS: Systemic administration of lipopolysaccharides resulted in no mortality to NP mice compared with 88% in preterm and 100% in term mice. A potent cytokine response was present in both NP and pregnancy. Systemic inflammation in pregnancy results in increased CD8 and CD11c expression in spleens.

CONCLUSION: Differences in cytokine response to systemic inflammation is unlikely to modulate the increased MM during pregnancy. Altered T-cell and dendritic cell responses in pregnancy may be responsible for the increase in MM.

Key words: immune response, maternal mortality, pregnancy


The immunologic conflict between the mother and fetus suggests that modulation of the maternal host immune response is essential for survival of the fetus. It has been thought that pregnancy is a state of immunosuppression with a T-helper cell type 2 (Th2) bias and, therefore, diminished cellular immunity.1,2 If the host were truly immunosuppressed both systemically and in the genital tract, then immunosuppression would lead to increased susceptibility to infection and endanger the host and pregnancy. When compared with the nonpregnant (NP) state, higher rates of maternal morbidity and/or mortality (MM) are reported with some bacterial and viral infections including acute pyelonephritis, varicella, and influenza.3-5 Death from these systemic illnesses is rarely observed in the NP state. The mechanism for these observations remains unknown.

Local (intrauterine) inflammation appears to play a significant role in a major cause of adverse obstetric outcomes, specifically preterm birth. Intrauterine infection and inflammation is estimated to be present in 25-40% of all spontaneous preterm births.6,7 A widely accepted paradigm view is that microorganisms stimulate a local inflammatory response in the cervix and uterus leading to the production of a number of proinflammatory cytokines and chemokines.

Local intrauterine infection, although strongly associated with preterm birth, is rarely associated with significant maternal illness or death.8 Activation of inflammatory pathways in adverse obstetric outcomes (preterm birth) that do not appear to significantly compromise the host begs the question: what is different in regards to the immune response during pregnancy between systemic and localized infection? The traditional paradigm of Th1 (proinflammatory) and Th2 (anti-inflammatory) in pregnancy may need to be reconceptualized. Research suggests that pregnancy entails a shift in the balance between the different components of the maternal immune response possibly leading to a less aggressive but competent immune system.9 The concept of immunosuppression/immune regulation may differ systemically, locally (reproductive tissues), and at maternal-fetal interface (placenta).10 Understanding the systemic inflammatory response will provide insight into the maternal MM observed in the setting of acute pyelonephritis, varicella, and influenza during...
pregnancy. Elucidating the mechanisms by which the inflammatory response to localized intrauterine infection is similar or divergent between the pregnant and NP state is essential as this could provide novel insight to mechanisms related to preterm labor and other adverse pregnancy outcomes. We sought to determine whether the host immune response to systemic and local inflammation is functionally different during the pregnant and NP states.

### MATERIALS AND METHODS

#### Animals

CD-1 outbred, timed-pregnant, and NP were purchased (Charles-Rivers Laboratories, Wilmington, MA). CD-1 mice have on average a 19-day gestation. Pregnant animals were shipped on day 8-12 after mating. Animals were acclimated for 3-7 days before use in these experiments. All the experiments were performed in accordance with the National Institutes of Health guidelines on laboratory animals and with approval from our university’s committee on animal use and care. All experimental groups of mice were treated contemporaneously.

#### Approach to assessment of the host immune response at baseline

A 2-pronged approach was used to assess the host immune response in pregnancy. First, the response to systemic inflammation, and second, a response to localized intrauterine inflammation were studied as described below. To evaluate the cytokines and mediators of early leukocyte and endothelial activation in the absence of an immune challenge, maternal serum was collected from NP CD-1 mice and on embryonic day (E)15 of gestation from timed-pregnant CD-1 dams (n = 8/group).

