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ORIGINAL ARTICLE

Inconsistencies in the management of neonates born to mothers with "thyroid diseases"

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Abstract

Although thyroid medications are frequently prescribed during pregnancy, paediatricians treating the respective neonates often have no information about the underlying maternal thyroid disease, and inconsistencies in postnatal diagnostics may result. We analysed a cohort of 1819 mothers admitted for delivery in 1 year to one hospital. We analysed the pre- and postpartum diagnostics in the mothers, the postnatal diagnostics in the neonates and their postnatal auxological development. Two hundred thirteen mothers (11.7%) had "thyroid disease"; 37 (2.0%) had Hashimoto thyroiditis, seven (0.4%) Graves' disease and 169 (9.3%) "thyroid disease of other origins". One hundred eighty-eight out of 213 (88%, 10.3% of the entire cohort) took levothyroxine. Pre- and postpartum diagnostics of the mothers and postnatal diagnostics of the neonates revealed striking inconsistencies. For example, 39 % of the gynaecologists routinely determined TSH, while only 59% carried out a dosage adjustment for known hypothyroidism. Second specialists were consulted in 86%. Unnecessary postpartum diagnostics were initiated in 19/213 neonates (9%). TRAb was analysed, however, in only one neonate born from the mothers with Graves' disease—a condition in which further diagnostic efforts are mandatory.

Conclusion: Although many pregnant women have thyroid dysfunction, we observed a lack of uniformity in the diagnostic approach of the women and their neonates.

What is Known:
- *Disturbed maternal thyroid function in pregnancy often has an adverse impact on both the mother and the foetus.*
- *Although detailed guidelines for managing impaired maternal thyroid function during pregnancy have been published, their application in clinical practice varies widely.*

What is New:
- *Recommendations for managing the newborn of a mother presenting with thyroid disease of unknown entity are remarkably inconsistent.*
- *This leads to a possible over-diagnosis in general and a potentially life-threatening failure to note neonatal hyperthyroidism requiring rapid treatment.*

Keywords Thyroid dysfunction · Neonatal thyroid function · Graves' disease · Thyroiditis

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Abbreviations

Ab	Antibody
ATA	American Thyroid Association
fT3	Free Triiodothyronine
fT4	Free Tetraiodothyronine
SDS	Standard deviation score
Tg	Thyreoglobulin
TPO	Thyroid peroxidase
TRAb	Thyrotropin (TSH)-receptor-antibodies
TSH	Thyroid-stimulating hormone

Introduction

Thyroid function disorders are among the most common diseases and are frequently observed in pregnant women. International surveys of such women show a prevalence of overt hypothyroidism of 0.1 to 2%, and of subclinical hypothyroidism of 2.5 to 10% [1–3]. The most common reason for acquired hypothyroidism is the autoimmune disease Hashimoto thyroiditis. A more frequent finding is that of positive thyroid autoantibodies with no alteration in thyroid function: up to 18% of all pregnant women are positive for thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody (TgAb) [4–6]. Numerous studies have shown a negative effect of manifest or even subclinical hypothyroidism on the course of pregnancy [7–10]. In addition, several studies have suggested an adverse effect of maternal hypothyroidism on neurological development of the foetus [11–15] and have indicated that even TPOAb positivity alone may have an effect on neurocognitive development [16, 17].

Although the above findings are currently the subject of debate [18–21], all three currently existing international guidelines [22–24] recommend levothyroxine replacement for women with subclinical hypothyroidism in order to achieve a successful pregnancy outcome. However, the current guideline of the American Thyroid Association [22] distinguishes five different subgroups, and levothyroxine therapy is *strongly* recommended only for those who exhibit subclinical hypothyroidism in addition to the presence of antibodies [22]. The Endocrine Society [23] explicitly recommends levothyroxine replacement for TPOAb-negative women with subclinical hypothyroidism *only for* "obstetrical outcome" whereas the European Thyroid Association recommends levothyroxine *independently of the antibody status* in order to achieve a TSH below 2.5 mIU/L [24]. These are distinctive and rather complicated stratified recommendations. In addition, the very low risk inherent in initiating low-dose levothyroxine treatment, and the well-known importance of an optimal treatment of maternal thyroid dysfunction in order to achieve a successful pregnancy outcome and a positive effect for the developing foetus may well be behind the frequent prescription of levothyroxine during pregnancy.

