Thieme

Reducing the Rate of Premature Births through Early Diagnosis and Pregnancy-Adapted Treatment of Hypothyroidism

Reduktion der Frühgeburtenrate durch frühzeitige Diagnostik und schwangerschaftsadaptierte Therapie der Schilddrüsenunterfunktion

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ABSTRACT

Introduction
The aim of this study was to determine the extent to which regular monitoring of maternal free thyroxine level and pregnancy-adapted L-thyroxine replacement therapy before and during pregnancy in patients with existing or newly diagnosed latent and manifest hypothyroidism as well as hypothyroxinemia can influence the rate of premature births.

Materials and Methods
This is a retrospective cohort study assessing 1440 pseudonymized survey questionnaires to evaluate the risks of premature birth with two study groups from the same medical practice, and a nationally recruited control group. Study group A (n = 360) had already been taking L-thyroxine prior to conception, study group B (n = 580) started taking it after conception. Both study groups had a maximum gestational age of 12 + 0 GW. In the study groups, TSH and free thyroxine levels were determined regularly for dose adjustment purposes. The aim was to keep the free thyroxine level in the euthyroid hyperthyroxinemic range within the pregnancy adapted reference range. The control group (n = 500) had taken L-thyroxine during pregnancy according to criteria that were not known, as the questionnaire did not include any questions regarding this matter. Taking other risk factors into account, the influence of pregnancy-adapted

L-thyroxine replacement therapy on the rate of premature births was determined using logistic regression analysis.

Results

Compared with the control group, the premature birth rate was 70 % lower ($p < 0.0001$) in study group A and 42 % lower in study group B ($p = 0.0086$), while the odds ratio, at 3.46, was particularly significant in study group A. High blood pressure (odds ratio 5.21), body mass index per kg/m^2 (odds ratio 0.91) and S. p. premature birth were identified as other independent risk factors.

Conclusion

The results show an association between more intensive thyroid diagnostics and pregnancy-adapted L-thyroxine replacement therapy and a decrease in premature births. Further studies should be conducted to confirm these results.

ZUSAMMENFASSUNG

Einleitung

Ziel war es, herauszufinden, inwieweit regelmäßige Kontrollen des mütterlichen freien Thyroxinspiegels und eine schwangerschaftsadaptierte L-Thyroxin-Substitution vor und in der Schwangerschaft bei bestehender oder neu diagnostizierter latenter und manifester Hypothyreose sowie Hypothyroxinämie die Frühgeburtenrate beeinflussen können.

Material und Methoden

Retrospektive Kohortenstudie mit Auswertung von 1440 pseudonymisierten Erhebungsfragebögen zur Evaluation von Frühgeburtsrisiken mit 2 Studiengruppen aus einer Praxis und einer bundesweit rekrutierten Kontrollgruppe. Studiengruppe A (n = 360) hatte bereits präkonzeptionell L-Thyroxin eingenommen, Studiengruppe B (n = 580) nach Eintritt der Schwangerschaft. Beide Studiengruppen hatten ein maximales Gestationsalter von 12 + 0 SSW. TSH und freier Thyroxinspiegel wurden zur Dosisanpassung regelmäßig in den Studiengruppen bestimmt. Ziel war es, den freien Thyroxinspiegel schwangerschaftsadaptiert im euthyreoten hyperthyroxinämischen Bereich zu halten. Die Kontrollgruppe (n = 500) hatte während der Schwangerschaft L-Thyroxin eingenommen nach Kriterien, die nicht bekannt waren, da im Erhebungsfragebogen nicht danach gefragt wurde. Unter Berücksichtigung anderer Risikofaktoren wurde mittels logistischer Regressionsanalyse der Einfluss einer schwangerschaftsadaptierten L-Thyroxin-Substitution auf die Frühgeburtenrate ermittelt.

Ergebnisse

Im Vergleich zur Kontrollgruppe war die Frühgeburtenrate in der Studiengruppe A um 70 % ($p < 0{,}0001$) und in der Studiengruppe B um 42 % ($p = 0{,}0086$) niedriger, wobei die Odds Ratio mit 3,46 besonders in der Studiengruppe A hoch signifikant war. Bluthochdruck (Odds Ratio 5,21), BMI pro kg/m^2 (Odds Ratio 0,91) und Z. n. Frühgeburt konnten als weitere unabhängige Risikofaktoren identifiziert werden.

Schlussfolgerung

Die Ergebnisse zeigen eine Assoziation von intensivierter Schilddrüsendiagnostik und schwangerschaftsadaptierter L-Thyroxin-Substitution mit einer Abnahme von Frühgeburten. Weitere Untersuchungen sollten die Ergebnisse bestätigen.

Introduction

Multiple factors contribute to the etiology of premature births. Premature births are now considered to be the clinical endpoint of various pathophysiological cascades, of a complexity that has to date made it impossible to provide causal therapy. Despite intense national and global efforts, it has not been possible to reduce the rate of premature births. Premature birth remains a medical challenge [1].

The prevalence of premature birth in Germany is 8.6 % [2, 3, 4, 5], one of the highest within the European Union [6]. 70% are etiologically classified as spontaneous premature births [5, 7, 8, 9], while 30% have medical causes and are iatrogenically induced. Over the past few decades, the prevalence of premature births in Germany has remained stable overall; however, the number of premature births occurring before the 28th GW has increased by 65% [4].

