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Review article

Seasonal variation in the prevalence of Down syndrome at birth: a review

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Abstract

***Study objective*—Many studies on seasonality in Down syndrome (DS) have been performed and have come to different conclusions. It is suggested that seasonal variation in hormone production by the hypothalamus-pituitary-ovarian axis just before ovulation leads to seasonality in conception rates of DS. This study aimed to determine whether there is seasonal variation in the prevalence of DS at birth as a proxy for seasonality in DS at conception.**

***Design*—All the English and Dutch articles on this topic were reviewed. Articles published between 1966 and January 1996 were traced by *Medline*, and by the reference lists.**

***Main results*—Twenty articles met the criteria for inclusion. Although seven of these studies reported seasonality in DS prevalence, no consistent seasonal pattern was found in DS at birth in these studies, or in the remaining studies. A seasonal pattern could not have been masked by the effects of maternal age, induced abortions, shortened gestation, or misclassification of DS.**

***Conclusion*—Seasonality in the prevalence of DS at birth does not exist. Evidence did not support the suggestion that DS occurrence is related to seasonality in hormone production.**

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It has been shown conclusively that the prevalence of Down syndrome (DS) at birth in any given population is related only to the maternal age of the childbearing population and to the use of prenatal diagnosis with subsequent termination of affected pregnancies.[1] The underlying mechanism for the higher prevalence of DS with advancing maternal age is not yet clear.

The most common hypothesis for the maternal age effect is ageing of the ovum itself.[2] Another hypothesis, the so called compromised microcirculation hypothesis proposed by Gaulden,[3] states that hormonal imbalance causes a less than optimal microvasculature to develop around the maturing and mature follicles. This would result in an oxygen deficit and consequently in a decrease in the intracellular pH of the oocyte. The consequence would be a smaller sized spindle, followed by displacement and non-disjunction of a chromosome. A more general hypothesis was proposed by Jongbloet[4] and presumes that hormonal imbalance may suppress the maturation of the oocyte during the follicular phase, which may be expressed, among other ways, by non-disjunctions. Both suggestions about hormonal imbalance causing non-disjunctions may apply to seasonal influence.

It has been hypothesised that there is seasonal variation in human reproduction as most mammals show a seasonal pattern in reproduction. This pattern may be dictated by photoperiodicity which regulates the production of melatonin and inhibits or stimulates the production of gonadal hormones.[5] It has been suggested that remnants of such a seasonal reproduction pattern may still be present in humans and may cause seasonal variation in reproductive errors.[4] Seasonal variation in human reproduction has been observed in ovulation,[6 7] in sperm production,[8] in early pregnancy loss,[9] in spontaneous abortions,[10 11 12] and in births.[13 14 15] A seasonal pattern in the prevalence of DS at birth can be expected as a consequence of seasonal variation in hormone production by the hypothalamus-pituitary-ovarian axis.

For this article, we reviewed studies on seasonality in DS. As it is presumed that the aetiologic moment occurs just before ovulation, our main interest was DS of maternal origin, preferably originating during first meiosis. Almost all DS cases (95%) have free trisomy 21, which is a consequence of non-disjunction during meiosis one or two.[16] About 95% of these extra chromosomes 21 are of maternal origin[17 18] and about 77% of DS cases of maternal origin result from non-disjunction during the first meiosis.[19] Based on these arguments, seasonality in DS can be studied without making any distinction between the type of DS, parental origin, or meiotic non-disjunction. As it is not possible to study the occurrence of DS at conception, we reviewed articles about the occurrence of DS at birth. A consistent seasonal pattern in DS at birth will support our hypothesis that seasonality in DS occurs as a consequence of a seasonally bound influence on the hormone production of the