In countries with sufficient iodine supplementation, Graves' disease is the most common cause of hyperthyroidism. The prevalence of maternal hyperthyroidism due to Graves' disease in pregnancy varies from 0.1 to 2.7% [25, 26]. The thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) cross the placenta, and stimulating TRAb may cause foetal or neonatal hyperthyroidism.

Only 2 to 10% of pregnant women with active Graves' disease have newborns with hyperthyroidism [25], but the mortality rate in cases of neonatal hyperthyroidism is about 20 to 25% [27–29]. If the mother has been on antithyroid drugs during pregnancy, neonates are at risk to develop hyperthyroidism after a latency of eight to 9 days, at which time the mother's transplacentally transmitted medication is completely decomposed [28, 29]. During the time in hospital and upon neonatal screening at the age of 36 to 72 h, neonates are usually free of any symptoms. Additionally, most commonly used neonatal screening programs only detect elevated TSH values, thus overlooking neonatal hyperthyroidism as well as central hypothyroidism [30]. This oversight is of critical importance, since rapid diagnosis and start of therapy are mandatory in order to control the potentially life-threatening symptoms of neonatal hyperthyroidism [27–31].

Our aim in this single-centre study was to determine the frequency of "thyroid disease" in mothers admitted for delivery. We therefore carried out a survey of all referring gynaecologists and an analysis of management after admission to the hospital as a means of studying practices relating to diagnostic pre- and postpartum work-ups regarding the mother and those carried out postnatally in the neonates.

Patients and methods

Patients

An initial cohort of 1819 mothers who had given birth in one obstetrical clinic in 1 year was analysed. The women selected for the study were taking thyroid drugs during pregnancy, had a documented thyroid disease or had pathological thyroid values. Overall, 213 mothers (11.7%) fulfilled at least one of these criteria and were collected in the sample labelled "thyroid disease". To select a comparable group, 213 mothers from the same initial cohort with none of these criteria were included in a "healthy" group. Thirty-seven (2%) of all 1819 mothers (17% of those with "thyroid disease") were diagnosed with "Hashimoto thyroiditis", seven (0.4% of all mothers) had "Graves' disease" (3% of those with "thyroid disease") and 169/1819 mothers (9.3%) were classified as having "other thyroid diseases". One hundred eighty-eight (88%) of those with thyroid disease took Levothyroxine. The latter group consisted of mothers diagnosed with "thyroid disease" without the presence of any autoantibodies. In

addition, we evaluated both groups regarding the following parameters: intrauterine growth retardation, placental insufficiency, pathological CTG, premature rupture of membranes, preterm birth, prolonged labour and birth weight, birth length and head circumference of the newborn, In addition, the auxological development until the second year of life of 53 children from mothers with thyroid diseases was analysed. All mothers have given consent to participate in this study. All involved gynaecologists were questioned about their diagnostic procedures in mothers with thyroid diseases. Therefore, questionnaires were sent to all 113 treating gynaecologists of the mothers of our study, with a response rate of 49.6% (56 answers). In total, there were 18 multiple choice questions on management of thyroid dysfunction and screening thyroid function in pregnancy. For most questions, however, the gynaecologists were also allowed to provide their own answers if these were not included in the questionnaire. A copy of the questionnaire is available as a supplementary file.

Statistical analysis

Data were analysed using SPSS Version 11.5. Descriptive statistics (mean, median, standard deviation) were used to describe the answers of the resident gynaecologists. A *t* test was used to compare the mean of the birth parameters of newborns from the mothers in the two groups ("thyroid disease" and "healthy") as well as different characteristics of "Hashimoto thyroiditis" and "Graves' disease". The *p* value for determining significance was 0.05. The standard deviation score (SDS) was used to compare the auxological parameters of children up to the second year of life with age-appropriate standard values.

Results

Diagnostic procedures in pregnant women/mothers with "thyroid disease"

To classify thyroid-specific prenatal diagnoses in pregnancy, we questioned resident gynaecologists about their diagnostic procedures and analysed the pre- and postpartum laboratory tests carried out in the obstetrical clinic.

