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Monthly variation in univentricular heart and transposition of the great arteries – 10–year national population-based cohort study

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ABSTRACT

Objective: Monthly variation in the total prevalence of the univentricular heart (UVH) and dextro-transposition of the great arteries (d-TGA) at gestational age 7 + 0 weeks was assessed to determine potential environmental factors, such as viral or bacterial infections, underlying the variation.
Study design: The nationwide retrospective ten-year population-based cohort consisted of 592 733 births and 2764 terminated pregnancies due to fetal anomaly. The pre- or postnatally diagnosed cases of UVH (n = 440) and simple d-TGA (n = 127) from five national registers included live births, stillbirths, and pregnancy terminations due to fetal anomaly. We evaluated the variation in the monthly total prevalence of UVH and d-TGA at gestational age 7 + 0 weeks. The monthly variation of UVH and d-TGA was also compared with monthly variation in reported viral and bacterial infections.
Results: In the UVH and d-TGA, we observed significant monthly variation in total prevalence. However, we observed no correlations in the studied viral or bacterial infections and the number of cases.
Conclusions: Assessing monthly variation in total prevalence at early pregnancy, including pregnancy terminations and stillbirths, and using first-trimester timing provides the most accurate information on the variation. The reasons for monthly variation remain unclear, but we observed no associations with specific viral or bacterial infections.

Introduction

Congenital heart defects are the most common birth defects, affecting about 1% of all newborns. These anomalies have an intricate inheritance pattern, and most congenital heart defects are proposed to occur due to a combination of genetic and environmental risk factors [1]. Well-known environmental risk factors include maternal diabetes mellitus and obesity and the use of teratogenic medications during pregnancy [1,2]. Previous studies have evaluated maternal hyperthermia induced by fever [3,4], infection [5–7], or external factors such as hot weather or environment [8–10] as potential risk factors for congenital heart defects; however, with conflicting results. In recent studies, air pollutions were not associated with univentricular heart (UVH) or dextro-transposition of the great arteries (d-TGA) [11,12], while exposure to rodenticides and herbicides has been reported to be a risk factor for d-TGA [13].

Studying the monthly variation of congenital heart defects provides an opportunity to assess environmental factors potentially affecting fetal development. Current data on monthly or seasonal variation are scarce [14–16]. Previous studies have excluded pregnancy terminations, assessing only the birth prevalence or live birth prevalence and not the actual total prevalence, including pregnancy terminations and stillbirths. This is a major weakness. Studying only live birth prevalence does not provide a full picture of the monthly variation. The result is skewed, first, due to the increase of pregnancy terminations over the years [17,18] and, second, because of the varying duration of the gestations. For this reason, when studying the monthly variation in total prevalence of congenital heart defects, the timing of the assessment should be in early pregnancy, for example, when the essential cardiac structures form, in the first 5–8 gestational weeks.

Abbreviations: UVH, Univentricular heart; HLHS, Hypoplastic left heart syndrome; d-TGA, Dextro-transposition of the great arteries.

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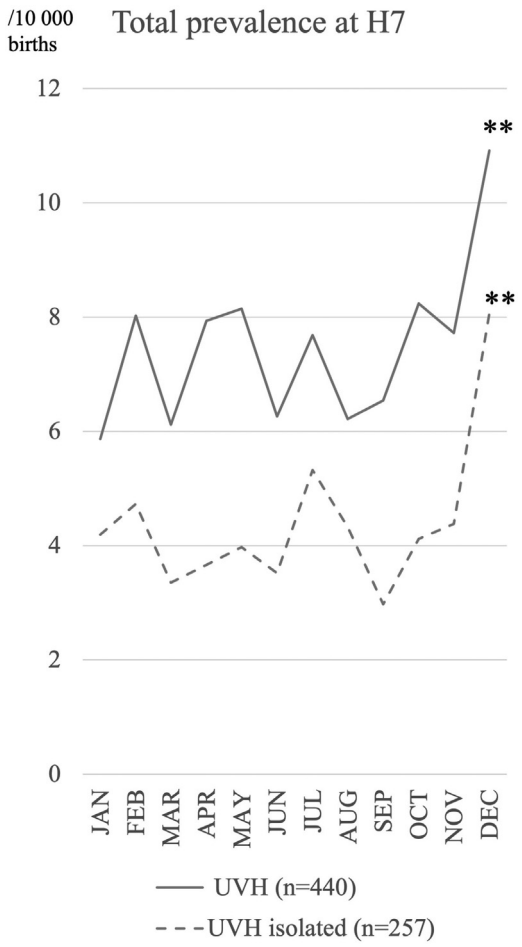