Table 1 Main reason for excluding publications from this review

Reason for exclusion	*Publication*
Not about seasonality in Down syndrome	Kessler & Lilienfeld (*Advances in Cancer Research* 1969;**12**:225–302.)
	Chen & Woolley (*Journal of Medical Genetics* 1971;**8**:153–59.)
	Kenna *et al* (*Quarterly Journal Medicine* 1975;**44**:17–44.)
	Safra *et al* (*Teratology* 1976;**14**:143–49.)
	Ikeda *et al* (*Journal of Mental Deficiency Research* 1977;**21**:139–51.)
	Paradise (*Pediatrics* 1980;**65**:917–43.)
	Klein *et al* (*Journal of Pediatric Surgery* 1984;**19**:370–74.)
	Jongbloet *et al* (*Diabetes Research* 1988;**9**:51–58.)
Not an original study	Pergament (*The Chigaco Medical School Quarterly* 1969;**28**:57–67.)
	Jongbloet (*Lancet* 1970;**2**:1317-8.)
	Lowe (*British Medical Journal* 1972;**3**:515–20.)
	Hecht (In: Hook & Porter eds. *Population cytogenetics. Studies in humans.* New York: Academic Press Inc, 1977; 237-50.)
	Stark & White (In: Hook & Porter (Eds.) *Population cytogenetics. Studies in Humans.* New York: Academic Press, Inc, 1977; 275-83.)
	Ament (*American Journal of Epidemiology* 1976;**103**:342–43.)
	Rothman (*American Journal of Epidemiology* 1976;**104**:585–86.)
	Janerich & Jacobson (*Lancet* 1977a;**1**:515–16.)
	Janerich & Jacobson (*Lancet* 1977b;**1**:1004–5.)
	Robinson (*Advances in Pathobiology* 1977;**6**:214–26.)
	Robinson & Puck (*Lancet* 1977;**2**:981–82.)
	Sever (*The Lancet* 1977;**1**:754.)
	Mikkelsen (*Human Genetics* 1981;**2 (suppl)**:211–26)
	Jongbloet (*The Lancet* 1983;**2**:347–48.)
	Anonymus (*The Lancet* 1983;**1**:1312–13.)
	ICPEMC (*Mutation Research* 1986;**175**:263–66)
Other publication on (almost) the same population included in this review	Nielsen *et al* (*Humangenetik* 1973;**19**:67–74)
	Nielsen *et al* (*Annales de Génétique* 1981;**24**:212–15)
Less than 50 Down syndrome cases	Robinson & Puck (*American Journal Human Genetics* 1967;**19**:112–29.)
	Haynes *et al* (*Neurology* 1974;**24**:691–700.)
	Seifert & Sommer (*American Journal of Diseases of Children* 1986;**140**:822–24.)
	Drugan *et al* (*Fetal Therapy: Clinical Advances* 1989;**4**:195–99.)
No Down syndrome prevalence per month	Leck (*Lancet* 1966;**2**:457–60.)
	Halevi (*British Journal of Preventive and Social Medicine* 1967;**21**:66–77.)
	Baird & Miller (*British Journal of Preventive and Social Medicine* 1968;**22**:81–85.)
	Hook *et al* (*Lancet* 1974;**1**:566–67)
	Iselius & Lindsten (*Human Genetics* 1986;**72**:133–39)
No Down syndrome prevalence at birth	Jongbloet (*Clinical Genetics* 1971;**2**:315–30.)
	Jongbloet (*In*: Blandau ed. *Aging Gametes.* Basel: S. Karger AG, 1975; 300–29.)
	Puri & Singh (*British Journal of Clinical Practice* 1995;**49**:129–30.)
Not compared to total or live births in corresponding period and place	Jongbloet *et al* (*Human Genetics* 1982;**62**:134–38.)
	Jongbloet & Vrieze (*Human Genetics* 1985;**71**:241–48.)

hypothalamus-pituitary-ovarian axis. However, if a seasonal pattern in DS is not obvious, this review cannot reject the hypothesis, as selective spontaneous abortions might have made such a pattern disappear.

Methods

A computerised literature search was performed by means of *Medline*. All the English and Dutch articles were selected which contained the words "Down syndrome", "Down's syndrome" or "trisomy 21" in combination with "season*" and were registered in the volumes published between 1966 and January 1996. Additionally, studies were traced via the reference lists of the articles. Unpublished work was not reviewed.

Studies were only included if they contained more than 50 DS cases, presented monthly results of DS prevalence at birth, and used a comparison group of total or live births in the corresponding period and area. Only original studies were included.

As photoperiodicity may influence hormone production and consequently the occurrence of non-disjunctions, the overview of seasonal patterns is arranged according to the latitude of the location of the study population. If a seasonal pattern exists, we expect to find a consistent seasonal pattern on the northern hemisphere and the opposite pattern on the southern hemisphere and that this pattern might be transient from the poles to the equator.

As seasonality is analysed and interpreted in various ways in the original studies, we used in this review the crude data of each study—ie the monthly DS rate compared to the average DS rate. As large differences existed in the overall DS prevalence between studies, presumably because of differences in maternal age, induced abortions after prenatal diagnosis, and in registration, DS prevalence per month was not compared and clearly could not be pooled. Moreover, exact numbers were not always presented in the studies.