Thyroid function disorders during pregnancy, such as manifest hypothyroidism or manifest hyperthyroidism, are established risk factors for the occurrence of premature birth [10]. Epidemiologically, thyroid disease is one of the most common diseases in women of childbearing age [11]. Due to its high prevalence and relatively few symptoms, thyroid disease, which is associated with decreased hormone production, is of particular relevance before and during pregnancy. From an epidemiological point of view, in addition to manifest and latent hypothyroidism, isolated hypothyroxinemia is also considered a risk factor for premature birth [10, 12]. This is defined in terms of laboratory testing as a combination of decreased free thyroxine level with normal TSH concentration in the expectant mother [13, 14].

To date, there is no consensus among the professional endocrinological associations on whether latent hypothyroidism or hypothyroxinemia during pregnancy requires treatment. The American Endocrine Society leaves the decision of whether to treat expectant mothers with L-thyroxine largely to the attending gynecologists [14], while the American Thyroid Association opposes treatment in the absence of thyroid antibodies and natural conception [15].

The European Thyroid Association calls for further studies to be able to more accurately assess the effects of thyroid hormone deficiency on the health of the unborn baby. Due to the potential risk to fetal brain development, treatment with L-thyroxine is still recommended, despite the lack of interventional studies [16].

The guidelines of the German Association of Scientific Medical Societies (AWMF) of October 2022 on prevention and treatment of premature birth do not mention thyroid dysfunction as a risk factor requiring treatment [5, 7, 8].

The aim of this study is to clarify the extent to which the rate of premature births is influenced by regular monitoring of the maternal free thyroxine level and pregnancy-adapted L-thyroxine replacement therapy before and during pregnancy in the case of existing or newly diagnosed latent and manifest hypothyroidism or hypothyroxinemia.

Patients and Methods

In this retrospective cohort study, we analyzed a total of 1440 anonymized survey questionnaires completed by women with a thyroid function disorder. The raw data were made available as an Excel file by Forschung Beratung Evaluation GmbH (FBE) in Berlin. This data is based on a survey questionnaire that queries a number of known risk factors for premature birth as well as perinatal data. In addition to biometric and demographic data, such as body mass index, maternal age, nationality, level of education, and parity, socioeconomic data, a family history, and a patient-reported history for the last 12 months prior to conception were also collected.

The questionnaire was completed by the pregnant women and their physicians and returned to the FBE for evaluation with their written consent.

Study group and control group

A total of 3489 survey questionnaires were provided from various medical practices. Of these, 500 women had taken L-thyroxine before and during pregnancy, as documented in their medical records. These 500 questionnaires were used as a control group. The criteria for the provision of L-thyroxine replacement therapy in the control group are not known, because the survey did not include any questions regarding these.

The study group consisted of 940 women from the same medical practice who had also completed the FBE questionnaire. These pregnant women had been taking L-thyroxine because of latent and manifest hypothyroidism or hypothyroxinemia. The study group was divided into group A, consisting of 360 pregnant women who had already been taking L-thyroxine prior to conception, and group B, consisting of 580 pregnant women who only took L-thyroxine after conception.

Inclusion and exclusion criteria

Only single pregnancies were included in the study. The study groups had a maximum gestational age of 12 + 0 GW. There was no information on gestational age in the control group. Underlying diseases, such as thrombophilia, hypertension, diabetes mellitus, etc. were not counted as exclusion criteria.

Laboratory tests

TSH and free thyroxine (fT4) levels were measured regularly for dose adjustment purposes in all women in the study groups as part of prenatal care. The aim was to maintain the free thyroxine level in the euthyroid hyperthyroxinemic range (high-normal area of reference range) within the pregnancy adapted reference range. There are no data on this for the control group.

The Ethics Committee of Baden-Württemberg did not consider an ethics committee vote to be necessary because the survey questionnaires were pseudonymized.

Statistical analyses

Statistical analyses were performed using the statistical software SAS, release 9.4 (SAS Institute Inc., Cary, North Carolina, USA). Absolute and relative frequencies are reported for qualitative factors; for quantitative variables, the mean and standard deviation are reported. The ages were divided into six groups; these age groups were considered to be an ordinal scaled variable. The following tests were used to compare the two groups: the Chi^2 test for nominally scaled factors, Fisher's exact test (if the conditions of the Chi^2 test were not met), the Cochran-Armitage trend test for ordinal scaling, the t-test for comparing two mean values for approximately normally distributed data, and the Mann and Whitney U test for quantitative, non-normally distributed data. For comparisons between three groups, the Chi^2 test (for nominal scaling) or the Kruskal-Wallis test (for quantitative, non-normally distributed data) was used. A test result with a p-value of < 0.05 was considered statistically significant; a result with a p-value between 0.05 and 0.10 was considered weakly significant. All factors for which a statistical association with the target variable "premature birth" was demonstrated in univariate tests were evaluated simultaneously by means of a multiple logistic regression analysis after assessing their medical significance and the quality and completeness of the data. The "Backward Selection" method was used: First, logistic regression was performed using all existing parameters. Then, in a second step, the parameter with the highest p-value was eliminated from the statistical model. This step was repeated until only statistically significant parameters remained in the model. For each parameter, the odds ratio (OR) was calculated as an approximation to the relative risk.