Fig. 1. Monthly variation of univentricular heart (UVH): total prevalence at gestational age 7 + 0 weeks. Significant months are indicated with **, $p < 0.01$. The UVH group includes all cases, and cases without extra-cardiac anomalies are marked as "isolated." Details in Table 1.

Comprehensive Finnish national registers, including the specific Register of Congenital Malformations, offer an excellent opportunity to assess the monthly seasonal variation of pregnancies with congenital heart defect. This study evaluated the monthly variation of the total prevalence of cases with UVH or simple d-TGA during organogenesis at gestational age 7 + 0 weeks. In addition, we assessed whether the nationwide monthly variations of reported viral or bacterial infections are associated with the monthly variation of studied congenital heart defects.

Material and methods

We retrieved nationwide retrospective, population-based observational data on all cases with simple d-TGA and UVH in Finland at gestational age 7 + 0 weeks between January 1, 2004, and December 31, 2013. We collected data from five different national registers, including three national registers at the Finnish Institute for Health and Welfare, i.e. 1) the Register of Congenital Malformations, 2) the Register of Induced Abortions, and 3) the Medical Birth Register, as well as 4) the National Register of Pediatric Cardiac Surgery maintained by Children's Hospital at Helsinki University Hospital5) the Cause-of-Death Register, maintained by Statistics Finland. All register data were verified from the patient records, as described in our previous article [18]. Reporting of all births and pregnancy terminations is mandatory in Finland. During the study period 592 733 births and 2764 pregnancy terminations due to fetal anomaly (Register of Induced Abortions) were at gestational age 7 + 0 weeks, and 592 092 children were born alive (Medical Birth Register). In total, 165 d-TGA and 440 UVH cases were diagnosed. The UVH group includes cases with Hypoplastic Left Heart Syndrome (HLHS) and other types of UVH. In addition, a subgroup of HLHS was evaluated separately (n = 217). The UVH was categorized as a cardiac malformation that could be treated only via palliative Fontan circulation after birth. d-TGA was considered simple if the ventricular septum was intact or in case of a small ventricular septal defect. Cases with more complex d-TGA were excluded (n = 38). Major extra-cardiac malformations were defined according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT) guidelines [19]. Isolated cases without major extra-cardiac anomalies or chromosomal anomalies were evaluated separately.

To evaluate true monthly variation, the gestational age 7 + 0 weeks was selected due to the embryological timing of heart development in both UVH and d-TGA [20,21]. Gestational age 7 + 0 weeks for cases and the total population was calculated from the estimated timing of conception based on gestational age at the end of pregnancy (Medical Birth Register or Register of Induced Abortions). The total prevalence at gestational age 7 + 0 weeks and live birth prevalence were calculated according to the EUROCAT guidelines [22]: 1) Total prevalence at gestational age 7 + 0 weeks: the number of cases at the gestational age of 7 + 0 (live births, stillbirths, and pregnancy terminations) was divided by the total number of births who were at gestational age 7 + 0 weeks (live births and stillbirths) and multiplied by 10 000. 2) Live birth prevalence: the number of liveborn cases was divided by the total number of live births and multiplied by 10 000.

The Finnish Institute for Health and Welfare records and follows all laboratory test-positive infections in the National Infectious Diseases Register [23]. The monthly variation of viral or bacterial infections was compared with the monthly variation of the number of isolated UVH, HLHS, or d-TGA cases. The infections included in this study were Influenza viruses, Respiratory Syncytial Virus, Chlamydia Pneumoniae, Parainfluenza, Mycoplasma Pneumonia, Hemophilus Influenza, Salmonella viruses, Yersinia, Shigella, Campylobacter, Listeria, Norovirus, Rotavirus, Giardiasis and Adenovirus.

