Pregnant and Healthy

- Selenium supplementation reduces the risk of pre-eclampsia and protects against postpartum depression
- Selenium reduces the risk of postpartum thyroid gland inflammation
- Supplementation with 5 mg folic acid would reduce the risk of a neural tube defect by 85 percent
- Supplementation with vitamin D3 during pregnancy lowers the risk of a premature birth
Selenium in general

- Selenium is essential for the thyroid gland
- Selenium deficiency impairs the thyroid gland and increases the prevalence of a thyroid gland inflammation
- Suboptimal selenium supply in Europe
- Selenium and iodine – the essential duo for the thyroid gland

Selenium deficiency in pregnant women

- Selenium deficiency increases the risk of pre-eclampsia or premature birth
- Selenium supplementation reduces the risk of pre-eclampsia and protects against postpartum depression
- Lower selenium status during pregnancy negatively influences the development of the baby

Pregnancy, thyroid gland and selenium

- Increased risk of thyroid gland malfunctions during the pregnancy
- Thyroid gland malfunctions have far-reaching consequences for mother and child
- Negative impact of a hypofunctional thyroid on the brain development of the baby
- Risk screening records only 20 percent of the affected cases
- Selenium reduces the risk of postpartum thyroid gland inflammation
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<th>Increased folic acid requirement during pregnancy</th>
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<td>Folic acid deficiency increases the risk of a defective neural tube</td>
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### Folic acid

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<td>The body forms most vitamin D₃ itself</td>
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</table>

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</table>
Selenium is essential for the thyroid gland

Selenium is an essential trace element. In the body, the thyroid gland is one of the organs richest in selenium.\(^1,2\) The high selenium requirements of the thyroid gland are based on the so-called selenium proteins. In the meantime, 25 different selenium protein genes are known. Numerous selenium proteins are indispensable for the thyroid gland function. They activate the thyroid gland hormones (deiodinase)\(^1,3\) and protect the thyroid gland from oxidative stress (glutathione-peroxidase)\(^1,4\).
Selenium deficiency impairs the thyroid gland

If the body absorbs too little selenium, this has a direct impact on the production of selenium proteins. If insufficient deiodinase is available for the thyroid gland, the conversion of inactive T4 into active T3 is disturbed. The relationship of T4 to T3 therefore increases in the serum. This can lead to malfunctions in the thyroid gland. The reduced production of glutathione-peroxidase leads to increased oxidative stress, since hydrogenperoxide is no longer sufficiently decomposed into water. Oxidative stress damages the thyroid gland tissue while simultaneously predisposing towards inflammation of the organ and disorders of the thyroid gland function (Fig. 1).
Selenium deficiency significantly increases the prevalence of thyroid gland inflammation

A total of 6,152 participants were involved in a large epidemiological study. In regions with adequate selenium soils, the median selenium concentration was almost twice as high compared to regions with selenium-poor soils (103.6 µg/l vs. 57.4 µg/l selenium in serum; p = 0.001). This large difference in the selenium status also influenced the frequency of pathological thyroid gland disorders. While only 18.0 percent of the participants suffered from thyroid gland disorders in regions with soils with adequate selenium, the prevalence significantly increased to 30.5 percent in regions with soils poor in selenium (p < 0.001).
Germany is a selenium-deficient country

Germany – like most of its neighboring countries – is poor in selenium. The mean selenium content of German tillage land lies between 0.074 mg/kg and 0.194 mg/kg. The optimal selenium content is clearly higher at 0.6–4.0 mg/kg. In comparison, the selenium content of the soils ranges from 0.1 mg/kg and 5.32 mg/kg in the USA.

Owing to the earth’s historical geological development, German soils contain little selenium. Since plants can only take up selenium from the soil, cereals in Germany, for example, contain only about a tenth of the selenium quantities compared to American cereals. In Germany and indeed all of Europe, it is therefore difficult to sufficiently cover the selenium requirements by way of food intake.

Optimal selenium content: 0.6–4.0 mg/kg
The selenium supply in Europe is suboptimal

The latest numbers from a large-scale European study conducted in 2015 have confirmed the suboptimal supply of selenium for the people in western Europe. In addition, there are differences between Central, Southern and Northern Europe (e.g. for women 79.0 vs 81.0 vs. 93.1). In Europe, the mean selenium concentration in the serum is 85.6 µg/l and thus almost within the reference range, which begins at 80 µg/l selenium in the serum (Fig. 2). In Germany, the serum selenium concentration on the average does not reach the reference range of 80 – 120 µg/l with 74.3 µg/l for men and 73.2 µg/l for women (Fig. 3). As most countries don't have an official reference range for selenium, the reference range of Germany is used to define selenium deficiency.