Results

In total, 53 English and Dutch publications were traced via *Medline*; only 13 of them met all the criteria for inclusion in this review. In table 1 the main reason for exclusion is given for each study. In addition, seven studies which met the criteria were found via reference lists.

In table 2; an overview is given of the remaining 20 studies on seasonality in DS. Because of the influence of photoperiodicity on hormone production, the studies are listed by latitude. If two studies were performed at the same latitude, the one with the largest number of DS cases is mentioned first. The authors of 13 studies concluded that no relation was present between the month of birth and DS prevalence.[20–32] Seven studies[33–39] reported seasonality in DS prevalence.

These seven studies[33–39] were not a selective group in the number of DS cases, the prevalence of DS or latitude. Their numbers of DS varied from 103 to 2469, and in the other 13 studies from 139 to 3810. The prevalence of DS was in the range from of 0.88 to 2.4 per

Table 2 Studies on seasonality and Down syndrome (DS), listed by latitude

Study	No of DS cases	Study population	Frequency per 1000	Compared to births*	Conclusion in study about seasonality in DS	Higher and lower DS birth prevalence†											
						Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Northern hemisphere																	
Leisti *et al*[26]	263	Live births in northern Finland 1965–79	1.73	Alive	No (NS‡)	−	+	−	−	+	+	+	−	−	−	+	+
Källén & Måsbäck[29]	1174	Born in Sweden 1973–83	1.08	Alive	No	−	+	−	+	−	−	−	+	+		+	
Lindsten *et al*[24]	1370§	Live births in Sweden 1968–77	1.28	Alive	No	−	−	−	+	+	−	−	+	+	−	+	+
Holloway & Emery[36]	978	Born in Scotland, registered by 13 health boards, 1960–74	0.88	Alive	Yes (NS); high in Jun, Nov, low in Jul	−	−	−	+	+	+	−		+		+	+
Videbech & Nielsen[38]	1972	Registered in Denmark (half born before 1965), 1968–80	Unknown	Alive	Yes; high in Oct-Jan ($p<0.05$), low in Feb-May, Apr-Sept	+	−	−			−	+	+	−	+	+	+
McDonald[21]	2398	Live and stillbirths in Quebec 1958–67	1.86	Alive	No	+	−	+	+	−	−	+	+	+	−	+	+
Baird & Sadovnick[27]	883.3	Live births and 70% of selective aborted fetuses in British Colombia 1964–83	1.21	Alive	No	−	+	−	−	−	−	+	+	−	+	+	+
Leck[37]	527	Born in Birmingham, UK 1950–65	1.64	Total‖	Yes, high in Jan-Jun	+	+	+		+	+	−	−	−	+	−	+
Knox & Lancashire[32]	354	Live and stillbirths in Birmingham, UK 1964–68	41.38	Total	No		+	+	−	+	−	+	−	+	−	−	−
Stoll *et al*[31]	139	Live and stillbirths in Strasbourg and surrounding areas, France, 1979–87	1.17	Normal	No	¶											
Czeizel[28]	1997	Live births in Hungary 1970–84	0.85	Total	No (NS); high in Jul, Dec, low in Jan, Jun	¶(−)					(−)	(+)					(+)
Stark & Mantel[40]	2431	Live births in lower peninsula of Michigan 1950–64	0.89	Alive	No (NS); high in Jun, low in Oct	−	−	+	+	−	+	+	−	−	−	+	−
Rothman & Fabia[35]	2469	Live births in Massachusetts 1950–66	1.35	Total	Yes ($p=0.03$); high in summer, low in winter	¶(−	)(−	)(−	)			(+)	(+)	(+)			
Castilla *et al*[30]	618	Born in hospitals in Italy, 1981–84	1.22	Total	No (NS)	¶											
Wehrung & Hay[20]	3810	Live births in 29 states and 2 cities of the US 1962–65	0.43	Alive	No (NS)	¶											
Gummere *et al*[25]	1364	Born in Ohio 1970–79	1.22	Alive‖	No (NS); high in Jan, May, low in Apr, Jun	+	+	−	−	+	−	+	+	−	−	−	−
Kanai & Nakamura[39]	291	Born in Kyoto, Japan, 1959–79	Unknown	Total	Yes	−	−	−	−	+	+	+	+	+	+	−	−
Kaplan & Ament[23]	299	Born in Jerusalem, Israel, 1970–72	1.03	Total	No	+	+	+	−	−	−	+	−	−	+	+	+
Harlap[34]	103	Born in Jerusalem, Israel, 1964–70	2.4	Alive	Yes (6 month cycle $p<0.001$); high in spring, autumn	−	+	+	+	+	−	−	+	+	+	−	−
Southern hemisphere																	
Castilla *et al*[30]	919 (n-t); 348 (t)	Born in hospitals in non-tropical (n-t) and tropical (t) South America 1982–86	1.58 (n-t), 1.21 (t)	Total	No (NS)	¶											
Collmann & Stoller[33]	1134	Live births in Victoria, Australia, 1942–57	1.45	Alive**	Yes; low in Jul ($0.01<p<0.02$)	+	+	+	+		+	−	−	−	+	+	−

