## **Editorial**

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## Preterm premature rupture of membranes (PPROM)

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Blastoff!

The phrase "It's not rocket science" stems from the fact that getting rockets to fly successfully is very difficult, requiring a high level of mathematics, and thus little else rises to that level of difficulty. I would argue that the study of biologic systems, and pregnancy in particular, is equally, if not more, difficult. So perhaps we should coin a new phrase, "It's not like figuring out pregnancy". The study of preterm premature rupture of the membranes (PPROM) is an example, which not only includes the interaction of immunologic factors (amniocytes), connective tissue physiology (cervix and chorioamniotic membranes), muscle physiology (myometrium), but also a water tight barrier (chorioamniotic membranes) that when disrupted leads to a risk of ascending bacterial proliferation – sometimes but not always. Because the topic is so complex, it should not be surprising that we have not solved the puzzle of the immunology of pregnancy - the balance between pro- and anti-inflammatory activity that allows pregnancy to continue.

The recent enhanced study of, and discoveries in, the depths of the ocean are surprising us all – witness the volcanic vents on the ocean floor that have the heat and nutrients necessary for the creation of life. Similarly, for the past 20 years or more, we are in an era of enhanced study of the amniotic cavity, where recent discoveries have been surprising. The best example is that amniocytes are not just flaked off skin cells that we can gather to diagnose fetal aneuploidy, they are immunologically active cells, and robustly so.

This issue of the *Journal of Perinatal Medicine (JPM)* shows discoveries in the amniotic cavity that have direct bearing on the diagnosis of intra-amniotic inflammation and infection (IAI/I), the prediction of morbidity, and the management of PPROM. The four articles in this edition of the *JPM* are markedly different in their design, approach and ability to help elucidate the course of events in the

setting of PPROM, although all are retrospective [1-4]. These articles, as well as others over the course of the last decades, show us that there is a differential response of the maternal immune system in the various bodily compartments - fetal, amniotic fluid, chorio-amniotic membranes, decidua, myometrium and maternal serum. It is becoming more clear that the amniotic cavity may be the best at determining the level of inflammation, and thus, predicting the outcome of the pregnancy. However, we must also remember that there are several different and distinct clinical presentations that must be distinguished, which include spontaneous preterm labor, cervical insufficiency and PPROM. The retrospective study of these conditions is fraught with problems, in large part due to their complexity. The 249 retrospective patients in the combined trials just in the current issue of this journal are not enough - undoubtedly we will need many hundreds of patients, if not thousands, to distinguish both the optimal use of amniocentesis, and which tests on which to focus, and we will need to study them prospectively.

The time may be ripe for a large, prospective, multicenter, funded trial studying whether amniocentesis is useful for PPROM, either for identifying IAI/I or for management or both. Such a trial could answer a number of questions that the current literature cannot, including: (1) Are there modifiable risk factors on which to focus, i.e. - change maternal behavior to improve outcomes? (2) Are there genetic predispositions affecting the risk of PPROM? (3) Which molecules should we focus on that may prevent or treat membrane damage? (4) What is the best combination of tests in amniotic fluid to detect irreversible IAI/I? (5) What is different about women who, after PPROM, proceed to 34-36 weeks without infection and can we mimic their experience in others to produce improved outcomes? Undoubtedly there are many more questions that will get asked, and hopefully answered, by the conduct of such a trial.

Put on your space suit, it's time to blast off. After all, this isn't rocket science – it's more difficult.

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