#### Mouse model of systemic inflammation

A mouse model of intraperitoneal (IP) inflammation was used to assess the systemic immune response in both pregnant and NP animals. NP, preterm (E15), and term (E18) timed-pregnant CD-1 dams underwent an IP injection of lipopolysaccharides (LPS) from *Escherichia coli* 055:B5 (Sigma, St Louis, MO). The pregnant dams received 250 μg and the NP dams received 125 μg (N = 10/treatment group). LPS or sterile saline solution (100 μL) was injected in the IP cavity. Six hours after infusion of LPS or

### TABLE 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total N</th>
<th>Mortalitya within 24 hrs</th>
<th>Mortalitya within 48 hrs</th>
<th>Mortalitya within 72 hrs</th>
<th>% dams with live births</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E15 IU 250 μg LPS</td>
<td>16</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>E18 IU 250 μg LPS</td>
<td>26</td>
<td>8%</td>
<td>12%</td>
<td>12%</td>
<td>62%</td>
</tr>
<tr>
<td>NP IU 125 μg LPS</td>
<td>4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Systemic Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E15 IP 250 μg LPS</td>
<td>8</td>
<td>13%</td>
<td>88%</td>
<td>88%</td>
<td>13%</td>
</tr>
<tr>
<td>E15 IP 50 μg LPS</td>
<td>15</td>
<td>13%</td>
<td>13%</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>E18 IP 250 μg LPS</td>
<td>7</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>N/A</td>
</tr>
<tr>
<td>E18 IP 50 μg LPS</td>
<td>17</td>
<td>0%</td>
<td>6%</td>
<td>6%</td>
<td>35%</td>
</tr>
<tr>
<td>NP IP 250 μg LPS</td>
<td>12</td>
<td>0%</td>
<td>8%</td>
<td>8%</td>
<td>N/A</td>
</tr>
<tr>
<td>NP IP 125 μg LPS</td>
<td>4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>N/A</td>
</tr>
<tr>
<td>NP IP 50 μg LPS</td>
<td>12</td>
<td>0%</td>
<td>0%</td>
<td>8%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* IP, intraperitoneal; IU, intrauterine; LPS, lipopolysaccharides; N/A, not available; NP, nonpregnant.

Mortality = mortality and animals that exhibited significant morbidity.


### TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Nonpregnant Controls</th>
<th>Pregnant Controls</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>IL-10 (ng/mL)</td>
<td>478.7 (25.9)</td>
<td>482.1 (23.3)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>258.6 (28.3)</td>
<td>275.5 (25.8)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-12 (pg/mL)</td>
<td>398.7 (51.3)</td>
<td>344.3 (61.2)</td>
<td>NS</td>
</tr>
<tr>
<td>TNF (pg/mL)</td>
<td>5.9 (14.2)</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>CXCL (pg/mL)</td>
<td>532.7 (33.5)</td>
<td>507.8 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>sE (pg/mL)</td>
<td>128.3 (56.1)</td>
<td>41.8 (54.7)</td>
<td>NS</td>
</tr>
<tr>
<td>sICAM (ng/mL)</td>
<td>529.3 (88.4)</td>
<td>250.7 (63.7)</td>
<td>.022</td>
</tr>
</tbody>
</table>

CXCL 10, CXC chemokine ligand 10; interferon-γ inducible protein IP-10; IL, interleukin; sE, selectin; sICAM, soluble intercellular adhesion molecule 1; TNF, T-helper cell type 1; T/H11005, in vitro.

* P value from pairwise comparison (Student-Newman-Keuls method) after statistical significance was reached (P < .05) by 1-way ANOVA.


A mouse model of intraperitoneal (IP) inflammation was used to assess the systemic immune response in both pregnant and NP animals. NP, preterm (E15), and term (E18) timed-pregnant CD-1 dams underwent an IP injection of lipopolysaccharides (LPS) from *Escherichia coli* 055:B5 (Sigma, St Louis, MO). The pregnant dams received 250 μg and the NP dams received 125 μg (N = 10/treatment group). LPS or sterile saline solution (100 μL) was injected in the IP cavity. Six hours after infusion of LPS or...
saline maternal serum and spleens were collected.