Results

A direct comparison of the premature birth rates in the three groups shows that the premature birth rate in group B, at 6.0 %, is almost twice that in group A, at 3.1 % ($p = 0.0396$); the premature birth rates in both group A and group B were significantly lower than the premature birth rate in the control group, which was 10.4 % ($p < 0.0001$ or $p = 0.0086$) (▶ **Table 1**). Since the variables age distribution and parity status are closely associated with the target variable "premature birth", these were compared with each other. On average, the women in group B are slightly younger than the women in group A and in the control group. The difference is statistically significant (Kruskal-Wallis test $p < 0.0001$) (▶ **Table 1**).

The three groups also differed significantly in terms of parity status ($p < 0.0001$) (▶ **Fig. 1**). The proportion of primiparae was significantly higher in the control group than in the study groups A and B (79.6% versus 40.0% and 49.3%, respectively). Since primiparity is epidemiologically associated with a higher risk of premature birth [17], the rates of premature birth in groups A and B were broken down according to parity status and compared to the corresponding rate in the control group (▶ **Table 1**).

▶**Table 1** Comparison of the study groups with the control group.

Variables	Test	Group A (n = 360)	Group B (n = 580)	Control group (n = 500)	Group A p-value	Group B p-value
Total premature births		3.06%	6.03%	10.40%	p < 0.0001	p = 0.0086
Premature births in primiparae		3.47% (n = 144)	8.04% (n = 286)	10.30% (n = 398)	p = 0.0117	p = 0.3169
Premature births in multiparae		2.78% (n = 216)	4.08% (n = 294)	10.78% (n = 102)	p = 0.0031	p = 0.0126
Age cohort (in years)	U-test				p = 0.1145	p < 0.0001
18 – 24		5.87%	0.17%	2.20%		
25 – 29		26.82%	12.59%	23.20%		
30 – 34		39.66%	30.00%	45.60%		
35 – 39		21.79%	37.93%	26.40%		
40 – 44		5.59%	15.52%	2.60%		
≥ 45		0.28%	3.79%	0.00%		
BMI	t-test	∅ 25.13 (SD 4.84)	∅ 24.75 (SD 4.87)	∅ 24.34 (SD 5.10)	p = 0.0237	p = 0.1740
German citizenship	Chi^2	85.75%	81.31%	96.77%	p < 0.0001	p < 0.0001
Education (in years)	U-test	∅ 10.4 (SD 1.6)	∅ 10.3 (SD 1.7)	∅ 11.2 (SD 1.0)	p < 0.0001	p < 0.0001
Smokers	Chi^2	19.44%	28.32%	16.60%	p = 0.2819	p < 0.0001
Participation in sports/exercise	Chi^2	48.61%	49.91%	46.68%	p = 0.5763	p = 0.2900
Fertility treatment/IVF	Chi^2	8.06%	5.21%	36.90%	p < 0.0001	p < 0.0001
Self-assessed health (good – moderate – poor)	Trend test	94.44% – 4.44% – 1.11%	95.34% – 4.14% – 0.52%	71.94% – 25.05% – 3.01%	p < 0.0001	p < 0.0001
Hypertension	Chi^2	2.55%	1.92%	6.00%	p = 0.0175	p = 0.0005
Diabetes	Fisher	1.99%	0.17%	1.00%	p = 0.2497	p = 0.1027
Eating disorders	Fisher	1.14%	1.05%	0.80%	p = 0.7239	p = 0.7568
Addiction problems	Fisher	0.28%	0.70%	0.00%	p = 0.4131	p = 0.1277
Migraine	Chi^2	12.22%	10.10%	19.00%	p = 0.0081	p < 0.0001
Vag. infection in the past 12 months (none – one – several)	Trend test	47.88% – 15.31% – 36.81%	43.18% – 22.52% – 34.30%	72.62% – 18.55% – 8.82%	p < 0.0001	p < 0.0001
Hospital treatment	Chi^2	17.32%	11.09%	19.32%	p = 0.4578	p = 0.0002
Family stress	Chi^2	90.20%	88.33%	34.07%	p < 0.0001	p < 0.0001
Occupation	Chi^2	70.00%	71.68%	93.17%	p < 0.0001	p < 0.0001
Workload	Chi^2	35.71%	42.22%	25.00%	p = 0.0030	p < 0.0001
S.p. gyn. surgery (none – one – several)	Trend test	54.24% – 32.77% – 12.99%	70.69% – 21.49% – 7.82%	64.16% – 22.75% – 13.09%	p = 0.0509	p = 0.0049
Premature births in FH	Chi^2	15.00%	14.17%	8.80%	p = 0.0061	p = 0.0081
Diabetes in FH	Chi^2	20.99%	17.52%	35.80%	p < 0.0001	p < 0.0001
Number of children	U-test	∅ 1.1 (SD 0.7)	∅ 1.3 (SD 1.1)	∅ 0.7 (SD 0.8)	p < 0.0001	p < 0.0001
S.p. induced abortion (none – one – several)	Trend test	2.06% – 4.53% – 93.42%	2.69% – 9.58% – 87.72%	1.61% – 16.13% – 82.26%	p = 0.0049	p = 0.2641
S.p. miscarriage (none – one – several)	Trend test	13.20% – 32.80% – 54.00%	4.79% – 20.36% – 74.85%	14.97% – 38.50% – 46.52%	p = 0.1812	p < 0.0001
S.p. premature birth (none – one – several)	Trend test	0.82% – 6.15% – 93.03%	0.93% – 6.48% – 92.59%	3.92% – 21.57% – 74.51%	p < 0.0001	p < 0.0001
Compl. last pregnancy	Chi^2	18.44%	14.20%	46.60%	p < 0.0001	p < 0.0001

