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Citation	Japanese Journal of Veterinary Research, 52(2), 85-94
Issue Date	2004-08
DOI	10.14943/jjvr.52.2.85
Doc URL	<a href="http://hdl.handle.net/2115/10513">http://hdl.handle.net/2115/10513</a>
Type	bulletin (article)
File Information	52(2)_85-94.pdf



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## Iodine intake as a possible cause of discontinuous decline in sperm counts : A re-evaluation of historical and geographic variation in semen quality

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(Accepted for publication : June 29, 2004)

### Abstract

In order to examine whether iodine supplements may have caused a global decline in sperm concentrations during the past several decades, the synchronicity of the decline in mean sperm counts and the introduction of iodine supplements was analyzed statistically. A positive correlation between the incidence of thyroid disease and sperm counts has been detected in Europe. In addition, it has been shown that sperm counts began falling around 1965 in the United States, 40 years after iodine supplements were introduced. Mean sperm counts before and after 1965 were  $111 \times 10^6/\text{ml}$  and  $70 \times 10^6/\text{ml}$ , respectively, in calculations weighted by the number of subjects included in each individual publication. The timing of the declines coincided with the introduction of iodine supplements in the United States, France, and the United Kingdom. The implications are that the global decline in sperm concentrations may be caused by iodine intake. Geographical variation in the types of sperm count decline also appears to be present.

Key words : geographical variation; iodine intake; sperm count

In 1992, Carlsen et al. reported that sperm counts have gradually fallen over the last 50 years in presumably fertile men<sup>6)</sup>. The results have stirred much debate, with the issue having recently been reviewed by Crissman et al.<sup>8)</sup>. As the cause of the worldwide decline in sperm counts, environmental oestro-

gens were suspected, namely the 'oestrogen hypothesis'<sup>7,9)</sup>. The decline might be related to endocrine disruptors which have become widespread in several decades. The suggested mechanism behind the oestrogen hypothesis is that the suppression of FSH levels caused by perinatal exposure to oestrogen could re-

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duce sperm counts in adulthood by permanently altering the number of Sertoli cells<sup>52,54</sup>).

However, it is difficult to explain the difference of several decades in timing of sperm concentration declines between the United States and European countries based on this hypothesis<sup>56</sup>. Additionally, an experimental study in a non-human primate, the marmoset, showed that neonatal suppression of FSH reduced Sertoli cell proliferation/numbers at the end of the neonatal period, but by the time such treated animals had grown to adulthood, Sertoli cell numbers had recovered to normal<sup>53</sup>.

It is known that sperm counts are related to hypothyroidism<sup>4,37</sup>, which is a major childhood disease in iodine-deficient regions. This disease has been prevented by introducing iodine supplements. Is there a cause-and-effect relationship between sperm counts and iodine supplements? Previous studies have shown that the deficiency in thyroid hormone increased Sertoli cell numbers and sperm production<sup>7,22</sup>. Crissman et al. found that a neonatal iodine deficiency increased testis weight due to increased Sertoli cell proliferation, and this significantly increased spermatogenic function in rats, and proposed that the sperm count decline has been, at least partially, due to optimization of the human iodine and thyroid status<sup>8</sup>.

In this paper we hypothesized that sperm counts have been affected by the introduction of iodine supplements, which have largely eliminated hypothyroidism. This hypothesis was examined from two different points of view. First, we reviewed the relationship between sperm counts and the incidence of thyroid disease using the data that Jorgensen et al. collected from four cities in Europe<sup>30</sup>. Second, we reanalyzed selected data, collected mainly in the United States by Carlsen et al. and Swan et al., since only a small number of

reports are available for meta-analysis in any other countries<sup>6,57</sup>.

The relationship between sperm counts and thyroid disease incidence was studied using Jorgensen's data<sup>30</sup>, which satisfies the criteria of Carlsen et al.<sup>6</sup>. It was analyzed with a linear regression weighted by the number of subjects.

To reanalyze the historical change in sperm counts over time, we selected 43 sets of data, which were published between 1934 and 1996 in the U.S., from the original 101 studies reported by Carlson et al. and Swan et al.<sup>6,57</sup>. They are listed in Table 1. Semen analyses were performed manually in all studies. There were more than 10 subjects per set. All available data was adapted to the criteria of Swan et al.<sup>57</sup>. Thus, a total of 9,229 fertile or presumably fertile men were included in this analysis.

Iodine supplementation started in 1924 in the United States<sup>38</sup>. The time at which sperm counts fell was determined by dividing the data into two groups for every year it was published. When a decline was believed to occur, for example in 1964, the data was divided into one group for studies published in 1934-1963 and another group for those done in 1964-1996. Then the differences were analyzed with the Mann-Whitney *U*-test.