Diagnostic procedure of gynaecologists

Fifty-four out of 56 gynaecologists (96%) recommended iodine supplementation during pregnancy. The dosage of this supplementation varied between 100 and 250 μg. The majority of gynaecologists (25 out of 56; 44%) prescribed 150 μg of iodine.

When questioned about the maximum acceptable TSH value of healthy pregnant women, most of the gynaecologists stated an upper limit of 2.5 mlU/L and a lower limit of 0.1 mlU/L (Fig. 1). Additional laboratory tests are shown in Table 1.

Fifty-nine percent (33/56) of gynaecologists answered that in pregnant women with known hypothyroidism who were already receiving levothyroxine, the dosage of thyroid medication was adjusted. Figure 2 shows the maximum accepted TSH value of these women. 69.3% of these values are between 1 and 3 mlU/L, 30.7% between 2.5 and 3 mlU/L.

Diagnostic procedures in the obstetrical clinic

Table 2 illustrates the laboratory tests performed in mothers from the "thyroid disease" group during their stay in the obstetrical clinic. The TRAb level was determined prior to delivery in only one of the seven mothers (14.3%) with Graves' disease.

Management of the newborns from mothers with "thyroid disease"

Additional measurements of thyroid parameters were carried out in 19 of 213 newborns (9%) during their stay in the obstetrical clinic without detecting any abnormal values and without any clinical correlation. TRAb level was measured in one of the seven children from mothers with Graves' disease.

Birth outcome and development of the newborns

Figure 3 shows the differences in childbirth risk. Upon analysis of single parameters (e.g. premature rupture of membranes), none showed significant differences between the groups. However, taking all parameters together, mothers suffering from Graves' disease have a significantly higher childbirth risk than patients with Hashimoto disease (*p* value: 0.03).

There were no significant differences among the following birth parameters: weight, length, head circumference, APGAR score and the pH value of the umbilical artery between the newborns of "thyroid disease" and "healthy" mothers. No differences were found for the birth parameters of newborns of mothers from the two major diagnostic groups "Hashimoto thyroiditis" and "Graves' disease".

Auxological development of 53 newborns of mothers from our "thyroid disease" group was normal up to the second year of life: SDS values for length/height, weight and head circumference in the entire period are located between the 25th and 75th percentile of the growth curve. No significant differences were found between the groups.

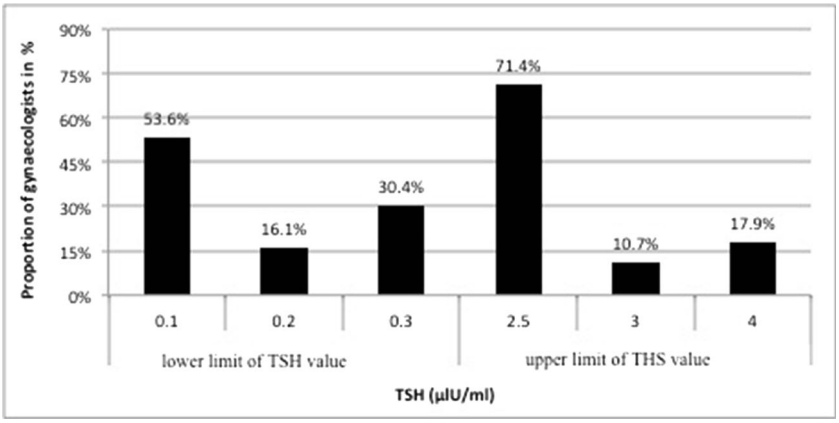

Fig. 1 Questionnaire to resident gynaecologists: "What do you consider the upper and lower limit of accepted TSH value of healthy pregnant women above which further thyroid diagnostics is mandatory?". Number of gynaecologists (in percent) and the lower (left hand side) and upper (right hand side) limit of TSH values are shown

Discussion

Our study had two major findings: (1) a high incidence of mothers admitted for delivery who were taking levothyroxine for "thyroid disease", and (2) a highly inconsistent response of physicians in selecting the required pre- and postpartum diagnostic procedures for both the mother and the newborn.