▶**Table 1** continued

Variables	Test	Group A (n = 360)	Group B (n = 580)	Control group (n = 500)	Group A p-value	Group B p-value
Fertility treatment	Chi^2	15.00 %	7.41 %	55.49 %	p < 0.0001	p < 0.0001
Caesarean section	Chi^2	17.66 %	18.40 %	36.44 %	p < 0.0001	p < 0.0001
Primiparae/Multiparae	Chi^2	40.00 %/60.00 %	49.31 %/50.69 %	79.60 %/20.40 %	p < 0.0001	p < 0.0001
Premature labor	Chi^2	0.28 %	2.24 %	4.60 %	p = 0.0001	p = 0.0313
Cervical insufficiency	Chi^2	0.28 %	0.69 %	4.60 %	p = 0.0001	p < 0.0001
Premature rupture of membranes	Chi^2	0.56 %	1.55 %	9.00 %	p < 0.0001	p < 0.0001
Child female/male	Chi^2	48.33 %/51.67 %	43.57 %/56.43 %	47.33 %/52.67 %	p = 0.7785	p = 0.2374

∅ = Mean; FH = Family history; Compl. = Complications; SD = Standard Deviation

The premature birth rates for the primiparae (3.5 %) and multiparae (2.8 %) in group A were significantly lower than those in the control group (10.3 % and 10.8 % respectively, with p = 0.0117 and p = 0.0031). In group B, only the multiparae were found to differ significantly from the control group (4.1 % versus 10.8 %; p = 0.0126), while there was no significant difference in the primiparae (p = 0.3169). In addition, the premature birth rate among primiparae in group A compared to group B is strikingly lower (p = 0.0669), while there was no significant difference for multiparae (p = 0.4304).

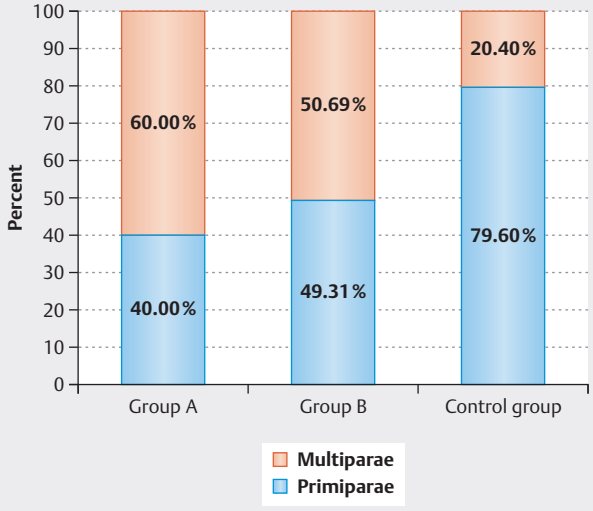
Evaluation of risk factors

Group A differs from the control group due to a lower proportion of women having undergone fertility treatment/IVF (8.06 % versus 36.90 %; p < 0.0001), fewer women with hypertension (2.6 % versus 6.0 %; p = 0.0175), more vaginal infections in the past 12 months (52.1 % versus 27.4 %; p < 0.0001), more multiparae (60 % versus 20.4 %; p < 0.0001), correspondingly fewer primiparae (40.0 % versus 79.6 %; p < 0.0001) and a smaller proportion of fertility treatments (15.0 % versus 55.5 %; p < 0.0001 (▶ **Table 1**).

In order to determine the statistically significant variables associated with the target variable "premature birth", the data from group A and the control group were combined, as both groups had already been taking L-thyroxine prior to conception (▶ **Table 2**).

BMI, poor self-assessed state of health, hypertension, group assignment (group A versus control group), vaginal infections in the past 12 months, hospital treatment, s.p. premature births, delivery by caesarean section, premature labor, cervical insufficiency, and premature rupture of membranes are statistically significant. Weakly significant variables are fertility treatment/IVF, occupation, family stress in the past 12 months, and primiparity.

Variables that are highly subjective in their assessment and difficult to quantify and operationalize, such as family stress, occupation, and self-assessed state of health, were not taken into account despite their significance or weak significance in the univariate analysis. Moreover, variables that are inextricably linked to the pathophysiology of premature birth, such as hospital admissions, type of delivery, premature labor, cervical insufficiency, and premature rupture of membranes were also not taken into account.



▶ **Fig. 1** Parity status in the study groups and the control group n = 1440.