The daily quantity of selenium recommended by the German Association for Nutrition (DGE) is 70 µg for men and 60 µg for women, based on weight. For nursing women, an increased daily intake of 75 µg is recommended, since 12.5 µg selenium per day are required for breastfeeding. In Germany, the average recorded daily quantity of selenium intake for women is 30 ± 16 µg.
Reference range of selenium in Germany

<table>
<thead>
<tr>
<th></th>
<th>Reduced</th>
<th>Healthy reference range</th>
<th>Start of toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μg/l</td>
<td>&lt;100</td>
<td>100–140&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥1,087&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>μmol/l</td>
<td>&lt;1.3</td>
<td>1.3–1.8&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥13.8&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>μg/l</td>
<td>&lt;80</td>
<td>80–120&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≥900&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>μmol/l</td>
<td>&lt;1.0</td>
<td>1.0–1.5&lt;sup&gt;3&lt;/sup&gt;</td>
<td>≥11.4&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1) Summary of selenase<sup>®</sup> product characteristics  
2) Yang et al. J Trace Elem Electrolytes Health Dis 3 (1989) 123-130  
3) Calculated from 1) and 2)

Fig. 2

Suboptimal selenium supply for women in Europe


Fig. 3
Selenium and iodine – an essential duo for the thyroid gland

Iodine is essential for the production of thyroid gland hormones. An iodine deficiency can lead to a thyroid gland inflammation. Thanks to comprehensive iodination, primarily of table salt, it has been possible to clearly reduce iodine deficiency in the world. On average, Germany's iodine status is in the lower middle range of the iodine intake recommended by WHO.\[12\] Consequently, Germany is no longer an iodine-deficient area, but is also not yet sufficiently supplied.

An adaptation of the selenium supply to the increased oxidative stress of an iodine deficiency can protect the thyroid gland

Iodine deficiency increases oxidative stress (ROS) in the thyroid gland, and selenium proteins are necessary for its breakdown, because selenium-dependent glutathione-peroxidase reduce ROS to water and thus protect the thyroid gland tissue from oxidative damage.\[13,14\] If there is both a selenium deficiency as well as an inadequate iodine supply, the negative effects cumulate. With a low selenium status, the thyroid gland is oxidatively attacked despite an optimal iodine supply. The equilibrium between selenium and iodine is therefore crucial for a healthy thyroid gland (Fig. 4).
The thyroid gland requires an equilibrium between selenium and iodine

<table>
<thead>
<tr>
<th>Selenium</th>
<th>Iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential for thyroid gland metabolism</td>
<td>Essential component of the thyroid gland hormones</td>
</tr>
<tr>
<td>Recommended daily consumption: 70 µg per day</td>
<td>Recommended daily consumption: 150 µg per day</td>
</tr>
<tr>
<td>Protects the thyroid gland from oxidative stress</td>
<td>Iodine surplus can promote oxidative stress</td>
</tr>
</tbody>
</table>

Fig. 4
Selenium deficiency increases the risk of pre-eclampsia

Pre-eclampsia is a pregnancy disorder that accompanies high blood pressure. It occurs in about two to seven percent of all pregnancies and is one of the most frequent causes for mortality and morbidity of mother and child in the western world. Together with other pregnancy disorders associated with high blood pressure, they increase the perinatal mortality by five-fold.\textsuperscript{[15, 16]}

A global study investigated the data of almost 6.5 million births.\textsuperscript{[17]} The global incidence of pre-eclampsia was 3.45 percent and thus more than 220,000 births. With increasing plasma selenium concentration a reduction in preeclampsia incidence was found. A comparison of the pre-eclampsia incidence for a cut-off value of 95 µg/l showed that a serum selenium concentration below this value significantly increases the pre-eclampsia frequency (p<0.0007) (Fig. 5).