In our group of 1819 women admitted for delivery in a single hospital during 1 year, 11.7% reported having "thyroid dysfunction" and/or were on thyroid medication. In the vast majority, the medication, but not the reason for the treatment, was known to the neonatologist/paediatrician. With the exception of known or suspected cases of maternal Graves' disease; however, no guidelines or algorithms exist to date for determining proper diagnostic and/or management procedures for the neonate of a mother presenting with "thyroid disease of uncertain entity" [29]. Our study underscored the fact that another algorithm is necessary to ensure that neonates at risk for thyroid disease are accurately diagnosed and unnecessary diagnostic procedures for those in whom neonatal screening is sufficient are avoided.

Thyroid diseases in pregnancy have been the subject of numerous publications in recent years (see [22] for a review). The complexity of the topic has already been illustrated by controversy regarding the question whether universal thyroid *screening* is required for all pregnant women [32].

Table 1 Laboratory tests that were performed by the 56 gynaecologists if TSH concentrations were below or up the accepted limit

Additional ordered laboratory test	Responder *n* (%)
fT3	35 (64.3)
fT4	33 (58.9)
T4	9 (16.1)
T3	9 (16.1)
TPO-Ab	22 (39.3)
TRAb	18 (32.1)

To further complicate the issue, different values for thyroid hormones for each trimester and different recommendations have been published regarding the response to laboratory results (manifest or subclinical hypothyroidism, with or without thyroid antibodies) [22–24]. Uncertainty also exists about the effects of maternal thyroid dysfunction on neurocognitive development of the foetus [33]. The complicated and partly contradictory nature of the available data also has an effect on recommendations for medical action.

Several studies have highlighted the inconsistency of procedures undertaken in caring for pregnant women with thyroid "problems" [34]. Our study too revealed not only a notable degree of inconsistency in the diagnostic and therapeutic procedures carried out during pregnancy by the treating gynaecologist but also a remarkable level of uncertainty in the hospital in determining the proper diagnostic procedure for both the mother and the newborn.

Pre- and postpartum diagnostics in mothers presenting with "thyroid disease"

Almost all gynaecologists in our study recommended iodine prophylaxis, albeit the respective dose varied: 25 of 56 reported prescribing a dosage of 150 μg, which is in line with the recommendations of the American Thyroid Association [22], while 50% chose higher doses (175 to 250 μg). The reason for this can only be hypothesised. Perhaps some gynaecologists misunderstood the term "iodine prophylaxis" and thought about the daily iodine requirement during pregnancy, which can vary from one country to another.

Inconsistencies were also found concerning the analysis of TSH limit values, which were considered to be the basis for further diagnostics. When gynaecologists measured TSH routinely in pregnant women, this was always performed in the first trimester. Fifty-four percent of the gynaecologists denoted 0.1 mlU/L TSH as the minimum and 71% a TSH of 2.5 mlU/L as the maximum acceptable value. This information corresponds to the TSH limits of the first trimester as set out in the guidelines [22–24]. The answers of the remaining

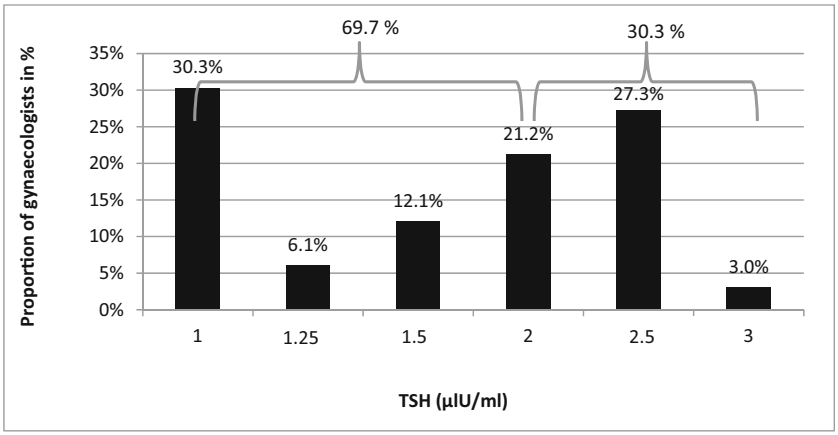

Fig. 2 Questionnaire to resident gynaecologists: "What do you consider as the maximum accepted TSH value in pregnant women with hypothyroidism before dosage adaptation is required?". Number of gynaecologists (in per cent) and their accepted TSH value are shown

