Correspondence

Periconceptional vitamin supplementation and the prevention of neural tube defects

Sir,

Seller and Nevin\(^1\) report their findings on periconceptional vitamin supplementation and the prevention of neural tube defects (NTD) in south-east England and Northern Ireland. They conclude that the beneficial effects of supplementation are apparent in both areas, although the reverse was true in the third cohort of SE England. They admitted that the design of the trial was unsatisfactory because ethical approval for the planned double blind placebo trial was not given.

In my opinion, the authors have demonstrated the beneficial effect, not of multivitamin treatment, but of optimum conception vs high risk conception. The treated mothers were motivated and had intended to become pregnant, that is, they were supplemented for not less than 28 days before conception and up to the time of the second missed period. The untreated ones were seen too late, that is, they were already in the early stages of pregnancy, to be included in the cohort.\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) While the former conceptions can be said to have been carefully planned the latter were either carelessly accepted (conceived during the restoration of the ovulatory pattern directly after an abortion or parturition or after a long fallow period) or they may not have been planned (resulting from inadequate attempts to postpone or to prevent a further pregnancy. This desire may be instigated by the birth of a severely handicapped child). In all these conditions the risk that the egg will be overripe before either ovulation or fertilisation is increased and, as in animal experiments,\(^3\)\(^4\) congenital malformations, particularly NTD, may result.\(^5\)\(^6\)

Ovopathy as a possible cause of NTD is illustrated by a fetus with extensive spina bifida cystica, despite vitamin supplementation, resulting from an unplanned conception within three months after the termination of a previous pregnancy,\(^7\) that is, during the post partum restoration of the ovulatory pattern. Also, the recurrence of an NTD child (No 6, table 6\(^4\)) in a diabetic woman despite full vitamin supplementation may point in that direction. In fact, reduction of the ovulatory pattern was seen in pancreatectomised rats\(^6\) and amenorrhoea, menstrual irregularities, and malformed progeny were very common in diabetic women before insulin became available. In spite of insulin treatment, irregular cycles, delayed ovulation, and offspring with congenital malformations still appear to be more frequent in diabetic women than in non-diabetic ones.\(^9\) This may be due to a hormonal imbalance during egg maturation.

We have argued that NTD, in spite of the inclusion of genocopies (for example, Meckel and Warburg syndromes) and phenocopies (as presumed by maternal hyperthermia during early pregnancy) fit the eight criteria necessary for assuming overripeness ovopathy as being the cause of a given disorder.\(^5\)\(^6\)\(^10\)\(^11\) (1) They do not or only rarely occur familially. (2) They occur concordantly and discordantly in monozygous twins, particularly in the smaller or weaker partner. (3) They are often accompanied by multiple congenital anomalies. (4) They are often accompanied by non-specific chromosomal aberrations. (5) They are often accompanied by hypogonadism. (6) They are often associated with a suboptimal reproductive state in the proband's mother. (7) They are often associated with high risk conceptions, illustrated by their unequal distribution with regard to maternal age, birth order, duration of pregnancy interval, hormonal balance, religious affiliation, socioeconomic status, month of birth, etc. (8) They are often accompanied by complications of pregnancy, birth, or neonatal life.

For all these reasons, I believe that the areas of higher vs lower NTD prevalence correspond with those with more vs less conceptopathology, that is, better vs poorer preconception care. And the apparent reduction of NTD after vitamin supplementation, particularly in the high prevalence areas, is only an indication of the beneficial effect of pre-pregnancy care, that is, optimisation of the conceptions for wanted pregnancies and avoidance of unplanned ones by optimum contraception.\(^6\)

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This letter was shown to Dr Seller and Professor Nevin, who reply as follows.

SIR,

We are grateful for the opportunity to reply to Dr Jongbloet. We feel that, regrettably, his letter is largely composed of false assumptions and points of doubtful accuracy.

(a) The first and most important false assumption is that the pregnancies in our untreated women “were either carelessly accepted . . . or they may not have been planned”. While this might have been true for a few women, it is not true of the group as a whole. It is our experience from genetic counselling clinics that most women who have had an NTD baby plan the next conception very carefully. It was because we did not know about these women soon enough or they had not heard of our project that they did not receive supplementation. It is difficult to know soon enough of everyone at risk. Our catchment areas are not simply the immediate locality of our respective hospitals, but the whole province of Northern Ireland for one and a large area of south-east England for the other. This point is borne out by the fact that in Northern Ireland, now that supplementation is widely publicised for women at risk, there are very few women left to form the unsupplemented control group.

(b) “Ovopathy as a possible cause of NTD is illustrated by a fetus . . .”. It is wrong to argue from a single anecdotal case report to a general concept. To focus on this one selected case in the light of available publications is totally erroneous.

(c) “The recurrence of an NTD child in a diabetic woman (despite full vitamin supplementation) may point in that direction.” The teratogenic mechanism in diabetes is not known. Both hyperglycaemia and hypoglycaemia have been suggested but most of this work is on animals. Insulin as a factor appears unlikely. Other factors could include vascular disease, hypoxia, ketone and amino acid abnormalities, glycosylation of proteins, or hormone imbalances. To assume, as Dr Jongbloet does, that it “may be due to hormonal imbalance during egg maturation” is to disregard all other possible teratogenic factors.

(d) Many of the statements made in “the eight criteria necessary for assuming overripeness ovopathy as being the cause of a given disorder” show a lack of knowledge of epidemiological and genetic data relating to NTD.

(1) NTD do occur in families; the evidence for this is overwhelming and there are numerous references to support it.

(2) NTD actually arise during the formation of the neural tube from the 19th to the 26th day after conception. It is difficult to imagine what evidence there is that one twin partner is “smaller or weaker” at this stage. It is well known that a secondary effect of an NTD is some form of subsequent growth retardation so that at birth the affected twin may well be “smaller or weaker”.

(3) This is erroneous. NTD are sometimes accompanied by multiple congenital abnormalities, but not “often”. What is striking is how frequently an NTD is an isolated defect. Martin et al. studied 991 liveborn and stillborn infants with an NTD in Utah (1940 to 1979) and found only 6% had other congenital abnormalities not part of the NTD field of defects. Also, Khoury et al. found in a nationwide birth defects surveillance system in the USA, 1970 to 1978, just 12% (1141 cases) of 8206 NTD had multiple congenital malformations.

(4) A number of studies have shown that persons with NTD as a whole do not have chromosome abnormalities. For example, in the study of Khoury et al. mentioned above, only 46 out of 8206 (0.56%) cases of NTD had a chromosome anomaly. Some specific chromosome abnormalities are associated with neural tube defects, among other abnormalities, but this group is considered to be of different aetiology to the multifactorial form of NTD.

(5) This is just not true.

(6) Certainly there are epidemiological factors of high risk in mothers with NTD, such as socioeconomic status, month of birth, etc, but to assume that all of the at risk factors lead to overripeness of the ovum is a ‘leap of faith’.

(8) Many of the complications observed—those