Due to numerous missing values the variables "pregnancies after fertility treatment" and "s.p. premature birth" were not included in the multiple analysis and were considered separately. Since fertility therapy/IVF is a significant risk factor [18], this variable was taken into account in the multiple regression analysis.

The multiple logistic regression analysis for group A was performed using the following variables: group assignment (group A versus control group), BMI, hypertension, vaginal infections in the past 12 months, and fertility treatment/IVF (▶ **Table 3**).

A higher risk of premature birth can be found for the variables group assignment (group A versus control group; OR = 0.289; p = 0.0005), hypertension (OR = 5.214; p = 0.0002), and BMI in kg/m^2 (OR = 0.91; p = 0.0061). Vaginal infections in the past 12 months and previous fertility treatments/IVF are not significant.

▶**Table 2** Associations of risk factors with premature birth, n = 860 (group A and control group).

Variable	Category	Proportion of premature births	Test	p-value
Age cohort (in years)			U-test	p = 0.8649
	18 – 24	3.13 %		
	25 – 29	6.13 %		
	30 – 34	9.73 %		
	35 – 39	5.71 %		
	40 – 44	3.03 %		
	≥ 45	0		
BMI		∅ 23.15 (SD 4.35)	t-test	p = 0.0131
Nationality	German – other	7.62 % – 4.48 %	Fisher	p = 0.4677
Smoking	Yes – no	6.54 % – 7.50 %	Chi^2	p = 0.6793
Sports activity	Yes – no	7.37 % – 7.33 %	Chi^2	p = 0.9832
Fertility treatment/IVF	Yes – no	10.38 % – 6.37 %	Chi^2	p = 0.0524
Self-assessed health	good – moderate – poor	6.72 % – 8.51 % – 21.05 %	Trend test	p = 0.0493
Hypertension	Yes – no	23.08 % – 6.63 %	Fisher	p = 0.0013
Diabetes	Yes – no	0 % – 7.50 %	Fisher	p = 1.0000
Eating disorders	Yes – no	0 % – 7.46 %	Fisher	p = 1.0000
Addiction problems	Yes – no	0 % – 7.40 %	Fisher	p = 1.0000
Migraine	Yes – no	8.70 % – 7.14 %	Chi^2	p = 0.5234
Vag. infection in the past 12 months	None – one – several	8.12 % – 10.85 % – 1.97 %	Trend test	p = 0.0404
Hospital treatment in the past 12 months	Yes – no	12.66 % – 6.17 %	Chi^2	p = 0.0048
Family stress	Yes – no	5.91 % – 9.39 %	Chi^2	p = 0.0544
Occupation	Yes – no	8.10 % – 3.52 %	Chi^2	p = 0.0560
Workload	Yes – no	8.00 % – 8.23 %	Chi^2	p = 0.9191
S.p. gyn. surgery	None – one – several	7.54 % – 7.21 % – 6.54 %	Trend test	p = 0.7209
Premature births in FH	Yes – no	7.61 % – 7.55 %	Chi^2	p = 0.9853
Diabetes in FH	Yes – no	6.88 % – 7.80 %	Chi^2	p = 0.6478
S.p. induced abortion	None – one – several	5.00 % – 9.76 % – 12.50 %	Trend test	p = 0.1305
S.p. miscarriage	None – one – several	4.50 % – 6.49 % – 6.56 %	Trend test	p = 0.4042
S.p. premature birth	None – one – several	1.65 % – 29.73 % – 16.67 %	Trend test	p < 0.0001
Compl. last pregnancy	Yes – no	5.38 % – 4.72 %	Fisher	p = 0.7829
Fertility treatment	Yes – no	8.00 % – 5.48 %	Chi^2	p = 0.2782
Delivery by caesarean section	Yes – no	13.85 % – 4.70 %	Chi^2	p < 0.0001
Primiparae	Yes – no	8.49 % – 5.35 %	Chi^2	p = 0.0879
Premature labor	Yes – no	33.33 % – 6.58 %	Fisher	p = 0.0002
Cervical insufficiency	Yes – no	37.50 % – 6.46 %	Fisher	p < 0.0001
Premature rupture of membranes	Yes – no	38.30 % – 5.54 %	Fisher	p < 0.0001
Gender of premature birth	female – male	6.43 % – 7.98 %	Chi^2	p = 0.3923

∅ = Mean; FH = Family history; Compl. = Complications; SD = Standard Deviation

Although L-thyroxine was only taken after conception in group B, the analysis was performed in the same way as for group A, as a comparable control group was not available. Statistically significant variables for the target variable "premature birth" included poor self-assessed state of health, hypertension, hospital admissions, occupation, previous miscarriages, s.p. premature births,

delivery by caesarean section, primiparity, premature labor, cervical insufficiency, and premature rupture of membranes. Weakly significant variables were a lower BMI, longer school education, fertility treatment/IVF, and induced abortion in the medical history.

Occupation, previous induced abortion, miscarriages, s.p. premature birth, hospital stay, type of delivery, premature labor, cervical insufficiency, premature rupture of membranes, and self-assessed state of health were not taken into account for the same reasons as in group A.

