

Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Methods

Methods

Data source and participants

To calculate incidence rates of situs inversus, medical records were reviewed from two obstetric centers, the International Peace Maternity and Child Health Hospital of the China Welfare Institute (IPMCH) in Shanghai and the Hunan Provincial Maternal and Child Health Care Hospital (HPM) in Changsha. Both participating hospitals serve as prenatal diagnosis centers, providing maternal care, as well as ultrasound and genetic assessment for patients diagnosed with fetal anomalies by local clinics in their respective provinces. Ultrasound diagnoses of fetal situs inversus from the preceding nine years, spanning January 1, 2014 through December 31, 2022, were collected from these centers to analyze annual incidence rates of situs inversus, situs inversus totalis (with dextrocardia) and partial situs inversus (with levocardia).^{1,2} We also collected ultrasound diagnoses of fetal situs inversus from January 1, 2023 through July 31, 2023, to analyze the incidence rates of situs inversus, situs inversus totalis, and partial situs inversus for that time period.

Methods for estimating the gestational age.

To calculate gestational age, 280 days (40 weeks) after the first day of the last menstrual period (LMP) was estimated as the date of confinement. Ultrasound measurement of crown-rump length (CRL) was used to verify the date of an embryo/fetus at 6 + 0 to 13 + 6 gestational weeks (GW).

Ultrasound diagnosis of fetal situs inversus.

Prenatal ultrasound examinations were performed following the Pregnancy Health Guidelines published by the National Health Commission of the People's Republic of China and the ISUOD^{3,4}, which recommend ultrasound observation at 6 + 0 to 13 + 6, 14 + 0 to 19 + 6, 20 to 24, 25 to 28, 29 to 32, 33 to 36, and 37 to 41 weeks of gestation, or 7-11 exams in total, potentially more for those with situs inversus fetus. Early ultrasound tests are usually performed between 6-13 weeks in order to estimate pregnancy dating and to determine whether the fetus is well developed. In addition, midterm ultrasound screening for developmental abnormalities around 20-24 GW is routinely performed. The ultrasound examiners in the current study each had at least 5 years of experience with fetal ultrasound scans and have earned Prenatal Diagnosis Certificates issued by the Chinese Maternal and Child Health Management Department following specialization training. The diagnosis of situs inversus was independently confirmed by two experienced fetal ultrasound experts. It should also be noted that no significant changes in ultrasound techniques or physician training were made shortly before or during 2023 in either hospital (IPMCH and HPM) in our study.

Among all 56 cases of fetal situs inversus in our study, 40 cases were diagnosed during midterm ultrasound screening for developmental abnormalities (around 20-24 GW), 3 patients were first diagnosed between 12-19 GW, and 13 cases were diagnosed after 27 GW. Among those 13 cases, 3 were first misdiagnosed in local clinics at 20-24 GW and were diagnosed as fetal situs inversus in our obstetric centers during later gestational age, while 10 were diagnosed as fetal situs inversus in their local clinics during their 20-24 GW ultrasound scan and were referred to our obstetric centers for further confirmation at a later gestational age.

Statistical analysis

To calculate the incidence rates of all situs inversus, situs inversus totalis, and partial situs inversus for each year from 2014 through 2022, the numbers of cases from each year were divided by the total number of pregnant women who received ultrasound tests in the hospital within the same year. To calculate all situs inversus, situs inversus totalis, and partial situs inversus rates for the period, spanning January 1, 2023 through July 31, 2023, the number of cases during this time period was divided by the total number of pregnant women who received ultrasound tests in both hospitals during the same period. The incidence rates represent the proportion of cases “per 10,000”.

Ethics

This study was approved by the ethics community of IPMCH (ethical approval number: GKLW 2023-201), HPM (ethical approval number: 202312), and Tongji University (ethical approval number: 2023tjdxsy034).

Acknowledgement

We appreciate the advice and assistance of Dr. Isaac Greenhut PhD, ELS in the revision and language editing of our manuscript.