Why 95 µg/l selenium in serum? This is the selenium concentration in the serum where selenoprotein glutathione peroxidase 1 is considered to reach maximum activity\textsuperscript{[18]} and an adequate selenium supply can be assumed. At the same time the results mean that no selenium deficiency must be present in order to increase the risk of a pre-eclampsia, since in Germany, selenium deficiency is only diagnosed for less than 80 µg/l\textsuperscript{[19]} selenium in serum (Fig. 6).
Selenium deficiency in pregnant women

Increased pre-eclampsia incidence at low selenium status

![Bar chart showing increased pre-eclampsia incidence at low selenium status](image)


*Fig. 5*

Increased risk of pre-eclampsia in the German reference range

![Graph showing increased risk of pre-eclampsia in the German reference range](image)

Derived from Figure 5 and Summary of product characteristics

*Fig. 6*
Selenium deficiency increases the risk of a premature birth

In a prospective Dutch study, the pregnancy of almost 1,200 women was investigated. In this study, 60 pregnant women (5.3 percent) had a premature birth. The serum selenium concentration in the 12th pregnancy week was significantly lower for women with a premature birth (75.8 µg/l ± 11.1 µg/l vs. 80.5 µg/l ± 10.3 µg/l; p = 0.001). Women with the lowest selenium values had twice as high risk of a premature birth (OR 2.18; 95% CI 1.25–3.77).

Selenium supplementation reduces the risk of a pre-eclampsia

In the so-called SPRINT study (double-blind, placebo-controlled pilot study), 230 pregnant women were supplemented with either 60 µg selenium per day or with a placebo. The study was conducted in Great Britain. At the beginning of the study, the participants showed a median selenium concentration of 104.2 µg/l selenium in the whole blood. Pregnant women were thereby found on the limit of selenium deficiency (<100 µg/l). The selenium supplementation (on excluding non-compliers) reduced the risk of pre-eclampsia or high blood pressure by 70 percent (OR 0.3; 95% CI 0.09–1.00; p = 0.049).
Selenium deficiency in pregnant women

Selenium supplementation protects against postpartum depression

Between 10 and 15 percent of women suffer from postpartum depression. Aside from a genetic predisposition, environmental, social, psychological and biological factors are among the risk factors. A biological factor is an inadequate diet. In the so-called APrON study, 475 participants were investigated on the relationship between postpartum depressions based on the “Edinburgh Postpartum Depression Scale” (EPDS) and their micronutrient intake.

Twelve percent show an EPDS ≥ 10 and therefore suffered under postpartum depression. At low EPDS the selenium intake was significantly higher (p = 0.0015). To determine the predictive factors for postpartum depression, only the prenatal consumption of selenium above the RDA recommendation (55 µg) could reduce the risk. Per 10 µg selenium, the risk declined by 24 percent (OR 0.76; 95% CI 0.74–0.78; p = 0.019) (Fig. 7). In comparison, the positive effect of social support reduced the risk by 15 percent (OR 0.85; 95% CI 0.74–0.97; p = 0.015).
Higher selenium status during pregnancy positively influences the baby's development

For 750 mothers, the selenium status and the development of their babies was investigated in a prospective cohort study. The children were examined at 1.5 years of age on their mental and psychomotoric development as well as their language understanding and mode of expression. In this study, the selenium concentration was determined in the erythrocytes as a measure of the long-term selenium status. An increase of selenium by 0.50 µg per gram hemoglobin improved language understanding by 3.7 points (SD = 0.5, CI 95%, p = 0.028). For girls, the psycho-motoric development improved by 12 points (SD = 0.9, CI 95%, p = 0.002) (Fig. 8).

A daily dose of 300 µg selenium is no cause for concern for pregnant women

Selenium dosage in pregnancy

Studies have shown that 200 µg selenium per day for pregnant women result in no adverse reactions. According to the EU, a daily dose of 300 µg selenium for pregnant women is also no cause for concern. However, low selenium dosages of under 100 µg were insufficient to achieve an optimal selenium status for pregnant women with selenium deficiency.
Why selenase®?

Caution is needed concerning the form of selenium intake. Only sodium selenite-pentahydrate is approved as an active substance for the manufacture of drug products. Sodium selenite is rapidly and specifically incorporated into selenium proteins in the body. Unrequired sodium selenite is eliminated from the body with the urine. selenase® contains sodium selenite-pentahydrate as the active substance and is approved as a drug product. The active substance is manufactured by biosyn in Germany according to GMP guidelines and is also used for the dietary supplement selenase® 100 XL and selenase® 200 XXL.

Additional selenium forms are approved as dietary supplements – among others, the organic selenium forms selenomethionine and selenium yeast. Selenomethionine is only partially specifically incorporated in the body. The other part is used in a non-specific manner. This process cannot be controlled by the body. On the one hand, the non-specifically incorporated selenium methionine cannot fulfill its tasks. On the other hand, it can lead to accumulation. Selenium yeast also consists mainly of selenomethionine. Therefore sodium selenite is recommended to improve the selenium status.