The multiple logistic regression analysis for group B was performed with the following variables: group assignment (group B versus control group), hypertension, and parity, as well as BMI despite its weak significance, given that BMI is a recognized risk factor (▶ **Table 4**).

A higher risk of premature birth is found for the variables group assignment (group B versus control group; OR = 0.623; p = 0.0437), hypertension (OR = 4.699; p = 0.0002), and BMI (OR = 0.940; p = 0.0221). Parity status was not significant.

Supplementary analysis for missing data

The variables vaginal infections, fertility treatment, and s.p. premature birth were missing a large number of data points. To analyze the extent to which these missing data points affect the result, we performed a simulation calculation.

Initially, all missing data points for vaginal infection were replaced with a "yes" and then with a "no". In either constellation, there was no effect on the rate of premature births. For the "fertility treatment" variable, 62 % of the data are missing in the control group, while in group A, the data are complete. Since the questionnaire in the control group was predominantly filled in by the participants themselves, it is reasonable to propose that the missing data should be replaced with a "no". As a result, the group difference would no longer be significant. In case the answer to the missing data was "yes", the difference would be significant. This does not change the outcome, as fertility treatment is not statistically associated with the rate of premature births (▶ **Table 2**).

A previous premature birth (s.p. premature birth) is a significant risk factor for another premature birth [19]. This risk factor was associated particularly frequently with the risk factors "self-assessed state of health", "stress", and "high blood pressure". Based on this association, logistic regression was used to estimate the probability for "s.p. premature birth". If the probability was greater than 50%, the parameter was assumed to be "yes"; otherwise it was assumed to be "no".

Even after including this variable in the multiple regression analysis for group A and group B, the result does not change. Again, group assignment (group A or group B versus control group) is a significant risk factor, with an OR = 0,30 (p = 0.0007) in group A and an OR = 0.629 (p = 0.0496) in group B. Other risk factors were hypertension (OR = 3.479, p = 0.0090) and BMI per unit (OR = 0.897, p = 0.0032), as well as the variable s.p. premature birth (OR = 3.555, p = 0.0006) (▶ **Table 5**, ▶ **Table 6**).

▶**Table 3** Multiple logistic regression analysis of group A and control group (n = 860).

Risk factor	p-value	Odds Ratio
Group assignment	p = 0.0005	OR = 0.29
Hypertension	p = 0.0002	OR = 5.21
BMI in kg/m^2	p = 0.0061	OR = 0.91
Vaginal infections in the past 12 months	p = 0.5504	
Fertility treatment/IVF	p = 0.4990	

▶**Table 4** Multiple logistic regression group B and control group (n = 1080).

Risk factor	p-value	Odds Ratio
Group assignment	p = 0.0437	OR = 0.62
Hypertension	p = 0.0221	OR = 4.70
BMI in kg/m^2	p = 0.0002	OR = 0.94
Parity	p = 0.1564	

▶**Table 5** Extended multiple logistic regression for group A and control group (n = 860).

Risk factor	p-value	Odds Ratio
Group assignment	p = 0.0007	OR = 0.30
Hypertension	p = 0.0090	OR = 3.48
BMI in kg/m^2	p = 0.0032	OR = 0.90
S.p. premature birth	p = 0.0006	OR = 3.56

▶**Table 6** Extended multiple logistic regression for group B and control group (n = 1080).

Risk factor	p-value	Odds Ratio
Group assignment	p = 0.0496	OR = 0.63
Hypertension	p = 0.0080	OR = 3.30
BMI in kg/m^2	p = 0.0196	OR = 0.99
S.p. premature birth	p = 0.0021	OR = 3.04

Discussion

Taking into account hypertension and BMI, as well as s.p. premature birth in the case of the simulation calculation, a low maternal free thyroxine level prior to conception seems to be another risk factor for premature birth. L-thyroxine replacement therapy prior to conception which increases the maternal free thyroxine level to a value within the high-normal range, such that euthyroid hyperthyroxinemia is already present at conception, appears to effectively reduce the rate of premature births. This is very clearly evident in group A, which has almost 70% fewer premature births compared to the control group. In group B, which only received L-thyroxine replacement therapy after conception, the effect was not quite so pronounced; however, with 40% fewer premature births compared to the control group, it was still clearly visible.

Despite many epidemiological studies on the correlation between maternal thyroxine deficiency and the risk of premature birth, there is no consensus on whether systematic screening before and during pregnancy and, if necessary, subsequent L-thyroxine replacement is useful in latent forms of hypothyroidism. A 2013 Cochrane study analyzed four randomized controlled trials with a moderate risk of bias. A total of 362 pregnancies were evaluated. This study showed that L-thyroxine replacement therapy prior to conception in euthyroid women, similar to group A, led to a 72% reduction in the rate of premature births. Nevertheless, the available data were considered insufficient, so no general recommendation was made [20]. In another Cochrane study from 2015, this effect could not be confirmed. L-thyroxine showed no advantages or disadvantages for the outcome of mother and child [21].

A recently published study of pregnant women with thyroid insufficiency before the 9 th GW receiving L-thyroxine replacement therapy, similar to group B, was able to show a 14–29% reduction in the rate of premature birth before the 32 nd GW. Replacement therapy with L-thyroxine was considered safe from a clinical point of view, and an improvement in the course of pregnancy was documented [22].

