Between 700-900 babies are born in Britain each year with Neural Tube Defects, (NTDs), where the nervous system of the fetus has failed to develop normally. Most of these babies die in the first few weeks of life; others are permanently handicapped.

This Factsheet:
• summarises the evidence that supplements of folic acid given to women around the time of conception dramatically reduce the chances of NTDs
• outlines the problems that governments must weigh-up when considering how scientific studies should influence health care policies
• gives examples of typical exam questions on experimental design

There are two major types of NTDs:
• spina bifida — where the posterior (caudal) neural tube of the fetus fails to close
• anencephaly — where the anterior (cranial) neural tube of the fetus fails to close. Parts of the brain, spinal cord, nerve roots and meninges therefore fail to form. This condition is always fatal.

Scientists still do not understand the causes of NTDs but there appear to be both genetic and environmental factors involved.

**Fig.1 Neural groove**

Fig 1. A cross section of the embryo three weeks after conception. The neural groove is in the process of closing.

**Fig.2 Closed neural groove**

Fig.2 shows a cross section of the middle portion of the embryo after the neural tube has closed. The neural tube, which eventually develops into the spinal cord, is now covered by surface ectoderm (later, the skin). The mesoderm will form the spine.

**Fig.3 Developmental and clinical features of the main types of NTDs**

**Fig 3a**

Fig 3a is a dorsal view of a developing embryo, showing a neural tube that is closed in the centre but still open at the cranial and caudal ends. The dotted lines refer to the cross sections shown in Fig 1 and Fig 2. The numbers refer to the region of the neural tube relevant to each defect.
Folic acid
Prof. Richard Smithells, a British paediatrician, first suggested that vitamins may prevent neural tube defects. He conducted a non-randomised controlled trial which showed that taking vitamins several weeks before and during the early weeks of pregnancy was associated with a much lower rate of NTDs in babies.

This raised two possibilities; that folic acid or another vitamin could prevent some cases of NTDs, or that women who chose to take the vitamins were a selected group with a better than average diet.

To clarify matters, the Medical Research Council (MRC) conducted an international, randomised double-blind trial held at 33 centres.

Key Terms
Randomised: Women would be allocated a pill containing folic acid or a pill containing other vitamins on a random basis
Double-blind: neither the women nor the people handing out the supplements knew which were the folic acid pills and which were the non-folic acid pills

Women were allocated, at random, to one of four groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>Folic acid?</th>
<th>Other vitamins?</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>✓</td>
<td>x</td>
</tr>
<tr>
<td>B</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>C</td>
<td>x</td>
<td>✓</td>
</tr>
<tr>
<td>D</td>
<td>x</td>
<td>✓</td>
</tr>
</tbody>
</table>

The trial involved 1,800 women with approximately equal numbers of women in each group. The mean ages of women was the same in each group as were their previous pregnancy histories. All of the women chosen were judged to be high risk of NTD because they had experienced NTDs or similar in previous pregnancies.

The results were unequivocal: folic acid supplements reduced the incidence of NTDs by 72 per cent. The other vitamins had no protective effect. The scientists predicted that if folic acid could prevent women having a second NTD pregnancy, it would also help prevent a first one.

Hungarian Study
In 1993 a large-scale randomised blind - trial into whether folic acid could reduce NTDs and congenital malformations was conducted in Hungary. Just under 4800 women, most of whom were childless, volunteered to take part. Women planning a pregnancy were given either:

- a multivitamin tablet containing 12 vitamins, including 0.8 mg of folic acid; 4 minerals; and 3 trace elements

Or

- a trace-element tablet containing copper, manganese, zinc, and a very low dose of vitamin C

All the women took a tablet daily for at least one month before conception and until the date of the second missed menstrual period or later.

Pregnancy was confirmed in 4753 women.

