

CORRESPONDENCE



Association of SARS-CoV-2 Infection during Early Weeks of Gestation with Situs Inversus

TO THE EDITOR: Situs inversus, including situs inversus totalis (with dextrocardia) and partial situs inversus (with levocardia), is a rare congenital condition in which visceral organization is inverted as compared with normal organ development. We noted a striking increase in the number of cases of fetal situs inversus that were diagnosed by means of ultrasonography at our hospital several months after the “zero-Covid” policies in China were lifted.

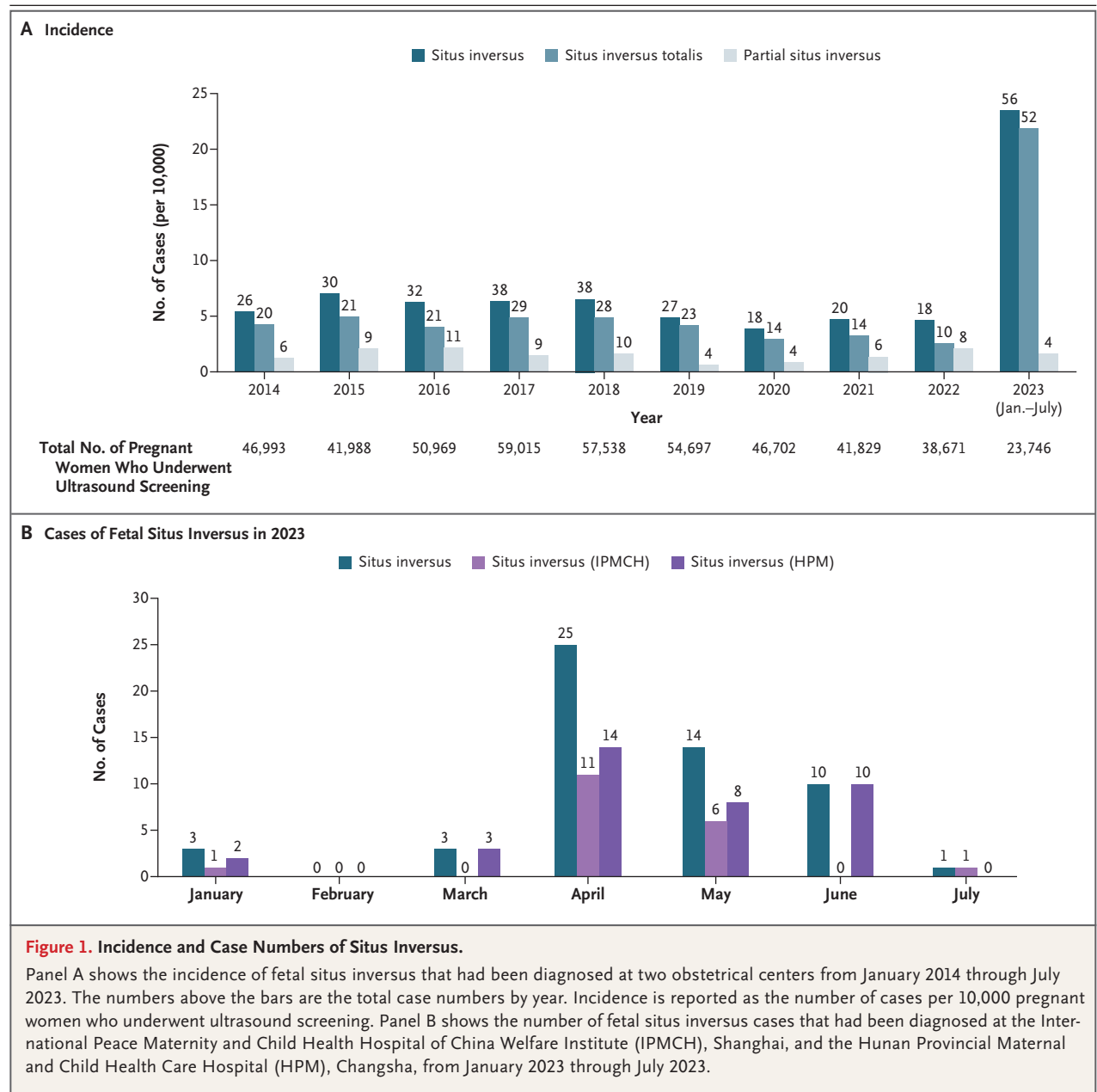
We determined the incidence of fetal situs inversus from January 2014 through July 2023 using clinical data from two obstetrical centers in different regions of China. During the first 7 months of 2023, the incidence of situs inversus (diagnosed by means of routine ultrasonography at a gestational age of approximately 20 to 24 weeks, with no change having been made in the diagnostic protocol or physician training) at these centers was over four times as high as the mean annual incidence from 2014 through 2022 (Fig. 1 and Fig. S1 and Table S1 in the Supple-