The Working Group for Obstetrics, Department of Maternal Diseases (AGG) of the German Society of Gynecology and Obstetrics (DGGG) recommends screening by means of a TSH test for all pregnant women with a history of risk factors. According to an established algorithm, L-thyroxine replacement therapy can be considered in the case of TSH concentrations of 2.5 to 4.0 mU/L and positive TPO antibodies (TPO-Ab). From a TSH value of 4.0 mU/L and with positive TPO-Ab, L-thyroxine replacement therapy should be given [23]. The AGG recommendations only apply post-conception, in line with group B, and do not take into account maternal free thyroxine level, which reflects the secretory performance of the thyroid gland regardless of the TSH level and TPO-Ab. Free thyroxine which can cross the placental barrier is considered as a measure of fetal hormone supply while TSH which can not cross the placental barrier indicates maternal metabolism [24]. Maternal euthyroidism does not rule out hypothyroxinemia, and thus insufficient thyroxine supply to the fetus.

From a pathophysiological point of view, little research has been done on a possible correlation between thyroxine deficiency and the risk of premature birth. It is considered certain that the maternal thyroid gland is subjected to considerable additional stress as a result of pregnancy. During pregnancy, thyroid hormone requirements increase by approximately 25–50%. Over 99% of thyroid hormones are bound to transport proteins in serum and are therefore not metabolically active. The dominant binding protein is thyroxine-binding globulin (TBG), the concentration of which increases two to three-fold from the baseline values depending on the estrogen level up to the 12 th–14 th GW. This additional TBG reduces the concentration of free thyroid hormones by an average of 10–15%, thus removing them from the metabolism. To maintain maternal euthyroidism, the synthesis and secretion of thyroid hormones is increased by approximately 30–100%.

TBG synthesis is continuously stimulated in the maternal and fetal liver by placental estrogen up until delivery. Since the estrogen level increases continuously during pregnancy, this leads to maximum continuous stimulation of the maternal thyroid gland, as well as the fetal thyroid gland. In a healthy, iodine-filled thyroid gland, thyroxine is predominantly synthesized and secreted. Physiological maternal euthyroid hyperthyroxinemia develops, and does not subside until 14 days after delivery [25, 26]. Women are five times more likely to suffer from latent and manifest hypothyroidism than men; nevertheless, the role of maternal thyroid function in preventing premature birth has received little attention to date [5, 7, 8].

Other risk factors include BMI and hypertension. This is consistent with a number of epidemiological studies [27, 28, 29, 30, 31]. Being significantly overweight or underweight increases the risk of premature birth compared to being of normal weight or mildly overweight. When BMI and the risk of premature birth is plotted on a graph, the result is a U-shaped curve in which the risk of premature birth is at its highest in women who are underweight or extremely overweight. In the present study, the risk of premature birth was higher for underweight women than for overweight or mildly obese women. However, too little weight gain during pregnancy has been shown to be a more suitable predictor of premature birth, with a particular increase in risk among women who have a low BMI prior to conception.

Due to a lack of data, the recognized risk factor s.p. premature birth had to be statistically estimated. The result confirms a recent epidemiological study, which has shown that s.p. premature birth is a significant risk factor [19]. The same applies to hypertension, which has long been known as a risk factor [31].

This study has limitations in terms of its design. In theory, it seems reasonable to conduct a double-blind randomized controlled trial. This would largely ensure both structural and observational uniformity. However, a study design of this kind would not be ethically acceptable.

Furthermore, in group A, three different degrees of thyroxine deficiency (hypothyroxinemia, latent hypothyroidism, and manifest hypothyroidism) have been combined into one group. It can be postulated that the women with manifest hypothyroidism are likely to have benefited the most. The extent to which women with hypothyroxinemia or latent hypothyroidism benefit from L-thyroxine replacement therapy would need to be clarified in a separate study. About the control group we only know that the women had hypothyroidism and were therefore treated with L-thyroxine. It can be assumed that the control group had significantly more manifest hypothyroidism and thus a more severe

thyroxine deficiency, especially since hypothyroxinemia, as the mildest variant of thyroxine deficiency, currently does not receive any attention from internal medicine or obstetrics. Even if it is not possible to accurately assess from this study which form of thyroid insufficiency carries the highest risk of premature birth, it still seems clear that women with hypothyroidism need to be given much better care prior to conception. This limitation also applies to group B.

Other variables that contributed to a structural inequality among the groups were taken into account in the analysis. In light of this, there is reason to believe that the results obtained in this study can be generalized. In order to verify the validity of the results, it would be desirable to follow this study up with a prospective observational study comprising a sufficiently large number of cases.

Conclusion

Inadequately treated hypothyroidism increases the risk of premature birth. Preconceptional intervention and L-thyroxine dose adjustment appear to most effectively reduce the rate of premature births. Compared to the control group, the premature birth rate was 70 % lower in study group A ($p < 0.0001$) and 42 % lower in study group B ($p = 0.0086$). In the multiple logistic regression analyses and in the simulation calculation, in addition to group assignment (A or B versus control group), hypertension, BMI, and a previous premature birth were identified as other independent risk factors. Inadequately treated manifest hypothyroidism is a significant risk factor for premature birth. Further studies should clarify whether hypothyroxinemia and latent hypothyroidism are also risk factors.

