Amniotic Fluid Cytokines Predict Pregnancy Outcome: Myth or Reality?

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Amniocentesis for genetic diagnosis began in the late 1960s and early 1970s as a tertiary procedure reserved for only the highest-risk patients.[1,2] Although this procedure is familiar in clinical practice, the role of amniocentesis continues to focus mainly on the detection of chromosomal abnormalities and well-known clinically evident or hereditary genetic diagnoses.[3] It is often applied in older women (age ≥ 34 years old) and high risk younger women (less than 1/270) who have undergone maternal blood Down syndrome screening. The main target for evaluation in amniocentesis is cells derived from amniotic fluid. However, the residual amniotic fluid without cells is often disregarded. It would be welcome if the contents of the amniotic fluid could provide further information regarding pregnancy outcome.

In this issue of the *Journal of the Chinese Medical Association*, a team of investigators from Taichung Veterans General Hospital pioneered a study of the chemokine, stromal cell-derived factor-1α (SDF-1α; also known as chemokine ligand12 [CXCL12]) of the amniotic fluid, and evaluated the clinical significance of SDF-1α in pregnant women.[4] They studied amniotic fluid obtained from mid-trimester women and found that the use of a cut-off value of SDF-1α of 6.42 pg/mL could provide optimal sensitivity and specificity in predicting pregnancy outcomes such as Apgar score at 1 minute, preterm birth rate, fetal birth weight and the possibility of being small for gestational age. This study offers a vision of reusing the "wasted amniotic fluid". In addition, the authors provide useful information to show that the concentration of SDF-1α in amniotic fluid might be a prognostic factor in the future. However, is this reality or only a myth? This issue requires our attention.

SDF-1α, a member of the superfamily of chemoattractant cytokines known as chemokines, regulates many essential biological processes, including cardiac and neuronal development, stem cell motility, neovascularization, angiogenesis, apoptosis, and tumorigenesis.[5] In mice genetically deleted of SDF-1α,[6] early-stage embryos exhibit profound defects in the formation of large vessels, as well as other morphological anomalies such as septal malformation during cardiac development and abnormal brain patterning, including a disorganized cerebellum. Ultimately, embryonic lethality is observed typically between days 15 and 18 of gestation, suggesting the critical role of SDF-1α in successful pregnancy outcome. Recently, Zhou et al[7] investigated the role of SDF-1α and its receptor CXCR4 in the interaction of trophoblasts and decidual stromal cells and found that CXCR4 was present in both human trophoblasts and decidual stromal cells, but only human trophoblasts secreted SDF-1α spontaneously *in vitro*. In addition, SDF-1α induced an apparent increase in the invasiveness of trophoblasts, and upregulated matrix metalloproteinase (MMP) 9 and MMP2 activity of both trophoblasts and decidual stromal cells in an autocrine and paracrine manner. The invasiveness and MMP9 and MMP2 activity of trophoblasts in co-culture with decidual stromal cells increased significantly, and these could be inhibited by anti-CXCR4 neutralizing antibody. These results suggest that SDF-1α secreted by human trophoblasts enhances the coordination between trophoblasts and decidual stromal cells via the regulation of MMP9 and MMP2, which may improve the functional maternofetal interface. However, Tseng et al's data[4] showed a relatively confusing result, since they found that higher concentration of SDF-1α in the amniotic fluid (≥ 6.42 pg/mL) might be correlated with low Apgar score at 1 minute, higher preterm birth rate, lower fetal birth weight and possibility of being small for gestational age. In addition, concentration

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of SDF-1α in the amniotic fluid was not correlated with other possible placental diseases, such as preeclampsia.[8] That seems to be different from Zhou et al's report, which showed that increased SDF-1α may improve the functional maternofetal interface.[7] The possible reasons include: (1) differential timing of SDF-1α secretions *in utero*; (2) SDF-1α functions in both autocrine and paracrine manners; and (3) concentration of SDF-1α in the amniotic fluid does not necessarily correlate with the biologic activity in target tissues. Of course, the other possible reason is only an incidental finding or a minor role of SDF-1α in Tseng et al's report, and testing concentration of SDF-1α in the amniotic fluid can be disregarded, because many articles testing the relationship between amniotic fluid levels of cytokines and future pregnancy outcome are finally not reproducible. For example, the hypothesis that amniotic fluid levels of annexin A5 (AF-AnxA5) may be associated with intrauterine growth restriction[9] was tested with failure to get the same conclusion.[10]

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