We determined that the year with the smallest *p* value was possibly the time when sperm counts began to decline. Mean sperm counts before and after this year were calculated by weighting the number of subjects included in each individual publication.

All statistical analyses were performed using a JMP statistical software package (version 4.0.5 J, SAS Institute Inc., Cary, NC).

Figure 1 shows the linear regression analysis of the mean sperm counts against the incidence of thyroid disease from data collected in the European countries of Denmark,

Table 1. Historical values of mean sperm counts in the United States. Mean sperm count values indicated in millions per mL. Data were cited from Carlsen et al. (1992) and Swan et al. (2000).

Publication Year	Mean sperm count	No. of specimens	Author	Ref No.
1934	119.0	15	Belding	(2)
1938	120.6	200	Hochkiss et al.	(25)
1941	107.0	22	Hochkiss	(26)
1943	66.9	25	Weisman	(64)
1945	134.0	100	MacLoed and Heim	(36)
1949	145.0	49	Farris	(15)
1950	100.7	100	Falk and Kauffman	(13)
1951	107.0	1000	MacLoed and Gold	(35)
1956	135.0	21	Lampe and Masters	(32)
1963	110	100	Rutherford et al.	(49)
1964	96.6	50	Zimmerman et al.	(70)
1969	48.4	13	Freund and Davis	(17)
1972	60.0	79	Santomauro et al.	(50)
1974	48.0	386	Nelson et al.	(42)
1975	79.0	1300	Naghma-E-Rehan et al.	(41)
1976	83.2	13	Glaub et al.	(20)
1978	100.2	33	Rehewy et al.	(46)
1979	114.0	21	Rogers et al.	(47)
1979	61.7	22	Glass et al.	(19)
1979	61.4	50	Smith et al.	(55)
1980	113.5	63	Venable et al.	(61)
1980	93.0	90	Milby and Whorton	(40)
1981	66.2	26	Wyrobek et al.	(68)
1981	128.7	34	Wyrobek et al.	(69)
1981	115.0	89	Meyer	(39)
1981	75.0	112	Farris et al.	(14)
1981	83.0	132	Dougherty et al.	(11)
1982	76.0	90	Hamill et al.	(21)
1982	66.0	4435	Tjoa et al.	(59)
1983	60.3	22	Borghi and Asch	(3)
1984	87.4	11	Ward et al.	(63)
1984	59.0	36	Swanson et al.	(58)
1985	65.0	20	Heussner et al.	(23)
1985	99.2	71	Rosenberg et al.	(48)
1986	68.0	12	Levin et al.	(33)
1987	68.7	43	Ratcliff et al.	(45)
1988	86.6	28	Giblin et al.	(18)
1988	78.6	40	Welch et al.	(65)
1988	47.4	45	Schrader et al.	(51)
1991	87.0	48	Eskenazi et al.	(12)
1992	132.8	10	Kolon et al.	(31)
1992	70.7	142	Levine et al.	(34)
1996	38.0	31	Weyandt et al.	(67)

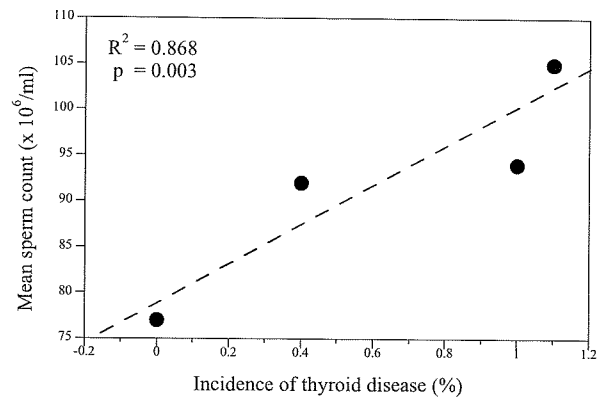


Figure 1. Positive correlation between mean sperm counts and incidence of thyroid disease. Each dot indicates the mean sperm counts from Denmark, United Kingdom, France and Finland, which are 77, 92, 94 and 105x 10<sup>6</sup>/ml, respectively (Jorgensen et al., 2001).

France, the United Kingdom and Finland by Jorgensen et al.<sup>30)</sup>. The mean sperm counts were weighted by the number of subjects. A good linear relationship is seen between them, with the respective parameters of  $R^2 = 0.868$  and  $p = 0.003$ . The regression coefficient was estimated to be  $20.2 \times 10^6/\text{ml}$  per 1 percent of thyroid disease incidence.