**Mouse model of systemic inflammation-observational studies**

Observational dose response studies were performed on the following treatment groups: (1) NP 50 μg LPS IP; (2) NP 125 μg LPS IP; (3) NP 250 μg LPS IP; (4) E15 50 μg LPS IP; (5) E15 250 μg LPS IP; (6) E18 50 μg LPS IP; and (7) E18 250 μg LPS IP (n = ≥ 4/treatment group; Table 1). The animals were monitored for MM every 12 hours for more than 72 hours. Animals were observed for any signs of morbidity (piloerection, decreased activity), vaginal bleeding, and/or preterm/term delivery (live or dead pups present in the cage). The principal investigator and first author were trained by university laboratory animal resources regarding signs and symptoms of morbidity. A grading system was used to gauge degree of morbidity (scale 1-4: 1 = alive and well; 2 = fair; 3 = very distressed; and 4 = moribund) and only dams with score of 4 were killed according to Institutional Animal Care and Use Committee guidelines for humane reasons. An inability to stand, minimal to no activity, no feeding, and piloerection were classified as 4. Mice requiring killing secondary to severe morbidity were classified as mortality for purposes of these studies.

**Mouse model of localized inflammation**

A mouse model of intrauterine (IU) inflammation, as previously described, was used to assess the localized immune response. NP, E15, and E18 timed-pregnant CD-1 dams were placed under isoflurane anesthesia. A mini-laparotomy was performed, and the lower right uterine horn was identified. LPS from *E. coli* 055:B5 (Sigma), 250 μg in a 100-μL volume or sterile saline solution (100 μL), was infused between 2 gestational sacs, with care not to inject into the amniotic cavity (n = 3-8/treatment group). Six hours from intrauterine infusion of LPS or saline maternal serum and spleen were collected.

**Assessment of cytokine and mediators of early leukocyte and endothelial activation**

To quantify the concentrations of Th1 cytokines (interleukin [IL]-6, IL-12, tumor necrosis factor [TNF]-α, IL-1-β, IL-17) and the Th2 cytokine (IL-10), enzyme-linked immunosorbent assays (Quantikine, R & D Systems, Minneapolis, MN) were performed on maternal sera. In addition, CXCL 10 (CXC chemokine ligand 10, also known as interferon-γ inducible protein-10), E-selectin, sICAM, soluble intercellular adhesion molecule 1, TNF, tumor necrosis factor.

were stained with the following polyclonal antibodies: CD4, CD8, CD11b, and CD11c (BD Pharmingen, San Jose, CA). Negative control experiments using control isotype IgG confirmed the absence of nonspecific staining. The paraffin-embedded tissues were deparaffinized in xylene, rehydrated in ethanol, then subjected to endogenous peroxidase quenching and antigen retrieval (ProteinaseK; DAKO, Glostrup, Denmark). After 30 minutes of pretreatment with normal serum, the primary antibodies were applied: CD4 (1:100), CD8 (1:100), CD11b (1:100), and CD11c (1:100). The biotinylated anti-IgG secondary antibody: antitat IgG and antihamster IgG (BD Pharmingen) were used and then developed with diaminobenzidine (Sigma) according to the manufacturer’s protocol. The tissues were counterstained with hematoxylin. Photographs were taken on a white field microscope at \( \times 4 \), \( \times 10 \), and \( \times 40 \) magnification and were reviewed with a trained immunologist (N.S.).

### Statistical analysis

Sigma Stat Software (Systat Software, San Jose, CA) was used. The concentrations of the mediators of the immune response between all study groups were compared by 1-way analysis of variance or analysis of variance on ranks if data were nonparametric. When significance was reached (\( P < .05 \)), pairwise comparison was performed by using Student-Newman-Keuls or Dunn method.