Statistics

Poisson regression was used to compare monthly variation in the prevalence of UVH, HLHS, and d-TGA. Prevalence with 95 % confidence intervals was calculated per 10 000 births, and relative risks (RRs) between months were calculated using the month with the lowest prevalence as a reference. The correlations between the monthly variation of viral or bacterial infections and the monthly variation of the number of isolated UVH, HLHS, or d-TGA cases were calculated with Spearman correlation coefficients. p-values < 0.05 were considered significant. Statistical analyses were done with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical approval

The Ethics Committee of the Helsinki University Hospital approved the study (April 20, 2017, HUS/1938/2016). The Finnish Institute for Health and Welfare authorized the use of the health register data in this study, as required by the national data protection legislation.

Table 1
Monthly variation in univentricular heart (UVH) (including hypoplastic left heart syndrome).

	Total prevalence at gestational age 7 + 0 weeks /10 000	95 % CI	RR	95 % CI	p -value
UVH at gestational age 7 + 0 weeks including cases with and without extra-cardiac anomalies					
January	5.87	4.05–8.50	1	reference	
February	8.03	5.86–10.99	1.37	0.84–2.22	0.21
March	6.11	6.11–8.70	1.04	0.63–1.74	0.87
April	7.93	5.80–10.86	1.35	0.83–2.20	0.22
May	8.15	6.00–11.07	1.39	0.86–2.25	0.18
June	6.26	4.43–8.86	1.07	0.64–1.77	0.80
July	7.69	5.62–10.52	1.31	0.81–2.13	0.28
August	6.22	4.42–8.75	1.06	0.64–1.75	0.82
September	6.54	4.66–9.20	1.11	0.67–1.85	0.67
October	8.23	6.09–11.15	1.40	0.87–2.26	0.16
November	7.73	5.60–10.67	1.32	0.80–2.15	0.27
December	10.92	8.18–14.58	1.86	1.16–2.98	<0.001**
UVH at gestational age 7 + 0 weeks, isolated (no extra-cardiac anomalies)					
January	4.19	2.70–6.50	1.41	0.72–2.75	0.32
February	4.74	3.15–7.13	1.59	0.83–3.05	0.16
March	3.35	2.09–5.40	1.13	0.56–2.26	0.73
April	3.66	2.31–5.81	1.23	0.62–2.44	0.55
May	3.98	2.56–6.16	1.34	0.68–2.61	0.40
June	3.52	2.22–5.59	1.18	0.59–2.35	0.63
July	5.32	3.65–7.76	1.79	0.95–3.36	0.07
August	4.33	2.88–6.52	1.46	0.76–2.73	0.26
September	2.97	1.80–4.93	1	reference	
October	4.12	2.69–6.32	1.38	0.71–2.69	0.34
November	4.39	2.86–6.73	1.348	0.76–2.86	0.25
December	8.07	5.77–11.29	2.71	1.48–4.98	0.001**

Results

Univentricular heart

Four hundred and forty UVH cases were found, 58.4 % (257/440) of which were isolated. Of all UVH cases, 52.7 % (232/440) were terminated, 2.7 % (12/440) were stillbirths, and 44.5 % (196/440) were live births. The total prevalence of UVH was 7.42/10 000 (440/592 733) and 4.33/10 000 (257/592 733) when excluding extra-cardiac anomalies (isolated). The live birth prevalence of UVH was 3.32/10 000 (196/592 092) and 2.38/10 000 (141/592 092) for isolated cases. The difference between total prevalence at gestational age 7 + 0 weeks and live birth prevalence was significant for both groups ($p < 0.001$). In total prevalence, a significant monthly variation was observed; the lowest monthly total prevalence of UVH in January and the highest in December ($p < 0.001$), and in isolated cases, in September and in December ($p = 0.001$), respectively (Details in Fig. 1 and Table 1).