Although the thyroid disease in Figure 1 included hypothyroidism and hyperthyroidism, Vanderpump et al. reported that the incidence of hypothyroidism was 5-fold higher than that of hyperthyroidism<sup>62)</sup>. Hollowell et al. also estimated that the prevalence of hypothyroidism (4.6%) was higher than that of hyperthyroidism (1.3%)<sup>24)</sup>. Thus, the most common thyroid disease is hypothyroidism. Moreover, sex and age are major factors for thyroid diseases. In Figure 1, although there is no description of the details of thyroid diseases, the eligibility criteria in this investigation are 20 to 45 years of age and male sex. Thus, we suggest that the etiological variety of thyroid diseases might not differ significantly among countries in this study. Sertoli cells are rich in thyroid hormone receptors in neonatal tes-

tes<sup>29)</sup>. A deficiency in thyroid hormone retards the maturation of Sertoli cells and prolongs the proliferation period during which the number of Sertoli cells increases. The number of Sertoli cells determines the number of spermatogenic clonal units. Thus thyroid disease incidence may increase the sperm-producing capacity of the testicles.

The mean sperm counts are plotted against the publication years in Figure 2. Each circle was weighted according to the number of subjects. The smallest  $p$  value was obtained when the critical line was drawn at the years between 1965 and 1969 (Figure 2). Before and after this period, the data was

analyzed for differences with the Mann-Whitney  $U$ -test ( $p=0.0005$ ). On drawing the critical line at the years between 1964 and 1969 or between 1951 and 1972,  $p$  values were found to be less than 0.001 or 0.01, respectively. Hence it was concluded that the sperm counts were significantly altered between 1965 and 1969 in the United States. The respective mean sperm counts were estimated to be  $111 \times 10^6/\text{ml}$  and  $70 \times 10^6/\text{ml}$  before and after these dates. Paulsen et al.<sup>44)</sup> and Fisch et al.<sup>16)</sup> also reported similar results in their longitudinal studies, indicating no alteration or a slight increase in sperm counts in the United States after 1970.

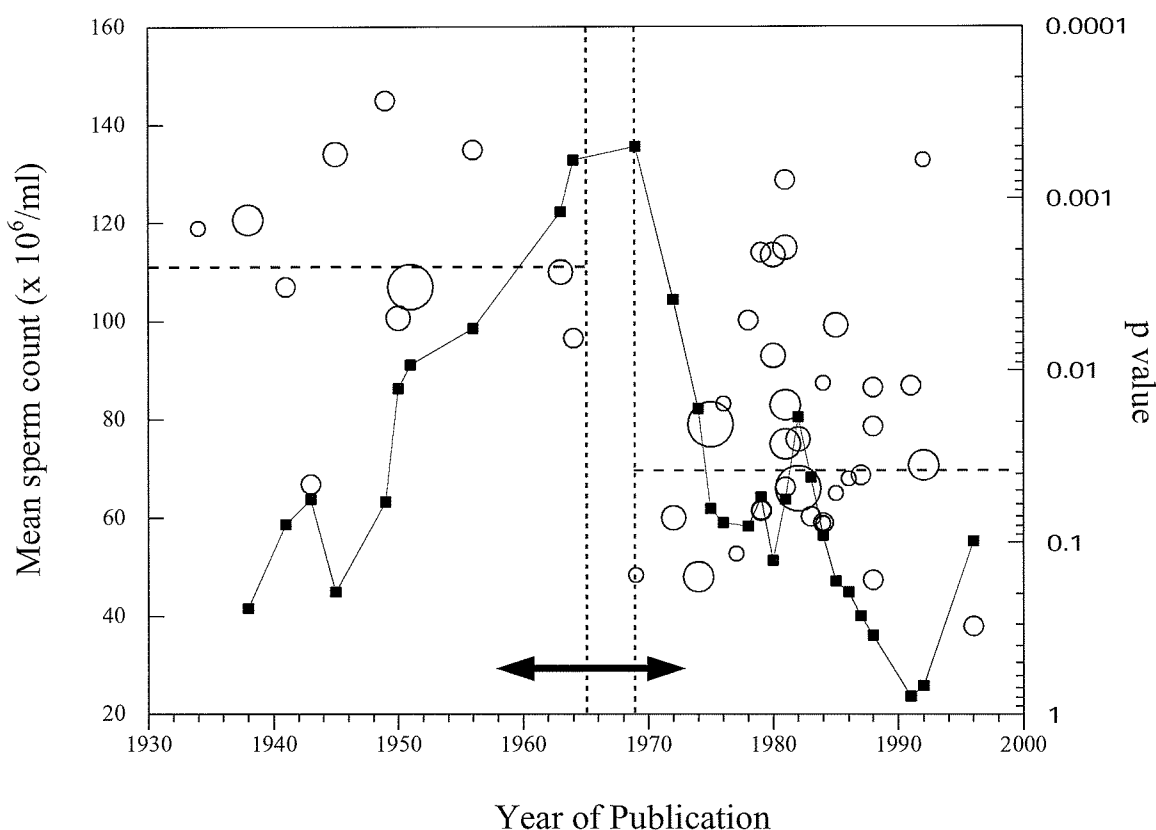


Figure 2. Mean sperm counts in 43 publications are represented by circles whose area is proportional to the number of subjects. The  $p$  values calculated with the Mann-Whitney  $U$ -test are represented by squares, which indicate the timing of the decline in sperm counts.

