Successful treatment of intraamniotic infection/inflammation: a paradigm shift

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Preterm birth (defined as birth at <37 completed weeks of gestation) is the most frequent cause of neonatal death and the leading cause of childhood death under the age of 5 years worldwide.[1,2]

Preterm birth accounts for an estimated 1 million neonatal deaths annually and complicates 1 in 10 pregnancies. In the United States, preterm birth is responsible for 75% of all neonatal deaths.[3]

Preterm birth represents a complex endpoint with multifactorial causes that vary as a function of demographic and ethnic factors and gestational age. Intraamniotic infection and/or inflammation is 1 of the most common, and potentially preventable, causes of preterm birth, especially among very early premature births, in which neonatal death and morbidity are greatest. Intraamniotic infection is present in 10−15% of patients with an episode of preterm birth[4,5] and nearly 50% of very early preterm births.[6] Importantly, most patients in preterm labor with intraamniotic infection or inflammation have no clinical signs or symptoms of infection (eg, fever, uterine tenderness); therefore, an accurate diagnosis requires amniotic fluid analysis via amniocentesis.[7] This is an invasive procedure that many providers are reluctant to perform in the setting of preterm labor. However, recent evidence suggests that the risk that is associated with amniocentesis in the third trimester is low[8] and that this procedure should be considered to evaluate patients with preterm labor, especially those with preterm labor at <32 weeks of gestation, where the frequency of intraamniotic infection/inflammation is particularly high.

Early case reports suggest that intraamniotic infection can be treated with antibiotics and prolong pregnancy.[9,10] Additionally, animal models that have used pregnant rhesus monkeys have indicated that antibiotics together with anti-inflammatory treatment of preterm labor in the setting of experimentally induced intraamniotic infection can eradicate microorganisms, reduce the proinflammatory intrauterine immune response, and prolong pregnancy.[11,12] However, in humans, randomized controlled trials of adjunctive antibiotic treatment in preterm labor have failed to prolong pregnancy or improve neonatal outcome and may be deleterious to the fetus.[13,14] Because only 10% of women who were enrolled in these studies would be expected to have intraamniotic infection or inflammation, 90% of patients enrolled in these trials were unlikely to benefit from antimicrobial agents. Perhaps the expectation that antibiotics would prolong pregnancy and reduce preterm birth when administered to all patients in preterm labor was misplaced. Nonetheless, professional organizations such as the American College of Obstetrics and Gynecology and the Society for Maternal-Fetal Medicine do not recommend treatment of preterm labor with adjunctive antibiotics.[15,16]

Two manuscripts in this issue of the *American Journal of Obstetrics & Gynecology*[17,18] report that antibiotic treatment can eradicate intraamniotic infection or inflammation successfully, prolong pregnancy, and improve short-term neonatal outcome in selected women with proven intraamniotic infection or inflammation that has been identified by amniocentesis. In these studies, women were identified as having intraamniotic infection (defined as recovery of bacteria from amniotic fluid by culture or polymerase chain reaction) or inflammation (defined as an elevated amniotic fluid interleukin-6 concentration in the absence of bacteria within amniotic fluid) by amniocentesis.[17,18] A third manuscript in this issue[19] reports clearing of bacterial sludge, which is a marker of intraamniotic infection,[20] by antibiotic treatment.

In the first study, Yoon et al[17] report a case-series of 62 patients with a singleton gestation of 20−34 weeks of gestation with evidence of intraamniotic infection (n=11) or inflammation (n=51). Fifty patients received a combination of broad-spectrum antibiotics, and 12 did not. Patients who received antibiotics had a longer median amniocentesis-to-delivery interval (11.4 days vs 3.1 days) and a lower rate of delivery within 4 weeks of amniocentesis (58% vs 92%) than patients who did not receive antibiotics, despite having a higher median amniotic fluid white blood cell count before treatment. Further, nearly 60% of those patients who did not receive antibiotic treatment delivered within 7 days of amniocentesis, and 82% delivered at <30 weeks of gestation. Resolution of intraamniotic infection/inflammation or term delivery was confirmed in 84% (16/19) of patients who had a follow-up amniocentesis, and most neonates survived without demonstrable short-term morbidity.