Hypoplastic left heart syndrome

HLHS was found in 217 of the UVH cases, 67.7 % (147/217) of which were isolated. Pregnancy termination was performed in 51.6 % (112/217) of HLHS cases. There were no stillbirths. Out of 105 live births, 77 % (81/105) were isolated. The total prevalence of HLHS was 3.66/10 000 (217/592 733) and 2.48/10 000 (147/592 733) for isolated cases, and live birth prevalence 1.78/10 000 (105/592 092) and 1.37/10 000 (81/592 092), respectively. The difference between total prevalence and live birth prevalence was significant in both groups ($p < 0.001$). The lowest monthly total prevalence was in June and the highest in December in cases including extra-cardiac anomalies ($p = 0.011$), and for the isolated group, the lowest in March and the highest in December ($p = 0.013$), respectively (Details in Fig. 2 and Table 2).

Transposition of great arteries

Altogether 127 d-TGA cases were found: 16 (13 %, 16/127) had an extra-cardiac anomaly and 87 % (111/127) were isolated. The majority (90 %, 114/127) of the d-TGA infants were born alive. One fetus was stillborn (1%, 1/127), and 9% (12/127) of cases were terminated. Out of the 114 live births, 96 % (109/114) were isolated. The total prevalence for simple d-TGA was 2.14/10 000 births (127/592 733) and 1.87/10 000 births (111/592 733) for isolated cases, and live birth prevalence 1.93/10 000 (114/592 092) and 1.84/10 000 (109/592 092), respectively. The difference between total prevalence and live birth prevalence was not significant in either group ($p > 0.4$). In total prevalence, a significant monthly variation was found; the lowest total prevalence for d-TGA was in February and the highest in March ($p = 0.014$). When observing the isolated cases, the peak months remained the same ($p = 0.041$) (Fig. 3).

Infections

No correlations were seen in the monthly variation of any reported viral or bacterial infections and the number of cases with isolated cases of UVH (range for r from -0.15 to 0.02, $p > 0.09$), isolated cases of HLHS (range from r from -0.13 to 0.03, $p > 0.10$), or isolated cases of d-TGA (range for r from -0.08 to 0.15, $p > 0.10$). However, the highest number of isolated UVH was observed in November and December 2009, while influenza, especially the H1N1 virus infection, was most common in October and November. During other studied years, the peak of the influenza epidemic was most often in February or March.

Discussion

To the best of our knowledge, this cohort was the first nationwide used to assess monthly variation of congenital heart defects with all cases of UVH, HLHS, and d-TGA, including live births, stillbirths, and pregnancy terminations. A significant

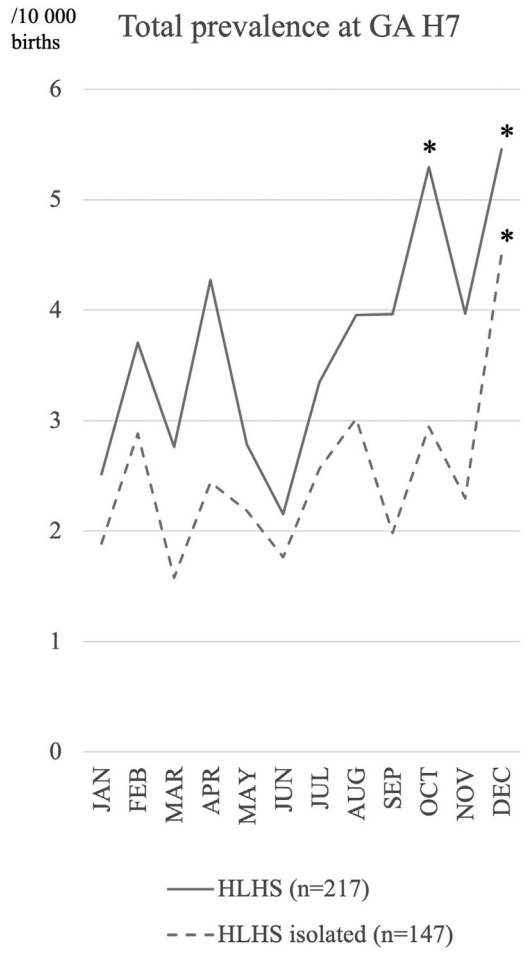

Fig. 2. Monthly variation of hypoplastic left heart syndrome (HLHS): total prevalence at gestational age 7 + 0 weeks. Significant months are indicated with *, $p < 0.05$. HLHS group includes all cases, and cases without extra-cardiac anomalies are marked as "isolated." Details in Table 2.

monthly variation in the total prevalence of UVH and d-TGA was observed. We did not find any analogous monthly variation of reported viral or bacterial infections and cases of UVH or d-TGA.