The most significant fall was detected between the two vertical lines (1965-1969) ( $p=0.0005$ ). Horizontal lines indicate the mean sperm counts of each group, weighted by number of subjects ( $111$  and  $70 \times 10^6/\text{mL}$ ). The arrow indicates the presumed period of sperm count decline caused by the introduction of iodine supplements in the United States (1958-1973). Data were cited from Carlsen et al. (1992) and Swan et al. (2000).

This conclusion supports the hypothesis that iodine supplementation to eliminate hypothyroidism decreases sperm counts. Hypothyroidism, an endemic goiter caused by a deficiency of iodine, was a common disease in children in iodine-deficient regions, such as the Dakotas, Minnesota, and the Great Lakes basin in the United States. Iodized salt was first introduced in Michigan in 1924 to prevent endemic goiter and a salt iodization policy was established in the rest of the United States within 15 years<sup>43)</sup>.

The mean age of sperm donors was calculated as 31 years in publications by Carlsen et al.<sup>6)</sup>. The time of sample collection always predated publication, often by several years. In Swan et al.<sup>57)</sup>, the mean time span between publication and sample collection was estimated to be 3 years. Therefore, 34 years was the time span between the donors' birth and sperm donation on the average. For example, sperm counts reported in 1958 would logically be attributed to donors who were born in 1924, when iodized salt was just introduced in the United States. Sperm counts reported in 1973 would logically come from donors who were born in 1939, when iodized salt was widely being used all over the United States. Thus, if iodine intake caused sperm counts to decline, the decrease would be exhibited between 1958 and 1973 in publications from the United States.

In France iodized salt was introduced in 1952<sup>60)</sup>. Sperm count decline was indicated in men born after the 1950s in a birth-cohort study<sup>9)</sup>. Mean sperm counts decreased in Paris between 1973 and 1992 from  $89 \times 10^6/\text{ml}$  to  $60 \times 10^6/\text{ml}$  in male donors averaging 34 years of age<sup>1)</sup>. Therefore, it would indirectly seem that sperm counts decreased in men born between 1939 and 1958. In Toulouse, France, however, no alteration was exhibited in sperm counts between 1977 and 1992 for donors whose mean

age was 34 years<sup>5)</sup>. Toulouse faces the Mediterranean Sea. The intake of seafood containing a large amount of iodine may have prevented iodine deficiency and thus caused no alteration of sperm counts in Toulouse.

There has been a three-fold increase in the amount of iodine in the British diet between 1952 and 1982 from  $80 \mu\text{g}/\text{day}$  to  $255 \mu\text{g}/\text{day}$ <sup>10,66)</sup>. Intake of  $150 \mu\text{g}/\text{day}$  was recommended for children by the Department of Health and Social Security in the United Kingdom. A birth-cohort study in Scotland indicated that  $98 \times 10^6/\text{ml}$  was the median sperm count of donors born in the 1950s, though  $78 \times 10^6/\text{ml}$  was that of donors born in the 1970s<sup>27)</sup>.

There is no endemic goiter in Japan because of the tradition of eating seafood. Sperm counts in Japan have shown no change in the last 25 years<sup>28)</sup>.

We suggest that iodine intake has been a factor in the decline in sperm counts in the United States and some European countries. Although environmental endocrine disruptors are suspected of affecting male gonadal development during the fetal period, obvious evidence for sperm count decline still has not been demonstrated at the concentrations to which humans are exposed to in daily life<sup>52)</sup>.

It should be noted that Crissman et al. reported recently that higher round spermatids and heavier testis weights were exhibited by 133-day old adult rats fed a low iodine diet only in the neonatal period and then fed a control diet afterward<sup>8)</sup>. This study mimicked the situation of men who are born in an iodine-deficient region and who receive an iodine supplement after their neonatal period.

#### Acknowledgment of financial support :

This work was supported in part by a Grant-in-Aid for Scientific Research (Projects No. No. 15201009) and a Grant-in-Aid for Sci-

entific Research on Priority Areas (A) (Project No. 13027201) from the Japanese Ministry of Education, Science, Sports, Culture and Technology.

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