gynaecologists (minimum limit values of 0.1 or 0.2 mlU/L and a maximum limit of 3 mlU/L) may have referred to the reference values of the following trimesters. Thirty-three of 56 gynaecologists (59%) reported changing the dosage of levothyroxine on their own responsibility when their patients became pregnant. This is also in line with the guidelines of the ATA, which recommend an immediate increase in dosage of 30 to 50% after pregnancy has been identified [22]. However, the target TSH value often did not coincide with the guidelines. Only a third of gynaecologists accept maximum TSH values of 2.5 and 3 mlU/L, which would be guideline-compliant regardless of the trimester specificity. The majority of the physicians (70%) aimed for a target TSH value below 2 mlU/L. In order to achieve such a low value, higher doses of levothyroxine are necessary than would be required by current guidelines, and women who need no therapy should also take thyroid drugs during pregnancy. It can only be hypothesised that this intensified therapy concept results from knowledge about the negative effects of maternal hypothyroidism during pregnancy [7–10]. However, Korevaar et al. [19] demonstrated that high levels of fT4 during pregnancy may also have a negative effect on the neurological development of children.

When diagnostic procedures during pregnancy and in the obstetrical clinic were analysed, it was alarming to find that diagnostic procedures in the routine care of patients with Graves' disease are sometimes inadequate. Consensus guidelines from the ATA and the Endocrine Society recommend that maternal TRAb levels should be determined between the 20th and 24th weeks of gestation in women with active or past Graves' disease [22, 23]. If maternal TRAb levels are negative, no specific follow-up is necessary [29]. If the pregnant woman takes thyreostatic drugs during pregnancy, the antibody status must be analysed in the last trimester. If TRAb is detected, neonatal hyperthyroidism must be excluded by postnatal diagnostics [22–24, 29, 30]. If TRAb levels are unavailable or positive, the newborn should be regarded as being "at risk" for hyperthyroidism. Five out of seven patients with Graves' disease used thyroid drugs during their stay in the obstetrical clinic. Although laboratory investigations were performed in four patients, TRAb measurement was performed only in one. This approach does not coincide with the cited recommendations. It is therefore important for neonatologists and paediatricians not to rely on the diagnostics performed in the mother but also to initiate diagnostic procedures in the neonate if necessary.

Postnatal diagnostics of newborns of mothers presenting with "thyroid disease"

Thyrotropin-based neonatal screening was performed in all children in this study. This type of screening detects only increased TSH values as an indicator of primary congenital hypothyroidism. In most countries, central hypothyroidism, which is associated with a normal or decreased level of the TSH, fT3 and fT4, is therefore overlooked, as is potentially life-threatening neonatal hyperthyroidism [29]. If hyperthyroidism is suspected, repeated measurements for TSH, fT3, fT4 and TRAb are required [29].

In our study, additional measurements beyond the usual neonatal screening procedure were carried out in 19 of 213

Table 2 Diagnostic procedure in the obstetrical clinic based on the individual diagnosis. Illustration of the laboratory tests in mothers of the sample "thyroid disease". Total numbers and percent (in brackets) are shown

Diagnosis	Measurement of TSH, fT3, fT4, TPOAb *n* (%)	Measurement of TRAb *n* (%)
Hashimoto thyroiditis ($n = 37$)	8 (21.6)	1 (2.7)
Graves' disease ($n = 7$)	5 (71.4)	1 (14.3)
On levothyroxine for other reasons ($n = 169$)	39 (32.1)	2 (1.2)