Previous reports on monthly or seasonal variation, including all types of UVH cases, do not exist. Earlier studies for the subgroup HLHS have provided conflicting results. Some reports have found no significant monthly variation in HLHS [16], whereas, an extensive report from the USA observed that the peak month of birth among infants with HLHS was June (GA at birth was not reported) [14]. For d-TGA, no variation has been found in monthly live birth prevalence in previous reports [15,24].

It is important to determine the risk factors for congenital heart defects. We found a significant variation in monthly total prevalence in all studied groups. If only born children are taken assessment, the increasing number of pregnancy terminations will lead to a decrease in the number of born infants with congenital heart defects. This distorts the results when assessing the variation only of live births. Above is especially true in the group of UVH defects, but to a lesser degree in the group of d-TGA. Further, the live birth prevalence is influenced by the variation related to the timing of the delivery. Premature births and clinical decisions, such as induction of labor, affect the results. This is especially important when studying the live birth prevalence; the gestational age of liveborn cases or background population cannot be taken into account. To assess the true monthly variation and factors affecting fetal development and to minimize confounders, specific timing in early pregnancy should be selected. We chose to study the variation of total prevalence at gestational age 7 + 0 weeks, as the gestational weeks 7–8 have been shown to be critical in the formation of both UVH and d-TGA [20,21]. Taken together, the obvious reasons for these conflicting results in monthly variation in prevalence include differences in populations and their case detection, differences in prenatal detection and pregnancy termination rates, and importantly, differences in the timing of assessment.

Congenital heart defects are known to be multifactorial, and the reasons for monthly variations remain unclear. First-trimester influenza exposure has been observed to increase the risk of right-

Table 2
Monthly variation in hypoplastic left heart syndrome (HLHS).

	Total prevalence at gestational age 7 + 0 weeks /10 000	95 % CI	RR	95 % CI	p -value
HLHS at gestational age 7 + 0 weeks including the cases with and without extra-cardiac anomalies					
January	2.52	1.43–4.43	1.17	0.52–2.65	0.71
February	3.71	2.34–5.88	1.72	0.81–3.64	0.16
March	2.76	1.64–4.66	1.28	0.58–2.83	0.54
April	4.27	2.79–6.55	1.98	0.97–4.12	0.07
May	2.78	1.65–4.70	1.29	0.59–2.85	0.52
June	2.15	1.19–3.89	1	reference	
July	3.35	2.08–5.39	1.56	0.73–3.32	0.25
August	3.96	2.58–6.07	1.84	0.89–3.81	0.10
September	3.97	2.56–6.15	1.84	0.88–3.84	0.10
October	5.30	3.63–7.72	2.46	1.22–4.96	0.012*
November	3.97	2.53–6.22	1.84	0.88–3.87	0.11
December	5.46	3.63–8.21	2.54	1.24–5.20	0.011*
HLHS at gestational age 7 + 0 weeks isolated (no extra-cardiac anomalies)					
January	1.89	0.98–3.63	1.20	0.41–3.10	0.71
February	2.88	1.71–4.87	1.83	0.69–4.35	0.17
March	1.58	0.79–3.16	1	reference	
April	2.44	1.39–4.30	1.55	0.70–3.78	0.34
May	2.19	1.21–3.95	1.39	0.56–3.44	0.48
June	1.76	0.92–3.39	1.12	0.43–2.89	0.82
July	2.56	1.49–4.41	1.62	0.64–3.92	0.28
August	3.02	1.85–4.92	1.91	0.84–4.46	0.14
September	1.98	1.07–3.69	1.26	0.47–3.18	0.63
October	2.94	1.77–4.88	1.86	0.75–4.40	0.16
November	2.30	1.27–4.15	1.46	0.52–3.62	0.42
December	4.51	2.88–7.07	2.86	0.94–6.56	0.013*

Table 3
Monthly variation in transposition of great arteries (d-TGA).