### Results

**Observational studies in the systemic and localized inflammation mouse models**

In NP mice, neither the systemic nor the localized intrauterine inflammatory models resulted in significant MM of the host after 72 hours (Table 1). However, in the systemic inflammatory model, in preterm mice (E15) a 250-\( \mu \)g dose of LPS induced 13% maternal morbidity by 24 hours and 88% maternal mortality after 48 hours. Furthermore, near term (E18), a 250-\( \mu \)g dose of LPS induced 100% significant maternal MM after 48 hours (Table 1). In contrast to the high rate of maternal mortality from systemic inflammation, in the localized intrauterine model at E15, a 250-\( \mu \)g dose of LPS induced no maternal mortality but only high rates of preterm birth (> 95%). At E18, in the intrauterine model the same dose resulted in 12% maternal mortality and arrested labor. In the systemic model, on E15 a 250-\( \mu \)g dose of LPS 24 hours after injection induced a 75% preterm delivery rate and 88% maternal mortality by 48 hours. Injections with sterile saline solution (100 \( \mu \)L) in the intrauterine cavity resulted in no MM or preterm delivery. With the IP cavity injection of sterile saline solution, 1 maternal death on E15 was observed from a total group of 12 but otherwise no MM or preterm delivery was observed.

As there was a divergent response to the same dose of LPS between local and systemic models during pregnancy, we sought to further assess a dose-response effect on maternal mortality in the systemic model. In pregnancy, maternal mortality was noted with 50 \( \mu \)g of LPS whereas 5 times this dose (250 \( \mu \)g) did not elicit mortality in the NP mice (Table 1).

### Baseline host immune profile

The baseline levels for the Th1/Th2 cytokines were not significantly different be-
tween NP when compared with the pregnant mice (Table 2). In a similar fashion, maternal serum mean values for early markers of endothelial and leukocyte activation levels were not significantly different between NP and pregnant controls at the exception of sICAM (P = .022; Table 2).

**Immune profile after systemic inflammation**

We compared the fold changes of cytokines and markers between LPS/saline in NP and pregnant mice 6 hours after LPS injection IP. For IL-12, the fold changes between LPS/saline were higher for NP (P < .006) vs for E15 (P < .002). For TNF-α, the fold changes between LPS/saline in NP immune response were higher (P < .001) and lower (P < .001) on E15, respectively. In contrast, IL-6 fold change between LPS/saline on E15 is higher (P < .001) compared with NP (P < .002; Figure 1). The host immune responses to systemic inflammation were not statistically different between pre-term (E15) and term (E18) (Table 3).

**Immune profile after localized inflammation**

As in the systemic model of inflammation, intrauterine injections of LPS up-regulated the immune responses measured in sera of all tested mice. The fold changes between LPS/saline in NP and pregnant mice for cytokines and markers were higher during pregnancy for CXCL 10, IL-6, and TNF-α (Figure 2). In contrast with the systemic model of inflammation, the host immune responses to localized inflammation were different when comparing E15 (preterm) with E18 (term). Significantly lower concentrations of cytokines were observed in at term vs preterm mice for CXCL 10, IL-6, IL-12, TNF-α, and IL-1-β (Table 4). The observations between E15 and E18 in the localized model are unlikely to be secondary to differences at baseline given that no difference was observed in the systemic model.

**Assessment of bacterial endotoxin systemically**

We assessed whether the altered maternal mortality between pregnant and NP mice challenged locally or systemically could be correlated to variations of serum endotoxin levels. As expected, serum concentrations of endotoxin were higher in NP and pregnant mice after systemic LPS administration compared with a local challenge. Despite significantly different mortality after systemic administration, LPS levels in serum were not different during pregnancy compared with NP. In the local model, more endotoxin was present in the serum of NP compared with pregnancy (Figure 3).