---

**Fig. 8**

<table>
<thead>
<tr>
<th>Point scale</th>
<th>Language understanding</th>
<th>Psycho-motoric development (girls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>3.7</td>
<td>p = 0.028</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>p = 0.002</td>
</tr>
<tr>
<td>6</td>
<td></td>
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<td>12</td>
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<tr>
<td>14</td>
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</table>

_Improvement of infant development for each 0.5 µg selenium/gram hemoglobin_

## Pregnancy, thyroid gland and selenium

### At a glance

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<th>Details</th>
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</tr>
<tr>
<td>Thyroid gland disorders have far-reaching consequences for mother and child</td>
<td></td>
</tr>
<tr>
<td>Risk screening recorded only 20 percent of those affected</td>
<td></td>
</tr>
<tr>
<td>Selenium supplementation protects against postpartum depression</td>
<td></td>
</tr>
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<td>Selenium reduces the risk of postpartum thyroid gland inflammation for TPO antibody positive pregnant women</td>
<td></td>
</tr>
<tr>
<td>Selenium reduces postpartal TPO antibody titer</td>
<td></td>
</tr>
<tr>
<td>Selenium arrests postpartum deterioration of thyroid gland inflammation</td>
<td></td>
</tr>
</tbody>
</table>
Pregnancy has large impact on the thyroid gland

The entire female body is exposed to great additional stresses during pregnancy – also the thyroid gland. The small organ works at full speed to meet the changed circumstances in the body. This can lead to thyroid gland malfunctions, which can have far-reaching consequences for mother and child if untreated.

The thyroid gland grows in the course of pregnancy: in countries with an adequate iodine supply, it increases by about ten percent – in iodine-deficient regions even by 20 to 40 percent. The distribution volume of thyroid gland hormones increases and in addition the thyroxine metabolism accelerates. Another important alteration in the metabolism of the thyroid gland is the increased demand for thyroid gland hormones: The increased production of thyroid gland hormones as well as an increase in iodine elimination causes the iodine requirement to increase (Fig. 9).
Increased risk of thyroid gland disorders during pregnancy

For women with iodine deficiency, the physiological changes in the first trimester of pregnancy can show normal thyroid gland function, but lead to a hypofunctional thyroid in the further course of pregnancy. A clinical hypofunctional thyroid occurs in about 0.4 percent of cases. The frequency of subclinical hypothyroidism is clearly higher at three to ten percent. For many affected women, the hypofunctional thyroid remains permanently. An autoimmune thyroid gland inflammation is one of the most frequent causes.

Somewhat more seldomly, pregnant women develop a clinical hyperthyroidism (0.1 to 0.4 percent). Subclinical hyperthyroidism is indicated in about four percent of pregnant mothers. Basedow disease and gestation hyperthyroidism are among the frequent causes. Up to 15 percent of pregnant women are thus affected by thyroid gland disorders (Fig. 10).

Thyroid gland disorders in pregnant women

- Hypofunctional thyroid
  - Subclinical: to 10%
  - Clinical: 0.8%

- Hyperthyroidism
  - Subclinical: 4%
  - Clinical: to 0.4%

Based on

Fig. 10
Risk factor TPO antibodies

About 10–20 percent of pregnant women are thyroid peroxidase (TPO) positive and euthyroid. This means that the thyroid gland functions normally.[29] Half of pregnant women with increased TPO antibodies developed a postpartum thyroid gland inflammation (Fig. 11). Among these 40 percent of women with a postpartum thyreoiditis develop a permanent hypofunctional thyroid.[29] The prevalence of a postpartum thyroid gland inflammation with 7.2 percent is clearly lower for TPO antibody negative pregnant women.[29]

Antibody risk factor

![Antibody risk factor diagram](#)


Fig. 11
Thyroid gland disorders have far-reaching consequences for mother and child

If thyroid gland disorders during pregnancy are not recognized and treated in a timely manner, they can have far-reaching consequences for mother and child. This applies both for thyroid gland hypofunction as well as hyperfunction. Both increase the risk of a spontaneous miscarriage as well as premature birth and stillbirth. The risk of pre-eclampsia also increases with a thyroid gland dysfunction.

A hypofunctional thyroid could impair the cognitive development of the child. This can lead to congenital cretinism with small stature, deafness and neuropsychological disabilities. According to screening studies, the birth and healthy development of annually around 3,500 children in Germany is at risk from a thyroid gland dysfunction.

Heart congenital malformation can be the consequence of hyperthyroidism in the mother.