	Total prevalence at gestational age 7 + 0 weeks /10 000	95 % CI	RR	95 % CI	p -value
d-TGA at gestational age 7 + 0 weeks including cases with and without extra-cardiac anomalies					
January	3.35	2.05–5.47	3.26	1.19–8.89	0.021*
February	1.03	0.43–2.47	1	reference	
March	3.55	2.24–5.64	3.45	1.28–9.29	0.014*
April	1.63	0.81–3.25	1.58	0.52–4.83	0.42
May	1.99	1.07–3.69	1.93	0.66–5.64	0.23
June	2.35	1.33–4.14	2.28	0.80–6.48	0.12
July	1.38	0.66–2.90	1.34	0.43–4.22	0.62
August	2.83	1.70–4.69	2.75	1.00–7.56	0.05
September	1.98	1.07–3.68	1.93	0.66–5.63	0.23
October	1.77	0.92–3.39	1.71	0.57–5.11	0.33
November	2.09	1.12–3.88	2.03	0.69–5.94	0.20
December	1.66	0.79–3.48	1.61	0.51–5.08	0.41
d-TGA at gestational age 7 + 0 weeks isolated (no extra-cardiac anomalies)					
January	2.93	1.74–4.95	2.85	1.03–7.91	0.04*
February	1.03	0.43–2.47	1	reference	
March	2.94	1.78–4.91	2.87	1.05–7.91	0.04*
April	1.42	0.68–2.99	1.38	0.44–4.34	0.58
May	1.79	0.93–3.44	1.74	0.58–5.19	0.32
June	1.96	1.05–3.64	1.90	0.65–5.56	0.24
July	1.18	0.53–2.63	1.15	0.35–3.76	0.82
August	2.83	1.70–4.69	2.75	1.00–7.56	0.051
September	1.59	0.79–3.17	1.54	0.50–4.70	0.45
October	1.57	0.78–3.14	1.52	0.50–4.66	0.46
November	1.67	0.84–3.34	1.63	0.53–4.96	0.40
December	1.42	0.64–3.17	1.38	0.42–4.53	0.59

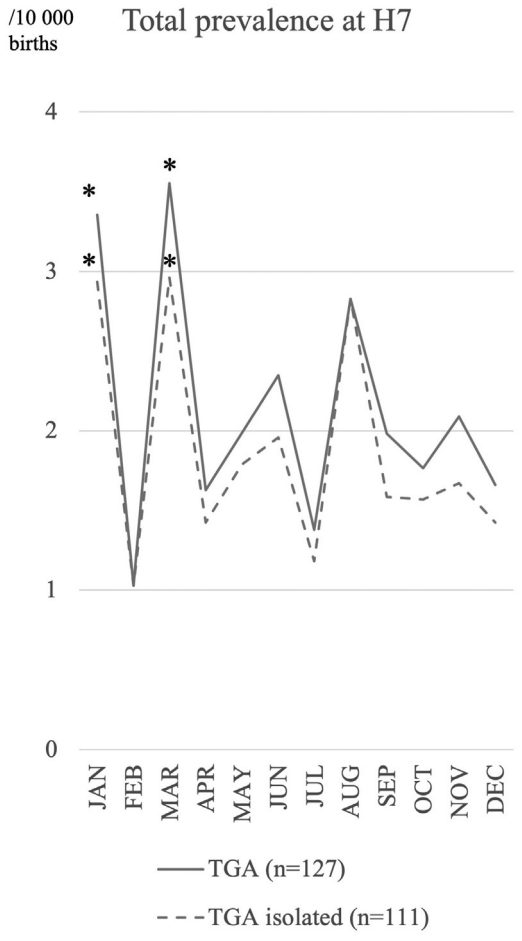

Fig. 3. Monthly variation of transposition of great arteries (d-TGA): total prevalence at a gestational age 7 + 0 weeks. Significant months are indicated with *, $p < 0.05$. The d-TGA group includes all cases, and cases without extra-cardiac anomalies are marked as "isolated." Details in Table 3.