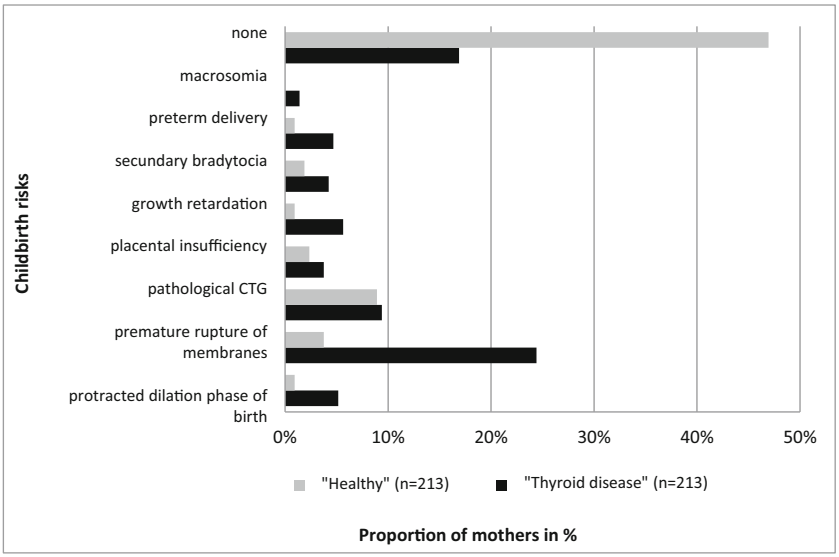

Fig. 3 Childbirth risks "thyroid disease" vs. "healthy": comparison of the various birth outcomes of mothers from the two samples "thyroid disease" and "healthy" of the present study

newborns (9%). Further examinations were performed in six of 37 newborns from mothers with Hashimoto thyroiditis. Because the presence of TRAb in Hashimoto disease is relatively rare, with a probability of 10 to 20%, and the remaining antibodies (TgAb and TPOAb) do not lead to the detection of thyroid gland alteration in the neonates, this procedure is to be regarded as unnecessary diagnostics [23].

The presence of TRAb in Graves' disease is much more common (80–95%). The recommended procedure in pregnant women with Graves' disease is described in the existing guidelines [22–24], and van der Kaay et al. [29] have recently provided an algorithm for the management of newborns born to mothers with Graves' disease. In our study, further diagnostic testing was performed in only one child from a mother with Graves' disease—a worrisome finding. This procedure does not correspond to the recommendations cited in the literature and may simply be explained by an insufficient communication about the underlying thyroid disease of the mother and the complexity of the required diagnostic work-up (ranging from "no further action necessary" to "repeated laboratory tests"). However, because neonatal hyperthyroidism is potentially life-threatening, some kind of uncomplicated, widely known and easily understandable diagnostic algorithm is of imperative importance.

Childbirth risk and auxological development of the neonate

Children from mothers with "thyroid diseases" did not differ from those of "healthy" mothers with regard to birth parameters (weight, length, head circumference, APGAR score and the pH value of the umbilical artery). In accordance with the literature, we found that overall "childbirth risks" were significantly higher in mothers with "thyroid diseases" and especially in those with Graves' disease, even when no significant differences were found in the individual parameters [10, 35]. However, a comparison of birth parameters of the "Hashimoto thyroiditis" and "Graves' disease" groups detected no significant differences. Auxological parameters of children of mothers with thyroid diseases remained unremarkable up to the second year of life. Length, weight and head circumference remained between the 25th and 75th percentile of the growth curve during the entire survey period. It was beyond the scope of the present study to provide any information on the neurological development of the children, and further long-term studies will be required in this respect.

Conclusion

In the present study, 11.7% of pregnant women admitted for delivery indicated that they were taking levothyroxine and/or had "thyroid disease". Reassuringly, the vast majority of their newborns needed no other diagnostic work-up than what is routinely done during newborn screening. However, a wide variation in clinical practices and in the management of thyroid disorders during pregnancy and, unfortunately, a frequent lack of adherence to clinical practice guidelines were found.

It is important to ensure an accurate diagnosis of "thyroid disease" and to communicate any maternal medication to the paediatrician or neonatologist. If the mother's antibody status is known, the neonatologist needs to know whether TRAb has been detected. These questions must be clarified in advance so that the neonatologist/paediatrician can decide whether further thyroid-specific diagnostic tests are required or whether neonatal screening is sufficient. In order to improve diagnostic procedures both for mothers with thyroid diseases and their neonates, a close collaboration of gynaecologists, general practitioners, internists, neonatologist/paediatricians and other treating specialists is required.

Authors' Contributions Patricia C. Weissenfels conducted the data collection, was involved in data analysis and wrote the initial manuscript.

Prof Joachim Woelfle was involved in data analysis and interpretation and carried out a critical revision of the article.

Dr. Eckhard Korsch was involved in extensive literature research data analysis and interpretation and carried out a critical revision of the article.

Dr. Mathias Joergens was involved in data collection and analysis and interpretation and carried out a critical revision of the article.

Prof Bettina Gohlke developed the study concept and design, wrote the final version of the manuscript and carried out data analysis and interpretation.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants in the study.

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