Supplementary Figures

Figure S1

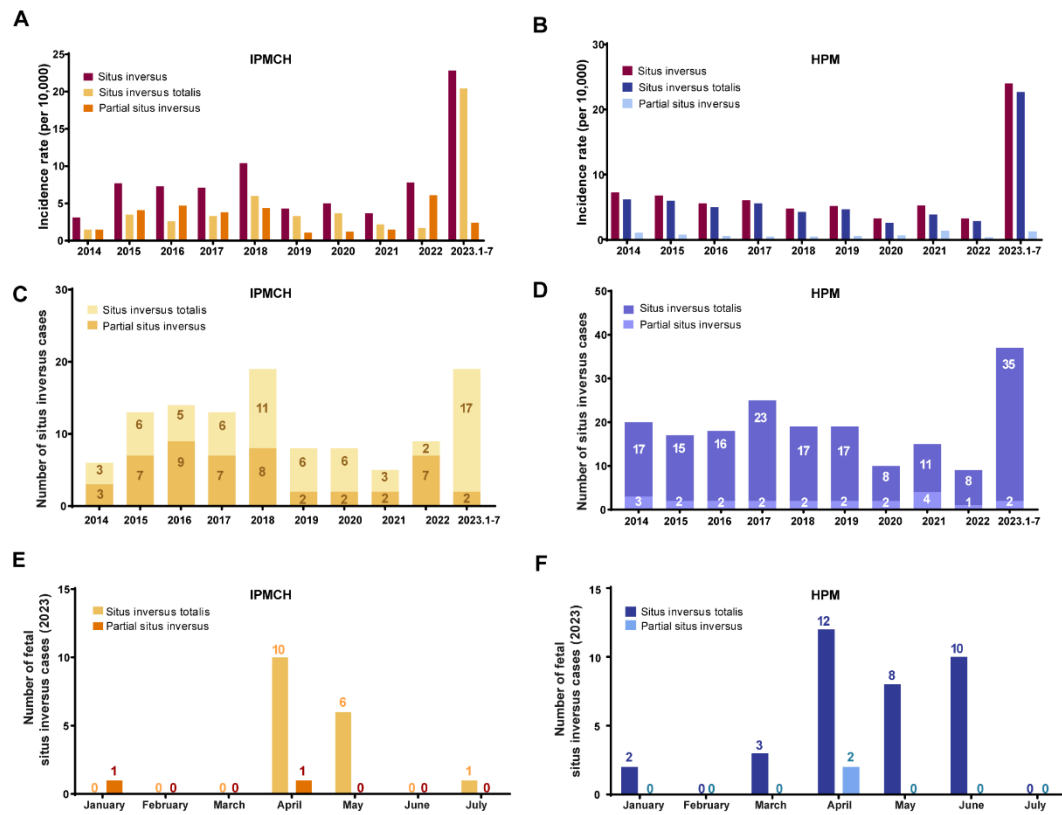


Figure S1. Incidence rates and case number of situs inversus diagnoses at each center.

A. Incidence rate from January 2014 through July 2023 at IPMCH.

B. Incidence rate from January 2014 through July 2023 at HPM.

C. Total diagnosed cases of fetal situs inversus from January 2014 through July 2023 at IPMCH.

D. Total diagnosed cases of fetal situs inversus from January 2014 through July 2023 at HPM.

E. Situs inversus cases by month from January 2023 through July 2023 at IPMCH.

F. Situs inversus cases by month from January 2023 through July 2023 at HPM.

Incidence rates are per 10,000 pregnancies screened by ultrasound.

Supplementary Tables

Table S1. Number of situs inversus cases per year and incidence rates from 2014 to July 2023.