The risks are not only increased for pregnant women with thyroid gland disorders. Also euthyroid pregnant women with a subclinical thyroid gland inflammation are already at a higher risks.
### Possible consequences of thyroid gland disorders for mother and child

#### Hyperthyroidism

<table>
<thead>
<tr>
<th>For the mother, increased risk of</th>
<th>For the child, increased risk of</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spontaneous miscarriage as well as premature birth or stillbirth</td>
<td>• Low birth weight</td>
</tr>
<tr>
<td>• Cardiac insufficiency</td>
<td>• Malformations, e.g. of the heart</td>
</tr>
<tr>
<td>• Pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>• Thyrotoxic crisis (very rare)</td>
<td></td>
</tr>
</tbody>
</table>

#### Hypofunctional thyroid

<table>
<thead>
<tr>
<th>For the mother, increased risk of</th>
<th>For the child, increased risk of</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Spontaneous miscarriage as well as premature birth and still birth</td>
<td>• Perinatal disease and mortality</td>
</tr>
<tr>
<td>• Increased blood pressure during pregnancy</td>
<td>• Impairment of cognitive development</td>
</tr>
<tr>
<td>• Pre-eclampsia</td>
<td>• Congenital cretinism with deafness and neuropsychological impairments</td>
</tr>
<tr>
<td>• Placental abruption</td>
<td>• low birth weight</td>
</tr>
<tr>
<td>• Anemia</td>
<td></td>
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</tbody>
</table>


Negative impact of hypofunctional thyroid on the brain development of the baby

Haddow et al. could already show in 1999 that with an untreated hypofunctional thyroid in the mother, the risk of the child having a reduced IQ significantly increases (full-scale IQ scores 7 points lower; \( p = 0.005 \)).\[^{[31]}\] 19 percent of the children showed an IQ of \( \leq 85 \). It was only five percent in the control group.

But not only clinical hypothyroidism has an impact on the brain development of the baby. Subclinical hypofunctional thyroid function already has this effect, as shown in a study from 2010 (Fig. 13).\[^{[32]}\] Both the IQ as well as the motoric scores were significantly lower than of the control group (mean BSID I intelligence score: 8.9 points lower \( [p = 0.008] \); mean motor score: 10.0 points lower \( [p < 0.001] \)).

In this study, the values were also determined for babies between 25 and 30 months of euthyroid mothers with increased TPO antibodies. The mean IQ values were even reduced by 10.6 points \( (p = 0.001) \). The values for the motor functions were 9 points lower \( (p < 0.001) \).

Another study could demonstrate the relationship between maternal thyroid gland function and the development of the child.\[^{[33]}\] In the so-called Generation R study, 3,139 children age 2.5 and 3 years as well as their mothers were investigated. Increased TPO antibody titer in the mother leads to an increased risk of Attention Deficiency Disorder or hyperactivity (odds ratio = 1.77; 95% CI 1.15–2.72; \( p = 0.01 \)). The authors point out that the impact of the results cannot be evaluated, since to date there is no specific treatment for TPO antibody positive pregnant women with normal thyroid gland function.
Changed thyroid gland parameters in the mother have a negative impact on the development of the baby

<table>
<thead>
<tr>
<th>Change in evaluation compared to the control group</th>
<th>Subclinical hypofunctional thyroid function</th>
<th>Euthyroid women with increased TPO antibody titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>Motor functions</td>
<td>IQ</td>
</tr>
<tr>
<td>-8</td>
<td></td>
<td>-8</td>
</tr>
<tr>
<td>-8.5</td>
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<td>-9</td>
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<td>-10</td>
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<td>-10</td>
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<td>-10.5</td>
<td></td>
<td>-10.5</td>
</tr>
<tr>
<td>-11</td>
<td></td>
<td>-11</td>
</tr>
</tbody>
</table>


Fig. 13
Risk screening recorded only 20 percent of the affected

A study by Chang et al. (2011) concluded that general screening is appropriate, since risk-oriented screening only diagnosed 20 percent of the women thyroid gland problems. Another study could confirm this result. The German maternity policy guidelines hitherto provide no general thyroid gland screening. The thyroid gland is therefore not routinely investigated for malfunctions, but only if there is a specific suspicion. The current recommendations of the European Thyroid Association (ETA) from 2014, however, recommend the universal screening of pregnant women.

The screening should at least encompass the TSH level, ideally also the TPO antibody titer. Screening at the gynecological determination of pregnancy is recommended, since the brain development of the baby already begins at a very early point in time and is dependent on a supply of maternal thyroid gland hormones.