side obstructive cardiac defects and aortic coarctation/stenosis, but no associations with HLHS or d-TGA were found [5–7]. Yet, maternal fever, as an indicator of infection, has been associated with the risk of tricuspid atresia, HLHS, and d-TGA [6]. The retrospective nature of these studies, varying timing of exposure, and self-reporting of the mothers create a risk of bias. In Finland, influenza infections are usually most common in February or March. In our material, UVH cases (including HLHS) have a peak month in December. This month is not co-incident with the peak months of influenza or any other studied viral or bacterial infections. Pregestational maternal diabetes is a well-known risk factor for congenital heart defects, and the role of gestational diabetes is more controversial [1,2]. We have also previously reported pregestational diabetes to be significantly more common in this heart defect cohort than in the all parturient population [18]. Diabetes is unlikely to be associated with the monthly variation. However, maternal dietary habits have seasonal variation in Finland, and this may affect early pregnancy glycemic control and the amount of vitamin D and especially folic acid intake from the diet since vegetable consumption is lowest during the winter months (from December to February) [25]. Extreme hot weather conditions are found to be associated with congenital heart defects [9,26]. In Finland, the annual mean temperature is -0.4 °C in Northern Finland and 5.9 °C in Southern Finland and during the summer months (June to August) 12.6 °C and 16.2 °C, respectively. Approximately ten days per summer in some parts of the country had an outside temperature of over 30 °C during the studied years (Finnish Meteorological Institute). Thus, it is safe to say that extreme hot weather is not a concern as a risk factor for congenital heart defects in Finland.

Several strengths exist. The Finnish population is relatively small and tax-paid public health care is provided for all. Reporting of all births and pregnancy terminations is mandatory. The Finnish Register of Congenital Malformations is concise and overlapping with other national registers. In addition, all congenital heart defects are operated on a single center (Children's Hospital at Helsinki University Hospital). These facts limit confounding factors and allow reliable assessment of monthly variation in total

prevalence at gestational age 7 + 0 weeks. However, there were some limitations. No information on maternal infections or vitamin use periconceptionally or during pregnancy is reported to the registers. Most importantly, even though the data were derived from a national population-based ten-year cohort, this cohort's size remained small due to the rarity of severe congenital heart defects.