Table 1 Characteristics and outcome of the study

<table>
<thead>
<tr>
<th></th>
<th>Group given vitamins including folic acid</th>
<th>Group given trace elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants with confirmed pregnancy</td>
<td>2420</td>
<td>2333</td>
</tr>
<tr>
<td>No. of evaluated pregnancies</td>
<td>2394</td>
<td>2310</td>
</tr>
<tr>
<td>Mean age (and SD)</td>
<td>26.8 ± 3.4</td>
<td>26.7 ± 3.3</td>
</tr>
<tr>
<td>No. of pregnancies with known outcome</td>
<td>2104</td>
<td>2052</td>
</tr>
<tr>
<td>Termination after prenatal diagnosis of defects</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>No. of stillbirths</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>No. of live births</td>
<td>2090</td>
<td>2032</td>
</tr>
<tr>
<td>Neural tube defects</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Down’s Syndrome</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Congenital hydrocephalus</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular malformation</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>


Typical Exam Question
(a) What is the aim of a double-blind trial (1)
(b) Why was it important to ensure that the women in each group had similar pregnancy histories?(1)

Markscheme
(a) prevent bias;
(b) ensure fair test / problems during earlier pregnancies might affect the likelihood of future problems;

Typical Exam Question
(a) Explain the term “randomised blind-trial” (2)
(b) Identify two ways in which the scientists attempted to achieve a fair test (2)

Markscheme
(a) Women were allocated either the vitamin tablet or the trace element tablet in a random way;
(b) Women didn’t know which tablet they were being given;

Again, the conclusions were clear: The risk of neural - tube defects and malformations is decreased in women who take folic acid or multivitamins containing folic acid during the periconceptional period i.e. around the time of conception.
Implications for governments?
Following the Hungarian study, many countries began advising women to take folic acid supplements before they conceived.

Fig. 4 shows how the incidence of NTD changed in three countries before and after widespread advice to do this.

**Fig 4. Changing incidence of NTDs**

Which of the following statements are valid?
- The advice to take folic acid supplements has reduced the incidence of NTDs
- The advice had the most dramatic effect in Ireland
- The advice was initially ignored in Norway

As you probably realized, this data is insufficient to validate these statements
- we simply don’t know whether women in the three countries heard or acted upon the advice
- we have no data on actual folic acid consumption
- the incidence of NTD was declining in England and Wales (slightly) and Ireland before the advice was given
- the incidence of NTD in Norway increased in the two years after the campaign
- The declining incidence of NTDs in Ireland could be due to other factors – improved living standards or overall diet, or an increase in screening and abortion, for example

**Typical Exam Question**

Low intake of folic acid in pregnant women’s diet is known to be a major risk factor for NTDs. Explain the term risk factor. (1)

Folic acid for everyone?
An alternative way to reduce the risk of NTD is to add folic acid to everyone’s food. In 1996 the US Government ruled that folic acid must be added to flour and other cereal products. Table 2 shows the incidence of NTDs in the USA before and after the ruling.

**Table 2**

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence of NTD/10,000 live births</th>
<th>Total no. of NTDs in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995-6</td>
<td>10.6</td>
<td>4130</td>
</tr>
<tr>
<td>1999-2000</td>
<td>7.6</td>
<td>3020</td>
</tr>
</tbody>
</table>

Thus, adding folic acid to flour appeared to cause a reduction in NTDs of about 30%.

Research has since shown that the addition of folic acid to flour in the US has resulted in a substantial increase in blood plasma folate concentration throughout the population. All countries that have ordered compulsory addition of folic acid to flour have seen significant reductions in the incidence of NTDs. The UK currently requires the fortification of flour with calcium, thiamine, iron and niacin and the fortification of margarines with vitamin A and vitamin D. But the government are still considering the issue of whether to add folic acid. The arguments for:
- Reduced distress and NTDs
- Reduced costs for NHS
- A possible reduction in the incidence of heart disease
- As many as 50% of pregnancies are unplanned; women with unplanned pregnancies are unlikely to be taking folic acid supplements
- The UK has a higher incidence of NTDs than many other European countries

**Fig 5. NTD incidence**

However, the government also has to assess the risks:
- Folic acid can interfere with drugs taken for epilepsy
- It masks vitamin B12 deficiency in older people, which could result in nerve damage
- There is some evidence that high doses of folic acid may increase the incidence of some types of cancer
- Loss of personal autonomy

The issues are complex!

**Further Research**
http://www.food.gov.uk/healthiereating/folicfortification/

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