* From the corresponding years of birth and place (region or hospital) as the DS groups;
† + higher than average, − lower than average;
‡ Not statistically significant;
§ 40 aborted fetuses with DS excluded;
‖ Corrected for maternal age;
¶ No information;
** Corrected for post- and prematurity, delay caused by registration

1000 in the seven studies, and from 0.43 to 1.86 per 1000 in the other studies. The seven studies were located between Scotland and Victoria, Australia. Overall, no consistent pattern was found in seasonal variation in these seven studies that reported a seasonal pattern, or in the trends reported in the other studies. An unexplained cluster of relatively high prevalences of DS births might be apparent in November/December at the extreme end of the northern hemisphere,[21 24 26 27 29 36 38] but in the other months there was no consistent pattern. As the studies with a low number of DS cases may have missed a seasonal pattern, we focused on studies with more than 1000 DS births which gave information on the monthly prevalence of DS.[21 24 25 28 29 33 35 38 40] In this selective group of studies, no comparable seasonal pattern was found in DS at birth. They showed the same direction in prevalence of DS in comparison with the average prevalence per month only in two single months. There was a relatively high prevalence of DS births during August and a relatively low prevalence during June in the northern hemisphere, while the opposite pattern was observed in the southern hemisphere. During the other months, some of these nine studies reported a relatively high prevalence of DS, whereas the others showed a relatively low prevalence.

Discussion

In this review, no obvious seasonal pattern was found in DS prevalence at birth. Some factors can influence the DS prevalence at birth: maternal age, induced abortions after prenatal diagnosis,[41] and shortened gestation.[42] Maternal age can only confound the relation between the season and the occurrence of DS if pregnancy planning during the year differs according to the woman's age. As this is not apparent, confounding by maternal age is not expected. If there is a seasonal pattern in DS at conception, induced abortions after prenatal diagnosis might have weakened this pattern,

but would not have changed the positions of the peaks and troughs of a seasonal pattern at birth. Although a seasonal pattern in preterm birth may exist,[43] it would only cause a minor shift in a seasonal pattern for DS. Thus, it is unlikely that these factors would have masked a seasonal pattern in DS at birth. Moreover, some misclassification of DS might have occurred. Only eight studies [24-28 31 38 39] mentioned the number of karyotyped cases of DS, the percentage of karyotyped cases varied from 15% to 100%. However, we do not expect that misclassification of DS was seasonally bound and thus it can not have masked any association between season and the prevalence of DS at birth.

Another source of bias could be a seasonal pattern in spontaneous abortions. In their review, Hassold and Jacobs [44] reported that approximately 2.3 % of all spontaneous abortions, 1.3 % of all stillbirths, and 0.13 % of all live births have trisomy 21. They estimated that trisomy 21 occurs in almost 0.45 % of all recognised pregnancies and that only 23.8 % of all conceptuses with trisomy 21 survive to term. As far as we know, there is only one article in which seasonality in DS was studied before birth. In that study, no seasonal variation was found in DS among 5292 samples for prenatal diagnosis.[45] However, as there were only 45 DS cases, the results were not very reliable.

In brief, we have to conclude that there is no seasonal pattern in DS at birth. Thus we cannot support the hypothesis that the season influences the hormone production, which results in DS. We cannot exclude the possibility, however, that a seasonal pattern in DS may exist at the time of conception, but disappears because of selective spontaneous abortions. To answer this question, a study using a very large number of prenatal karyotypes from an aselect group of women may provide more insight, especially if the non-disjunctions during the first meiosis of maternal origin are considered separately.

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