Conclusions

The ten-year nationwide data, including all cases with d-TGA and UVH (including HLHS), showed significant monthly variation in total prevalence in all groups. The reasons for monthly variation remained unclear, but no associations with specific viral or bacterial infections were observed. When evaluating monthly variation, timing in early pregnancy and including all cases, i.e. not excluding pregnancy terminations, is the recommended method of choice.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Pierpont ME, Brueckner M, Chung WK, et al. Genetic basis for congenital heart disease: revisited: a scientific statement from the american heart association. Circulation 2nd ed 2018;138(21 November) 20;268–59.
[2] Øyen N, Diaz LJ, Leirgul E, et al. Prepregnancy diabetes and offspring risk of congenital heart disease: a nationwide cohort study. Circulation Am Heart Assoc, Inc 2016;133(23 June)2243–53 7.
[3] Shi QY, Zhang JB, Mi YQ, Song Y, Ma J, Zhang YL. Congenital heart defects and maternal fever: systematic review and meta-analysis. J Perinatol. Nature Publishing Group 2014;34(9 May)677–82 8.
[4] Botto LD, Panichello JD, Browne ML, et al. Congenital heart defects after maternal fever. Am J Obstet Gynecol 2014;210(4 April)359 Elsevier 1 e1–359. e11.
[5] Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. Hum Reprod 2014;29(4 March)809–23 11.
[6] Botto LD, Lynberg MC, Erickson JD. Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. Epidemiology 2001;12(5 September)485 1.
[7] Oster ME, Riehle-Colarusso T, Alverson CJ, Correa A. Associations between maternal fever and influenza and congenital heart defects. The J Pediatrics Mosby, Inc 2011;158(6 June)990–5 1.
[8] Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C. Ambient temperature and congenital heart defects. Hum Reprod 2013;28(8 August):2289–97.
[9] Lin S, Lin Z, Ou Y, et al. Maternal ambient heat exposure during early pregnancy in summer and spring and congenital heart defects – a large US population-based, case-control study. Environ Int Elsevier 2018 Sep;1(118):211–21.
[10] Zhang W, Spero TL, Nolte CG, et al. Projected changes in maternal heat exposure during early pregnancy and the associated congenital heart defect burden in the United States. JAHA 2019;8(3 Febuary)1–12 5.
[11] Chen E, Zmirou-Navier D, Padilla C, Deguen S. Effects of air pollution on the risk of congenital anomalies: a systematic review and meta-analysis. IJERPH 2014;11(8 August):7642–68.
[12] Vrijheid M, Martinez D, Manzanares S, et al. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect 2011;119(5 May):598–606.
[13] Loffredo CA, Silbergeld EK, Ferencz C, Zhang J. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. Am J Epidemiol 2001;153(6 March)529–36 15.
[14] Eghtesady P, Brar A, Hall M. Seasonality of hypoplastic left heart syndrome in the United States: a 10-year time-series analysis. J Thorac Cardiovasc Surg. The American Association for Thoracic Surgery 2011;141(2 Febuary)432–8 1.
[15] Bound JP, Harvey PW, Francis BJ. Seasonal prevalence of major congenital malformations in the Fylde of Lancashire 1957-1981. J Epidemiol Commun Health. 5 ed. 1989;43(4 December)330–42 1.
[16] Siffel C, Alverson CJ, Correa A. Analysis of seasonal variation of birth defects in Atlanta. Birth Defects Res Part A Clin Mol Teratol 2005;73(10 October):655–62.
[17] Lytzen R, Vejlstrup N, Bjerre J, et al. Live-born major congenital heart disease in Denmark. JAMA Cardiol 2018;18(July):1–9.
[18] Hautala J, Gissler M, Ritvanen A, et al. The implementation of a nationwide anomaly screening programme improves prenatal detection of major cardiac defects: an 11-year national population-based cohort study. Bjog Int J Obstet Gynaecol 2019;126(7 June):864–73.
[19] Eurocat. Minor Anomalies for Exclusion. Available from: http://www.eurocat-network.eu/content/Section%203.2-%2027_Oct2016.pdf (Accessed January 5, 2021).
[20] Nakajima Y. Mechanism responsible for D-transposition of the great arteries: Is this part of the spectrum of right isomerism? Congenital anomalies. John Wiley & Sons, Ltd; 2016. p. 196–202 September (10.1111)1;56(5).
[21] Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. Pediatr Res. Nature Publishing Group 2005;57(2 Febuary):169–76.
[22] Eurocat. Calculation of Prevalence Rates. Available from: http://www.eurocat-network.eu/accessprevalencedata/interpretationguide/calculationofprevalencerates (Accessed January 5, 2021).
[23] Finnish Institute for Health, Welfare. Infectious disease register. Available from: https://thl.fi/en/web/infectious-diseases-and-vaccinations/surveillance-and-registers/finnish-national-infectious-diseases-register (Accessed January 5, 2021).
[24] Tikkanen J, Heinonen OP. Maternal hyperthermia during pregnancy and cardiovascular malformations in the offspring. Eur J Epidemiol Kluwer Academic Publishers 1991;7(6):628–35.
[25] Prasad M, Lumia M, Erkkola M, et al. Diet composition of pregnant Finnish women: changes over time and across seasons. Public Health Nutr 2010;13(6A June)939–46 Cambridge University Press1.
[26] Auger N, Fraser WD, Sauve R, Bilodeau-Bertrand M, Kosatsky T. Risk of congenital heart defects after ambient heat exposure early in pregnancy. Environ Health Perspect 2017;125(1 January):8–14.