On deviating TSH values, a measurement of the T4 and T3 values, a determination of the TR and TPO antibodies as well as an ultrasound examination is appropriate. If there are abnormal results, the physician should regularly examine the thyroid gland values (Fig. 14). The European Thyroid Association recommend the universal screening of pregnant women.
Recommendations for thyroid gland screening for pregnant women

**Pregnancy**

- Screening for TSH values and TPO antibody
  - Normal findings
  - No treatment is required
  - Increased TPO antibody and/or deviating values
    - Measurement of the thyroid gland hormones T3 and T4
      - **Hyperthyroidism**
        - Controls:
          - During the pregnancy:
            - TSH every four weeks
            - T3 and T4 every four weeks
            - Determination of the TR antibody (TSH antibody) in the 22nd to 28th week of pregnancy
          - Until three months after birth:
            - every four to six weeks TSH, T3 and T4
      - **Hypofunctional thyroid**
        - Controls:
          - During pregnancy:
            - TSH every four to six weeks
          - For women with autoimmune thyroid disorder (positive TPO antibody) until one year after birth:
            - TSH four weeks after delivery, thereafter every three months

Selenium therapy for pregnant women with thyroid gland inflammation

In a prospective, randomized, placebo-controlled study, 2,143 pregnant women with normal thyroid gland function were investigated. 7.9% of the pregnant women were TPO-AK positive (Fig. 15). During the pregnancy and the postpartum period, 77 TPO-AK positive women were supplemented with 200 μg selenium per day, while 74 TPO-AK positive women received a placebo. For the control, both groups were compared with 81 TPO-AK negative pregnant women.


Fig. 15
Selenium reduced the risk of a postpartum thyroid gland inflammation for TPO antibody positive pregnant women

The study by Negro et al. confirmed that about 50 percent of the TPO antibody positive pregnant women develop postpartum thyroid gland inflammation (48.6 percent).\cite{29} In the selenium-supplemented group, the proportion was reduced by 20 percent to 28.6 percent (vs. 48.6 %; p<0.01) (Fig. 16). Also the development of a permanent hypofunctional thyroid was significantly reduced by selenium therapy from 20.3 percent to 11.7 percent (vs. 20.3 %; p<0.01).

Positive effect of a selenium supplementation for TPO-AK(+) pregnant women


Fig. 16
Selenium arrests postpartum deterioration of thyroid gland inflammation

Negro et al. moreover investigated the echogenicity of the thyroid gland of pregnant women during pregnancy (at 10 week gestation) at birth and after 12 months. At the end of the postpartum period, most participants in the selenium-supplemented group had no or only mild (grade 0-1) thyroid gland inflammation (72.7% vs. 55.4%). However, the placebo group showed increased rates of moderate or advanced (grade 2-3) thyroiditis (44.6% vs. 27.3%; p < 0.01) (Fig. 17). Furthermore, the echogenicity of the thyroid gland significantly worsened only in the placebo group (p < 0.05).

Treatment of pregnant women with thyroid gland inflammation

The treatment of thyroid gland dysfunction in pregnancy is dependent on the form and degree of severity (Fig. 18). A selenium therapy with 300 µg selenium in the form of sodium selenite is possible during pregnancy, and free of lactation problems. According to the EU, a daily intake of 300 µg selenium is also possible for pregnant women without any side effects. A combination of selenium with L-thyroxine or antithyroid agents is not problematic.

Modified according to


Fig. 18
Folic acid

At a glance

<table>
<thead>
<tr>
<th>Increased folic acid requirement during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid deficiency increases the risk of a defective neural tube</td>
</tr>
<tr>
<td>Supplementation with 5 mg folic acid would reduce the risk of a neural tube defect by 85 percent</td>
</tr>
<tr>
<td>Recommended for several risk groups</td>
</tr>
<tr>
<td>Time period: 12 weeks from conception until end of the first trimester</td>
</tr>
</tbody>
</table>

Increased folic acid requirement during pregnancy

The daily folic acid requirements for women is 300 µg (German Association for Nutrition [DGE]). A investigation of 1,341 women in the framework of the Baby Care Program of the statutory health insurance providers showed that 74 percent of the women show a daily folic acid intake that is below 70 percent of the desired value (< 210 µg/day), whereas 34 percent of the women attain not even 50 percent of the recommended daily quantity (< 150 µg/day).