In the second study, Oh et al[18] report a retrospective case series of 22 women with cervical insufficiency and intraamniotic infection or inflammation before treatment with antibiotics. Again, clinical management was individualized; some patients received cervical cerclage; others did not. They found resolution of inflammation (by repeat amniocentesis)

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and successful prolongation of pregnancy to greater than >34 weeks of gestation in 59% (13/22) of patients without short-term neonatal complications. This represents a significant improvement in outcome. Previous studies have reported a poor prognosis for patients with cervical insufficiency and intraamniotic infection or inflammation, with 84% delivering at <34 weeks of gestation.[21]

In support of the observation that intraamniotic infection/inflammation can be treated with antimicrobial agents, a third report in this issue of the Journal by Dinglas et al[19] shows that intraamniotic "sludge" disappears after antimicrobial treatment, which is a finding also recently reported by Hatanaka et al.[22] An important caveat in the study by Oh et al[18] is that, of the 3 patients with intraamniotic infection rather than inflammation, 2 women delivered very early (20 and 28 weeks of gestation) and 1 woman, who was infected with *Urealyticum spp* delivered at 34 weeks of gestation.[18] This suggests that intraamniotic inflammation without microbial invasion of the amniotic cavity may be more amenable to treatment than intraamniotic infection.

Although the data that are presented in these articles are encouraging, there are a few noteworthy limitations. First, the first 2 studies represent case series that were collected over several years, and treatment was individualized by each provider. This is not the same as an observational study in which patients were treated with a standardized protocol. Therefore, replication of these observations is needed.

Second, the main conclusions of the 2 studies by Yoon et al[17] and Oh et al[18] are based on serial amniocentesis. These procedures were used first to diagnose the presence or absence of intraamniotic infection/inflammation and to monitor response to therapy. The resistance of clinicians to use amniocentesis may be due, in part, to the lack of clinical evidence that intraamniotic infection/inflammation could be treated successfully. These 2 studies go beyond the standard case report and provide an experience based on 2 case series of patients with preterm labor and intact membranes and cervical insufficiency. The risks of amniocentesis for the diagnosis of intraamniotic infection/inflammation in preterm labor and cervical insufficiency need to be considered in the context of what has been reported recently, namely, that the risk of amniocentesis is low and that the potential benefits of successful treatment with antimicrobial agents is something that may outweigh the risks of the procedure.

Timely diagnosis and intervention requires availability of simple point-of-care tests, as were used in these studies. Recent data indicate very good test performance for rapid MMP-8 and interleukin-6 point-of-care tests and should be validated in prospective studies.[23] Development and validation of noninvasive diagnostic tests for intraamniotic infection or inflammation (eg, protein biomarkers in cervical-vaginal fluid[24,25]) will also be useful to facilitate identification of women with intraamniotic infection or inflammation. Long-term follow-up studies of children who were exposed to intraamniotic infection or inflammation will be necessary to establish the safety of adjunctive antibiotic treatment in preterm labor. Data derived from animal studies in multiple species indicate that intrauterine inflammation has adverse developmental consequences on fetal brain, lung, and heart, even in the absence of overt microbial invasion of the amniotic fluid.[26–30] In humans, the association between clinical or histologic chorioamnionitis and subsequent cerebral palsy is well known[31,32]; fetal exposure to intraamniotic inflammation (fetal inflammatory response syndrome) with or without intraamniotic infection has also been reported as a risk factor for the development of cerebral palsy, bronchopulmonary dysplasia, and intraventricular hemorrhage.[33–35] More recently, severe maternal infections that include clinical chorioamnionitis have been linked to autism spectrum disorder in children.[36,37] Unanswered questions remain about whether the addition of immune modulator therapy to down-regulate the robust proinflammatory response that is seen in intraamniotic infection or inflammation, when added to appropriate antibiotic treatment, might mitigate or prevent some of these potential adverse neonatal sequelae and whether an antibiotic that has a known effect on reducing inflammation (like clarithromycin, which was used in the current studies) should always be used along with bactericidal antibiotics that disrupt bacterial cells wall and potentially increase inflammation?

Despite these limitations, these are intriguing and novel data that require a reexamination of our approach to preterm labor. The recognition that preterm labor that is associated with intraamniotic infection and inflammation can be treated successfully and that pregnancy can be prolonged without short-term neonatal sequelae shifts the conventional paradigm that nothing can be done to prevent preterm delivery once intraamniotic infection is present. The question remains at what cost, if any, to the neonate. Does the benefit of pregnancy prolongation outweigh the risks of potential harm? Large multicenter randomized controlled trials with standardized diagnostic and management protocols will be necessary to answer these questions, and this should be a research priority. The design and organization of such trials is an important challenge to obstetrics and maternal-fetal medicine, but this is necessary, given the evidence that intraamniotic infection/inflammation are linked causally to preterm labor and that these conditions are prevalent and can now be diagnosed and treated. ■

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