mammalian-binding molecules) in the biology of FL B cells. Furthermore, because normal B cells express N-linked glycans much less frequently, the development of FL might involve a selection for such modified smIgs.

Finally, the findings reported here and previously suggest approaches that might lead to better defined categorization of FL clones among patients and to potentially novel ways for prevention and therapeutic targeting. As suggested by the authors, treatment with antibiotics to clear the opportunistic bacteria might represent a potential therapy for FL. Therefore, identification of FL clones that exhibit/develop amino acid replacements leading to N-glycosylation sequences that might support “disadvantageous,” high-mannose sugar expression could allow a new type of patient subclassing. Patients bearing such clones might then be candidates for antibiotic prophylaxis. Alternatively, appropriate clones might be amenable to targeting the specific carbohydrate epitope by monoclonal antibodies or small molecules, should such reagents be made V-domain specific. Finally, it is intriguing to consider that the carbohydrate-specific IGHVDJ epitopes developed by SHM might represent neoantigens that could be recognized by autologous T lymphocytes. This recognition might support the outgrowth of a population of T cells that provide “help” for the survival and expansion of the FL clone; T cells with such specificities therefore might be therapeutic targets. Conversely, T-cell recognition could lead to cytotoxic cells recognizing the neoantigens; these cells might be harnessed therapeutically to control FL cell growth. T-cell recognition of IGHVDJ antigens, albeit presumably protein in nature, has been suggested as a means for clonal regulation in lymphoma.

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Pregnancy in sickle cell disease is at very high risk

Mariane de Montalembert1 and Catherine Deneux-Tharaux2 1HOPITAL UNIVERSITAIRE NECKER-ENFANTS MALADES; 2INSERM U1153 CENTER FOR EPIDEMIOLOGY AND STATISTICS SPC

In this issue of Blood, Oteng-Ntim et al present the first systematic review and meta-analysis of observational studies quantifying the excess risk of maternal and perinatal adverse outcomes in women affected with sickle cell disease (SCD).
Due to major progress in the management of SCD, most women now survive to an age where they are able to become pregnant. However, life expectancy is only 42 years in women (38 years in men), with pregnancy being a major factor for death in women. Pregnancy exacerbates the preexisting pathophysiological characteristics of SCD: anemia, increased infectious risk, vaso-occlusion, and procoagulant profile. 

Interestingly, plasmatic levels of the placenta growth factor, which rise throughout pregnancy, are already elevated at baseline in SCD and have been correlated with the frequency of acute pain episodes. Therefore, pregnancy is associated with an increased incidence of painful crises, infections, pulmonary complications, thromboembolic events, and antepartum bleeding, even in women who previously had few symptoms. Furthermore, women at childbearing age may accumulate several comorbidities, such as pulmonary hypertension, renal dysfunction, retinal disease, and avascular necrosis of the hip, complicating the outcome of pregnancy. The severity of the disease varies widely according to patients; one of the major factors controlling this clinical expression is the genotype of SCD: patients with HbSS disease have the most severe forms, whereas patients with HbSC disease usually experience less severe complications. Chronic fetal hypoxia related to impaired placental blood flow seems the most plausible explanation for a high incidence of perinatal complications. Oteng-Ntim et al show that women with HbSS disease have a sixfold increased risk of maternal death compared with controls and markedly increased risks for preeclampsia, stillbirths, preterm deliveries, and small-for-gestational-age infants. Those risks are less significantly increased in mothers with HbSC disease and in their offspring. Although many reports have previously documented the adverse outcomes of pregnancy in women with SCD, the heterogeneity of the populations studied, of the data sources, and of the quality of the information collected made it difficult to have a clear picture of the extent of this excess risk. The paper by Oteng-Ntim et al is the first published attempt to provide a quantification of the risks associated with pregnancy in women with SCD, based on a synthesis of the available evidence. Their efforts to avoid duplication of cases from distinct papers, to assess the quality of included studies and its influence on the outcomes reported, to study the impact of countries’ gross national income on reported outcomes, and to stratify the results by genotype must be acknowledged, as they minimize some of the major drawbacks of this literature.

Interestingly, their results show that the higher risk of complications during pregnancy is more marked for lethal events—maternal deaths and stillbirths—than for less severe conditions. This finding has important implications in terms of prevention, as it implicates inadequate management of acute pregnancy-related events, leading to increased lethality in women with SCD. Prevention should focus on improving the early detection and treatment of complications of SCD during pregnancy and postpartum.

Conversely, this review also highlights the paucity of good studies on this major topic. Some studies are old and their results may not reflect the current standards of care. Very few of the studies included large representative samples and accurate case identification and documentation. Some maternal adverse events are rarely studied and could not be included in the meta-analysis, although they are likely responsible for the majority of deaths in these women, notably sepsis and thrombotic events. Finally, because results are presented as relative risks, it is impossible to assess whether the impact of SCD in pregnancy differs according to the absolute rate of perinatal adverse events in the control population.

This publication makes possible the first step needed to reduce mortality, namely, making physicians aware that pregnancy is very risky, even in women with “more benign” disease such as HbSC disease. Awareness of this risk makes it mandatory to manage pregnant women with SCD in reference centers combining excellence in obstetrics, sickle cell disease, intensive care, and transfusion management. In France, the vast majority of maternal deaths in women with SCD reported between 1996 and 2007 were due to complications of SCD and not to obstetrical causes, and 40% were judged to be preventable if multidisciplinary care had been adequately provided.

A preliminary step must be preconceptional counseling, testing the partner, and clearly explaining the risks of pregnancy. The quantified results provided by Oteng-Ntim et al will be useful for such counseling. A complete workup of the clinical condition of the mother is mandatory, including heart, lung, renal, and ophthalmologic examinations. Pregnant women need to be followed both by an obstetric team that is knowledgeable in the care of women with SCD and by the sickle cell team. Appropriate protocols for pain management and transfusion indications must be available. An active management of pregnancy implemented in Benin, Africa, based on education about SCD, improvement of nutritional status, malaria prevention, early detection of bacterial infections, and restricted use of transfusion has decreased the mortality rate from 27% to 1.8%.

More research is needed, with good-quality population-based observational studies that are large enough to have sufficient power to assess rare outcomes and with a prospective design to ensure the validity of case ascertainment and of information collected. A better understanding of the reasons why mothers and fetuses die will allow relevant strategies for interventional studies, especially for the role of prophylactic transfusions.

Conflict-of-interest disclosure: M.d.M. is a member of the Novartis speakers’ bureau. C.D.-T. declares no competing financial interests.

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