For pregnant women, the daily folic acid requirements increases to 550 µg (DGE). 21,433 pregnant women in the Baby Care Program were investigated for their folic acid status. Consequently, for 94 percent of the pregnant women, the value was below 385 µg folic acid per day (70% of the desired value). Also half of the recommended daily requirement of folic acid is not attained by 70 percent of the pregnant women examined (Fig. 19).
Folic acid deficiency for pregnant women in Germany is increased (Baby Care Program)

Fig. 19

Folic acid deficiency increases the risk of neural tube defects

Neural tube defects (NTD) are an important cause of mortality in newborns. Approximately 0.5–8 infants per 1,000 births are affected. Worldwide, about 300,000 newborns are afflicted with neural tube defects.\(^{38}\)

The risk of a neural tube defect increases at a folic acid concentration below 700 nmol/l in the red blood corpuscles threefold compared to values with 900 nmol/l.\(^{39}\) The folic acid concentration of 900 nmol/l in the red blood corpuscles is regarded as an optimal value in order to minimize the risk of neural tube defects.
Supplementation with 5 mg folic acid would reduce the risk of a neural tube defect by 85 percent

Already since the 1960s, it is known from epidemiological studies that folic acid supplementation reduces the risk of a neural tube defect. The guidelines in Germany recommend supplementation with 400 µg folic acid per day for women that are pregnant or want to be.

A Canadian study, however, showed that despite enrichment of foods with folic acid and supplementation with prenatal multi-vitamins, 40 percent of women in child-bearing age and 36 percent of pregnant women did not achieved the optimal folic acid concentration of 900 nmol/l in red blood corpuscles.

400 µg folic acid per day additionally would reduce the risk of a neural tube defect by about 36 percent. An increase of the supplement to 5 mg per day would even reduce the risk by 85 percent (Fig. 20).


Fig. 20
For whom are five mg folic acid per day recommended?

A supplement of five mg per day is recommended for women who are or want to be pregnant (Fig. 21).[^41] Women with

- neural tube defects in the family or in earlier pregnancies
- specific genotypes that are associated with an increased risk of neural tube defects
- diseases with absorption malfunctions (i.e. Crohn disease)

- adiposity with a BMI > 35 kg/m²
- diabetes
- inadequate compliance (therapy loyalty)
- problematic lifestyle (smoking)

Women who take anti-epileptic medications or folic acid antagonists (methotrexat, sulfonamides)


Fig. 21
Over which time period are five mg folic acid per day recommended?

A supplementation with five mg folic acid per day is recommended 12 weeks before conception until the end of the first trimester\[^{41, 42}\] (Fig. 22). In humans, the neural tube is formed between the 19th and 28th day of pregnancy. Folic acid supplementation is therefore primarily important in the first part of pregnancy.

Recommended consumption time period: 12 weeks before conception until end of the first trimester

Is there the risk of pernicious anemia for high-dose folic acid supplementation?

Until now, it was recommended to eliminate any risk of vitamin B\(_{12}\) deficiency before taking high-dose folic acid, since the folic acid supplementation could mask pernicious anemia. However, this could not be demonstrated.\[^{42}\] According to the recommendation of the latest Canadian Guideline of 2015, it is therefore not necessary to test for a vitamin B\(_{12}\) deficiency before starting folic acid supplementation.\[^{42}\] It remains to be seen whether this recommendation will also prevail in Germany.
Dosage recommendation for folic acid during the pregnancy

<table>
<thead>
<tr>
<th>Recommended dosing [mg]</th>
<th>Previously before conception</th>
<th>12 weeks before conception</th>
<th>End of the 12th week</th>
<th>Remaining pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
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</tr>
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<td>5</td>
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</tbody>
</table>

Based on


Fig. 22

Does cancer risk increase with folic acid supplementation?

Based on a few individual studies, it has recently been argued that supplementation with folic acid increases cancer risk.\[43\] Primarily supra-physiological quantities were under suspicion.\[43\] The results of epidemiological studies were not unambiguous until now.\[44\] A large meta-analysis which analyzed 13 randomized studies with 50,000 participants could demonstrate no increase in general cancer risk or for any specific cancer type.\[45\]

In a recently published population-based cohort study, the data of 429,000 women who had taken folic acid supplements before and during pregnancy was analyzed and compared to a group without additional folic acid intake.\[44\] The folic acid supplementation had no impact on the cancer risk – neither for the mother nor the child.\[44, 46\]

Therefore the folic acid supplementation guidelines continue to be recommended for women who are pregnant or want to be.
Vitamin D3

At a glance

98 percent of pregnant women have a vitamin D3 deficit during winter

Increased risks for mother and child with vitamin D3 deficiency

Optimal vitamin D3 supplementation: daily 4,000 I.E.

The body forms most vitamin D3 itself

Vitamin D3 has a special position among the vitamins. It is only supplied by food to 10–20 percent. The body forms 80–90 percent of vitamin D3 with the help of sunlight itself. One should therefore expect that vitamin D3 deficiency in Germany, at least in the summer, should not present a problem.