mentary Appendix, available with the full text of this letter at NEJM.org); the incidence peaked in April 2023 and remained elevated through June 2023. Overall, 56 cases of situs inversus were identified from January 2023 through July 2023 (52 cases of situs inversus totalis and 4 cases of partial situs inversus). The increase followed the surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections that occurred after the zero-Covid policies were discontinued; this surge, which ultimately was estimated to affect approximately 82% of the population in China, began in early December 2022, peaked around December 20, 2022, and ended in early February 2023.¹ Although no conclusions can be made regarding causality, our observations suggest a possible relationship between SARS-CoV-2 infection and fetal situs inversus that warrants further study.

Congenital situs inversus has been linked to aberrant morphogen distribution and cilia dysfunction of the left–right organizer in visceral lateralization during the early weeks of gestation.² Although vertical transmission of SARS-CoV-2 is debated,³ fetal infection early in gestation could hypothetically affect visceral lateralization; alternatively, SARS-CoV-2–mediated maternal inflammatory responses^{4,5} might indirectly affect left–right organizer function and impair visceral lateralization. Further analysis is necessary to verify that genetic abnormalities in primary ciliary dyskinesia–related genes that may not have been detected during prenatal genetic screening did not contribute to the incidence of these cases and to assess the potential contribution of environmental factors. It is notable that situs inversus diagnoses remained extremely rare despite the increase in incidence at our centers after the SARS-CoV-2 surge.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Health Consequences of Thymus Removal in Adults

TO THE EDITOR: Kooshesh and colleagues (Aug. 3 issue)¹ found that the risks of cancer, autoimmune disease, and death from any cause were higher among patients who had undergone thymectomy than among controls. The authors also found a lower diversity of T-cell receptors and a higher frequency of proinflammatory cytokines in the plasma in the thymectomy group. This phenotype may be related to immunosenescence caused by thymus removal; however, sufficient data were not provided in this article to speculate on the biologic processes that were involved in these findings.

In mice, thymectomy, along with aging, induces the emergence of a CD4⁺ T-cell subgroup that is characterized by positivity for programmed death 1 (PD-1) and CD153 and increased expression of CD44.² These cells, called senescence-associated T cells, are implicated in diminished acquired immunity, proinflammatory traits, and increased risk of autoimmunity.³⁻⁵ Since it is not clear whether senescence-associated T cells are also present in patients who have undergone thymectomy, it would be helpful if the authors could provide data regarding PD-1, CD153, and CD44 levels in CD4⁺ T cells in the patients in their trial.

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TO THE EDITOR: As academic specialists in myasthenia gravis, we were interested in the study by Kooshesh et al., which showed an increased risk of cancer in patients undergoing thymectomy. Most of these patients had a cancerous or suspected thymic mass. We are concerned that the findings in this nondifferentiated population will cause confusion for patients with myasthenia gravis and their clinicians. Thymectomy is part of the established care for generalized acetylcholine-receptor-positive myasthenia gravis.¹ Contrary to the current study, multiple studies have