**IHC results**

IHC of spleens from the localized (IU) or systemic (IP) host immune models at E15 showed no difference in CD4, CD8, and CD11c staining. In the systemic model, an increased infiltration of monocytes and macrophages (CD11b) compared with the localized model was observed (Figure 4). When comparing saline with LPS in the systemic model no conclusive difference could be observed in the infiltration of CD4 (data not shown). However, in the systemic model, spleen infiltration of T cells (CD8) and dendritic cells (CD11c) was increased in E15 when compared with NP (Figure 5).

**COMMENT**

The maternal immune response appears to be dynamic and functionally different in regard to whether the inflammatory challenge is local (the genital tract) or systemic. Our data demonstrate that, in a
significantly different. (Dunn method) comparing NP saline intrauterine vs E15 saline IP vs E15 LPS IP were:

<table>
<thead>
<tr>
<th></th>
<th>E15</th>
<th>E18</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL (pg/mL)</td>
<td>32776 (9337)</td>
<td>13 (10)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>sE (pg/mL)</td>
<td>437 (295)</td>
<td>143469 (26080)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>sICAM (ng/mL)</td>
<td>1395 (398)</td>
<td>993 (363)</td>
<td>.003</td>
</tr>
<tr>
<td>IL-10 (ng/mL)</td>
<td>1071 (471)</td>
<td>2555 (1359)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>64780 (24390)</td>
<td>31654 (29887)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-12 (pg/mL)</td>
<td>392 (36)</td>
<td>195 (162)</td>
<td>.004</td>
</tr>
<tr>
<td>TNF (pg/mL)</td>
<td>556 (335)</td>
<td>152 (90)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>IL-1 beta (pg/mL)</td>
<td>161 (44)</td>
<td>134 (75)</td>
<td>Do Not Test</td>
</tr>
<tr>
<td>IL-17 (pg/mL)</td>
<td>258 (113)</td>
<td>273 (101)</td>
<td>Do Not Test</td>
</tr>
</tbody>
</table>

CXCL 10, CXC chemokine ligand 10; inducible protein IP-10; IL, interleukin; sE, selectin; sICAM, soluble intercellular adhesion molecule 1; Th1, T-helper cell type 1; TNF, tumor necrosis factor.

* statistically significant P value from pair-wise comparison (Student-Newman-Keuls) after statistical significance was reached (P < .05) by 1-way ANOVA.


Mean values (SD) of concentration of endotoxin using limulus amebocyte lysate (LAL) chromogenic end point assay in maternal serum from nonpregnant (NP) and embryonic day (E)15 CD-1 mice in systemic and localized model of inflammation. Lipopolysaccharide (LPS) doses were: 125 μg for NP intraperitoneally (IP) and 250 μg for all other groups. After statistical significance was reached by 1-way analysis of variance (P < .001), pairwise comparison (Dunn method) comparing NP saline intrauterine (IU) vs NP LPS IU, NP saline IP vs NP LPS IP, and E15 saline IP vs E15 LPS IP were significantly different.

Nonchallenged state, mediators of the adaptive immune system (Th1/Th2) and early markers of endothelial and leukocyte activation are not significantly different between the pregnant and NP state. Key findings from this study are the demonstration that: (1) the immune response to systemic inflammation during pregnancy is functionally different than in NP state; (2) compared with NP state, during pregnancy, the uterus serves to “protect” the host and can prevent release of endotoxin systemically to the mother; and (3) the response to localized inflammation appears to be functionally different during pregnancy with different mortality and preterm birth rate in preterm compared with near-term mice. With pregnancy being associated with higher rates of mortality compared with the NP state, our findings suggest increased “sensitivity” in pregnancy to gram-negative infections. As endotoxin levels in serum are not different between pregnant and NP mice, the altered mortality in pregnancy from systemic inflammation argues for a functional difference in the host immune response. To our knowledge, this is the first time that these observations are reported. As the cytokine response from systemic inflammation was profound in both NP and pregnancy, it is difficult to conclude that alterations in cytokine production are mechanistically responsible for the observed maternal mortality. We also note differential expression of cytotoxic T cells and dendritic cells in maternal spleens after systemic inflammation in pregnancy compared with NP. The dendritic cells are potent antigen-presenting and play a key in T-cell activation. Changes in the dendritic cell phenotype or function in NP mice have been found to contribute to sepsis-mediated immu-