In 2015, the vitamin D3 status of Germans was investigated in a large-scale study (n=6,995). [47] 61.6 percent show a value below 20 ng/ml 25-Hydroxy vitamin D3, and thus had a vitamin D3 deficiency. For 30.2 percent of Germans, the 25-hydroxy vitamin D3 concentration was even below 12 ng/ml (Fig. 23). This corresponds to a serious vitamin D3 deficit. Only 11.8 percent of the participants showed optimal vitamin D3 status (≥ 30 ng/ml).

Up to 98 percent of pregnant women show a vitamin D3 deficit during winter

How does it look with the vitamin D3 supply of pregnant women? Within the scope of a study conducted in 2013, 261 blood samples of pregnant women and 328 samples of umbilical cord blood were investigated. [48] In the winter months, 98 percent of the pregnant women and 94 percent of the umbilical cord blood samples showed a vitamin D3 deficiency (<20 ng/ml 25-hydroxy vitamin D). The values subsided in the summer months to 49 percent for the women and 35 percent for the umbilical cord blood samples (Fig. 24).
Serious vitamin D₃ deficit for almost a third of Germans

![Vitamin D status chart]


Fig. 23

98 percent of pregnant women have a vitamin D₃ deficiency during winter (<20 ng/ml 25-hydroxy-vitamin D₃)

![Prevalence chart]


Fig. 24
Increased risks for mother and child from vitamin D₃ deficiency

In order to determine the vitamin D₃ status, the concentration of 25-hydroxy vitamin D₃ – a hormone precursor – in the blood is measured. A 25-hydroxy vitamin D₃ concentration of less than 20 ng/ml is considered a vitamin D₃ deficiency (Fig. 25).

A lower maternal vitamin D status is meanwhile associated with increased risk of pre-eclampsia, pregnancy diabetes and bacterial vaginosis. For the babies of affected mothers, an increased risk of reduced bone mineral content, respiratory infections and wheezing could be determined (Fig. 26). A Cochrane analysis could demonstrate that supplementation during pregnancy reduces the risk of a premature birth (RR 0.36; 95% CI 0.14–0.93), low birth weight (<2,500 g) (RR 0.40; 95% CI 0.24–0.67) and head circumference at birth (RR 0.43; 95% CI 0.03–0.83). A trend to reduced risk was moreover shown in this analysis for pre-eclampsia (RR 0.52; 95% CI 0.25–1.05) and size at birth (RR 0.70; 95% CI -0.02–1.43).

Vitamin D₃ barometer

Fig. 25
Vitamin D deficiency increases the risk for mother and child

<table>
<thead>
<tr>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia</td>
<td>Birth weight ↓</td>
</tr>
<tr>
<td>Premature birth</td>
<td>Head circumference ↓</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>Respiratory infection ↑</td>
</tr>
<tr>
<td>Pregnancy diabetes</td>
<td>Bone mineral content ↓</td>
</tr>
<tr>
<td></td>
<td>Size at birth ↓</td>
</tr>
</tbody>
</table>


Fig. 26

Optimal vitamin D₃ supplementation: daily 4,000 I.E.

Which dose of vitamin D₃ is necessary to achieve an optimal vitamin D₃ status that is simultaneously safe for mother and child? In a US-American study, pregnant women were supplemented with different vitamin D₃ doses (400 I.E., 2,000 I.E. or 4,000 I.E. per day).[61] The most effective was supplementation with 4,000 I.E. vitamin D₃ per day. This dosage was moreover safe. No side effects occurred in the study which could be attributed to the vitamin D₃ supplementation. A second study could also demonstrate that in a comparison between a daily dosing of 2,000 I.E. versus 4,000 I.E. vitamin D₃, the greater dose led to significantly more pregnant women reaching an adequate vitamin D₃ status (p < 0.0001).[62] For 4,000 I.E. vitamin D₃ did a trend towards a reduction of diseases during pregnancy become compared to 2,000 I.E. and the control group.

In 2012, the EU moreover increased the upper limit for daily vitamin D₃ intake from 2,000 I.E. to 4,000 I.E. per day for adults, pregnant and nursing women.[63] The Cochrane analysis on supplementation with Vitamin D₃ in pregnancy shows that daily supplementation reached a higher concentration of vitamin D at the end of the pregnancy compared with women who received a single dose of Vitamin D₃.[60]


19. Summary of product characteristics.


27. Glinoer D. Thyroid. 1998 Sep; 8(9): 859-64. Thyroid hyperfunction during pregnancy.


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Pregnant and Healthy

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