IPMCH					HPM				
Year	Number of pregnant women receiving ultrasound	SI	SIT	SIP	Number of pregnant women receiving ultrasound	SI	SIT	SIP	
2014	19433	6	3	3	27560	20	17	3	
2015	16968	13	6	7	25020	17	15	2	
2016	19049	14	5	9	31920	18	16	2	
2017	18226	13	6	7	40789	25	23	2	
2018	18215	19	11	8	39323	19	17	2	
2019	18447	8	6	2	36250	19	17	2	
2020	16038	8	6	2	30664	10	8	2	
2021	13502	5	3	2	28327	15	11	4	
2022	11490	9	2	7	27181	9	8	1	
2023.1-7	8321	19	17	2	15425	37	35	2	
Incidence rate (per 10,000)		SI	SIT	SIP		SI	SIT	SIP	
2014		3.1	1.5	1.5		7.3	6.2	1.1	
2015		7.7	3.5	4.1		6.8	6.0	0.8	
2016		7.3	2.6	4.7		5.6	5.0	0.6	
2017		7.1	3.3	3.8		6.1	5.6	0.5	
2018		10.4	6.0	4.4		4.8	4.3	0.5	
2019		4.3	3.3	1.1		5.2	4.7	0.6	
2020		5.0	3.7	1.2		3.3	2.6	0.7	
2021		3.7	2.2	1.5		5.3	3.9	1.4	
2022		7.8	1.7	6.1		3.3	2.9	0.4	
2023.1-7		22.8	20.4	2.4		24.0	22.7	1.3	
IPMCH+ HPM									
Incidence rate (per 10,000)		SI	SIT	SIP					
2014		5.5	4.3	1.3					
2015		7.1	5.0	2.1					
2016		6.3	4.1	2.2					
2017		6.4	4.9	1.5					
2018		6.6	4.9	1.7					
2019		4.9	4.2	0.7					
2020		3.9	3.0	0.9					
2021		4.8	3.3	1.4					
2022		4.7	2.6	2.1					
2023.1-7		23.6	21.9	1.7					
Incidence rate (per 10,000) ±SD		SI	SIT	SIP					
From 2014 to 2022		5.6 ±1.1	4.0 ±0.9	1.5 ±0.5					
From Jan.1 to Jul. 31 in 2023		23.6	21.9	1.7					
Increase (fold)		4.2	5.4	1.1					

SI, situs inversus; SIT, situs inversus totalis; SIP, partial situs inversus.

Table S2. Date of diagnosis of fetal situs inversus from two centers in 2023.

No.	Date of diagnosis of SI fetus yyyy/mm/dd	Fetal status
Patient 1	2023/5/9	SIT
Patient 2	2023/1/28	SIT
Patient 3	2023/1/28	SIT
Patient 4	2023/3/16	SIT
Patient 5	2023/3/21	SIT
Patient 6	2023/3/27	SIT
Patient 7	2023/4/10	SIT
Patient 8	2023/4/18	SIT
Patient 9	2023/4/18	SIT
Patient 10	2023/4/19	SIT
Patient 11	2023/4/19	SIT
Patient 12	2023/4/21	SIT
Patient 13	2023/4/24	SIT
Patient 14	2023/4/25	SIP
Patient 15	2023/4/27	SIT
Patient 16	2023/4/29	SIT
Patient 17	2023/5/4	SIT
Patient 18	2023/5/9	SIT
Patient 19	2023/4/27	SIT
Patient 20	2023/4/27	SIT
Patient 21	2023/6/21	SIT
Patient 22	2023/5/30	SIT
Patient 23	2023/6/9	SIT
Patient 24	2023/6/1	SIT
Patient 25	2023/6/5	SIT
Patient 26	2023/6/15	SIT
Patient 27	2023/6/19	SIT
Patient 28	2023/5/25	SIT
Patient 29	2023/6/9	SIT
Patient 30	2023/5/30	SIT
Patient 31	2023/6/7	SIT
Patient 32	2023/5/4	SIT
patient 33	2023/5/8	SIT
patient 34	2023/4/27	SIT
patient 35	2023/6/5	SIT
patient 36	2023/6/12	SIT
patient 37	2023/4/28	SIP
patient 38	2023/1/10	SIP
patient 39	2023/4/10	SIT
patient 40	2023/4/12	SIT
patient 41	2023/4/13	SIT
patient 42	2023/4/18	SIP
patient 43	2023/4/19	SIT
patient 44	2023/4/19	SIT
patient 45	2023/4/19	SIT
patient 46	2023/4/21	SIT
patient 47	2023/4/25	SIT
patient 48	2023/4/25	SIT
patient 49	2023/5/3	SIT
patient 50	2023/4/27	SIT
patient 51	2023/5/4	SIT
patient 52	2023/5/5	SIT
patient 53	2023/5/5	SIT
patient 54	2023/7/19	SIT
patient 55	2023/5/16	SIT
patient 56	2023/5/12	SIT

Patients 1-37 were from HPM; patients 38-56 were from IPMCH. Patient 14 is associated with manifestations of heterotaxy syndromes, including levovercion, corrected transposition of the great arteries, double outlet right ventricle, pulmonary artery stenosis and ventricular septal defect.

SI, situs inversus; SIT, situs inversus totalis; SIP, partial situs inversus.

Supplementary references

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