The study by Mazza and colleagues\(^1\) assessed pregnancy characteristics, risk factors, and maternal mortality of amniotic fluid embolism (AFE), analyzing a sizeable cohort that encompasses the national US inpatient population during a 3-year period with almost 15 million deliveries and 880 cases of AFE. The estimated incidence of AFE was 6 per 100,000 deliveries, with a slight yet significant increase during the study period. Among various variables, including maternal, pregnancy, and delivery features, the authors confirmed a significant association with known factors (of which the most significant were placenta abruption, advanced maternal age, and preterm birth) and revealed for the first time the impact of placenta accreta spectrum (PAS). Placenta accreta spectrum showed a mean adjusted odds ratio (aOR) for AFE of 10.0 and a higher association for severe forms (accreta aOR, 7.6; increta/percreta aOR, 17.3). Overall, 4% of patients with AFE presented with PAS. Moreover, the study showed the extent of the AFE association with other severe maternal morbidities (coagulopathy aOR, 25; cardiac arrest aOR, 25; and adult respiratory distress syndrome aOR, 11). The mean AFE mortality in this study was 17.0%, increasing up to 45.0% when AFE was combined with other morbidities. The classification tree model showed that the risk of AFE was 6.5% in the high-risk group with PAS associated with abruption and preterm birth, which decreased to 0.4% in women older than 40 years and 0.001% in low-risk cases (term vaginal deliveries).

This scientifically sound and clinically relevant study contributes significantly to expanding current knowledge on AFE. Given the large sample size, the study would be not easily reproducible, making it even more valuable. The main limitation is related to the retrospective design from a nationwide database for clinical administrative use and not specifically designed for research. It may therefore include inaccuracies and lack of some covariates that could influence the interpretation of results. This limitation was appropriately disclosed by the authors and does not diminish the study's importance and generalizability.

Amniotic fluid embolism is a rare and serious pregnancy complication represented by unexpected cardiorespiratory arrest or hypotension, with respiratory compromise, hypoxia, or reduced oxygen saturation and disseminated intravascular coagulation occurring before significant hemorrhage and during labor, delivery, or immediately postpartum in absence of maternal hyperpyrexia.\(^2\) This definition was recently developed for research purposes because in clinical practice, atypical variants of AFE that are missing some components may be occasionally diagnosed. The standardized classification may also facilitate distinction of common differential diagnoses, such as hemorrhagic, septic, or anaphylactic shock, anesthetic accident, or pulmonary thromboembolism.

The origin of AFE is not fully understood. The invasion of amniotic, fetal, or trophoblastic components into the maternal circulation is a common feature. However, the extent of the phenomenon varies, and it can also occur in patients without AFE.\(^2\) The observation that pulmonary embolism does not have clinical features commonly found in AFE, such as coagulopathy, cardiovascular collapse, and neurologic symptoms, also suggests that a purely mechanical event is not sufficient to explain the pathogenesis of AFE.

An immune-mediated theory involves the breakdown of the maternal-fetal barrier with exposure of fetal or trophoblastic material that prompts in individual pregnant women the generation of inflammatory mediators, leading to a severe acute response and subsequent AFE. In support, complement C3a decreases in the blood, suggesting possible complement activation in AFE, possibly reflecting the access of fetal constituents to the maternal circulation.\(^3\) Alternatively, mast cells may massively degranulate, independent of classic antigen-IgE antibody anaphylaxis.
mechanisms. In support of this possibility, acute postpartum myometritis with invasion of leukocytes and mast cells, uterine atony, and postpartum hemorrhage, is frequently associated with AFE.

In summary, given similarities with findings observed in the vascular events typical of anaphylaxis and sepsis, immune responses affecting vascular homeostasis particular to pregnancy might play a major role in AFE.\(^2\)\(^-\)\(^5\) Indeed, the activation of the immune system and the coagulation cascade are closely intertwined in different physiologic and pathologic conditions. The atypical forms of AFE may reflect the different relative involvement of these 2 components.\(^6\)

The perceived importance of AFE in relation to the risk of maternal death is greater in developed countries, where it accounts for approximately 15% of cases, whereas in developing regions, despite the higher incident rate, it is responsible for less than 3% of deaths because of higher rates of other preventable pregnancy complications.\(^7\) In addition, AFE presents significant risks of fetal-neonatal loss and long-term morbidity and disability in survivors, both mothers and offspring. The risk of AFE was unsuccessfully assessed by previous researchers, and its identification is often delayed because it is based on nonspecific clinical signs and exclusion of the major differential diagnoses. Given the rarity, poor biological understanding, and major clinical consequences of AFE, research is particularly necessary. The study by Mazza et al\(^1\) clearly shows that both the risk of AFE and the failure to recover after AFE are increasing from baseline to cases with more frequent and complex risk factors, with an interesting and statistically significant progression.

The finding of PAS as a risk factor for AFE supports a pathogenetic role for the breakdown of the maternal-fetal barrier with increased exposure of fetal or trophoblastic constituents in the maternal circulation. Future studies may explore in this light the extent and characteristics of fetal or trophoblastic material in the maternal blood of patients with PAS or AFE compared with healthy pregnant patients. Improved etiologic and pathophysiologic understanding may contribute to the identification of high-risk patients, favoring earlier diagnoses and prompt interventions, potentially improving maternal-fetal outcome.

Beyond expedited delivery and cardiopulmonary resuscitation with intensive care, treatment opportunities comprise early massive transfusion protocols as well as plasma exchange, uterotonic, tranexamic acid, and hemostatic surgical procedures. Other discussed treatments include hemofiltration, high-dose corticosteroids, and complement inhibition, with the aim of suppressing innate immune activation and bradykinin production. These approaches may also increase uterotonic activity and hinder coagulopathy.

It would be theoretically possible to imagine AFE risk assessment for all woman during pregnancy. However, the absolute risk of AFE is so low (even in the high-risk group) that the performance of any screening test based on the available features would probably be poor. This failure would be mainly attributable to the very low positive predictive value, given the low prevalence of AFE, even with an unrealistic sensitive and specific test. In other words, to approach the concept of a test for AFE, research should clarify why AFE develops rarely in specific women and not in most of the population. To achieve this goal, large-scale prospective studies are required, investigating established and new candidate markers or risk factors as well as protective physiologic signatures of healthy pregnancies. Finally, given the importance of the placenta in the pathophysiology of AFE, the extent to which assessment of placental function (and dysfunction) contributes remains to be determined.

Although the risk assessment of AFE remains unrealistic for individual patients today, this study is certainly a step in this direction. As research progresses, PAS should be considered an important new risk factor for AFE, particularly when additional hazards are present. All reasonable preventive strategies should be implemented in high-risk cases, starting with referral to centers with availability of maternal-fetal medicine and intensive care units for both the mother and the neonate.
ARTICLE INFORMATION
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