**FIGURE 3**

LAL assay for endotoxin

**FIGURE 4**

Immunohistochemical staining of CD11b in maternal spleens

A Localized intrauterine  
B Systemic intraperitoneal

Immunohistochemical staining of CD11b in maternal spleens 6 hours after lipopolysaccharide infusion in A, localized (intrauterine) and B, systemic (intraperitoneal) host immune models. Sections are imaged at ×40 magnification.

nosophrosis.\textsuperscript{15} Therefore, it is plausible that dendritic cell changes are more profound in the setting of pregnancy. In human pregnancy when compared with the NP state, higher rates of MM are reported with various infections. For example, pregnancy increases the likelihood of varicella pneumonia complicating the primary infection.\textsuperscript{4} Influenza infection usually is not life threatening in healthy adults, but pregnant women do not tolerate serious pulmonary involvement\textsuperscript{5} and mortality from influenza is dramatically increased during pregnancy. Whether the observed changes in T cells and/or dendritic cells play a key role in maternal mortality from systemic illness requires further investigations. It is also biologically plausible that altered maternal mortality during pregnancy may reflect a functional difference in toll-like receptor (TLR)-4 activation. TLR-4 is known to be the cognate receptor for LPS. The signal transduction pathways involved in TLR-4 activation are complex\textsuperscript{16}; further work is warranted to determine whether these pathways are altered during pregnancy.

Although several cytokines have been demonstrated to be increased in preterm birth, the mechanistic role of these immune mediators in adverse obstetric outcomes and/or maternal illness remains unclear. Our studies suggest that the host immune response to systemic inflammation is altered during pregnancy as reflected by the significantly different serum concentrations of sE, IL-10, and IL-6. Similarly, the response to localized intrauterine inflammation appears altered during pregnancy, compared with NP, as supported by the increase in serum concentrations of CXCl, sICAM, IL-10, IL-6, IL-12, and TNF-\alpha. We acknowledge that the peripheral cytokine levels measured are not necessarily representative of biological activity of these cytokines and that unidentified differences between mice and human beings in regard to immune system must be considered for interpretation. In addition, an intrinsic limitation to our study is that we collected serum at 1 time point only. Alterations in the cytokine concentrations could have been missed with this design. Yet, consistent with our data, previous works demonstrated in a rat model that plasma levels of proinflammatory cytokines and anti-inflammatory cytokines were unaffected throughout gestation after IP injection of LPS (50 \(\mu\)g/kg)\textsuperscript{17} while in a rat model of localized inflammatory response due to intramuscular turpentine, a significant reduction in circulating IL-6 was observed during late pregnancy.\textsuperscript{18} Collectively, these data show that host immune responses to local intrauterine inflammation, but not to systemic inflammation, diverge during gestation.

These studies demonstrate a possible protective role for the pregnant, compared with the NP uterus. The lack of circulating endotoxin after intrauterine LPS injection suggests that the uterus behaves as a protective barrier for the host serving to contain, and perhaps protect the host, from infection. The mechanisms by which endotoxin is prevented from getting to the maternal circulation are unknown but can be theorized to be secondary to an increased presence of macrophages and/or uterine natural killer cells in the pregnant uterus.

Our data suggest that a new conceptualized framework for the immune response in pregnancy is necessary. This new paradigm must take into account the complex maternal-fetal interactions and the teleological need to conserve the mother and propagate the species. Understanding the differential immune response in pregnancy may provide insight into adverse obstetric outcomes associated with inflammation and provide novel potential therapeutic targets to reduce both maternal mortality and preterm birth.

**REFERENCES**

1. Marzi M, Vigano A, Trabattoni D, et al. Characterization of type 1 and type 2 cytokine production profile in physiologic and pathologic hu-