Contributors' Statement

The authors declare to have made an equivalent contribution to this publication.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References/Literatur

[1] Stepan H, Verlohren S. Frühgeburtlichkeit. Frauenheilkunde up2date 2010; 4: 235–247. doi:10.1055/s-0030-1247486

[2] Ivanov ID, Buzalov SA, Hinkova NA. Prevention of Preterm Birth. J Biomed Clin Res 2018; 11: 95–104. doi:10.2478/jbcr-2018-0013

[3] Institut für Qualitätssicherung und Transparenz im Gesundheitswesen (IQTIG). Bundesauswertung zum Erfassungsjahr 2017. Geburtshilfe. Qualitätsindikatoren. 01.08.2018. Accessed June 13, 2022 at: https://iqtig.org/downloads/auswertung/2017/16n1gebh/QSKH_16n1-GEBH_2017_BUAW_V02_2018–08–01.pdf

[4] Schleussner E. The prevention, diagnosis and treatment of premature labor. Dtsch Arztebl Int 2013; 110: 227–235. doi:10.3238/arztebl.2013.0227

[5] Abele H, Bahlmann F, Berger R et al. Prävention und Therapie der Frühgeburt. Leitlinie der DGGG, OEGGG und SGGG (S2k-Niveau, AWMF-Registernummer 015/025. 2022. Accessed December 19, 2022 at: https://register.awmf.org/de/leitlinien/detail/015–025

[6] Euro-Peristat Project. European Perinatal Health Report Core indicators of the health and care of pregnant women and babies in Europe in 2015. 2018. Accessed June 13, 2022 at: https://www.europeristat.com/index.php/reports/european-perinatal-health-report-2015.html

[7] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry Number 015/025, September 2022) – Part 1 with Recommendations on the Epidemiology, Etiology, Prediction, Primary and Secondary Prevention of Preterm Birth. Geburtshilfe Frauenheilkd 2023; 83: 547–568. doi:10.1055/a-2044-0203

[8] Berger R, Abele H, Bahlmann F et al. Prevention and Therapy of Preterm Birth. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry Number 015/025, September 2022) – Part 2 with Recommendations on the Tertiary Prevention of Preterm Birth and on the Management of Preterm Premature Rupture of Membranes. Geburtshilfe Frauenheilkd 2023; 83: 569–601. doi:10.1055/a-2044-0345

[9] Dudenhausen JW, Friese K, Kirschner W. Präkonzeptionelle Gesundheitsberatung und Beratung zur Wahl der Geburtsklinik als weitere Instrumente zur Verringerung von Frühgeburten. Z Geburtshilfe Neonatol 2007; 211: 142–146. doi:10.1055/s-2007-960658

[10] Korevaar M, Derakhshan A, Taylor PN et al. Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth: A Systematic Review and Meta-analysis. JAMA 2019; 322: 632–664. doi:10.1001/jama.2019.10931

[11] Unuane D, Velkeniers B. Impact of thyroid disease on fertility and assisted conception. Best Pract Res Clin Endocrinol Metab 2020; 34: 101378. doi:10.1016/j.beem.2020.101378

[12] Nasirkandy MP, Badfar G, Shohani M et al. The relation of maternal hypothyroidism and hypothyroxinemia during pregnancy on preterm birth: An updated systematic review and meta-analysis. Int J Reprod Biomed 2017; 15: 543–552

[13] Dosiou C, Medici M. Management of Endocrine Disease: Isolated maternal hypothyroxinemia during pregnancy: knowns and unknowns. Eur J Endocrinol 2017; 176: 21–38. doi:10.1530/EJE-16-0354

[14] De Groot L, Abalovich M, Alexander EK et al. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2012; 97: 2543–2565. doi:10.1210/jc.2011-2803

[15] Alexander EK, Pearce EN, Brent GA et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27: 315–389. doi:10.1089/thy.2016.0457

[16] Lazarus J, Brown RS, Daumerie C et al. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J 2014; 3: 76–94. doi:10.1159/000362597

[17] Koullali B, van Zijl MD, Kazemier BM et al. The association between parity and spontaneous preterm birth: a population based study. BMC Pregnancy Childbirth 2020; 20: 233. doi:10.1186/s12884-020-02940-w

[18] Cavoretto P, Candiani M, Giorgione V et al. Risk of spontaneous preterm birth in singleton pregnancies conceived after IVF/ICSI treatment: meta-analysis of cohort studies. Ultrasound Obstet Gynecol 2018; 51: 43–53. doi:10.1002/uog.18930

[19] Díaz-Rodríguez A, Feliz-Matos L, Ruiz-Matuk CB. Risk factors associated with preterm birth in the Dominican Republic: a case-control study. BMJ Open 2021; 11: e045399. doi:10.1136/bmjopen-2020-045399

[20] Reid SM, Middleton P, Cossich MC et al. Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. Cochrane Database Syst Rev 2013(5): CD007752. doi:10.1002/14651858.CD007752.pub3

[21] Spencer L, Bubner T, Bain E et al. Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. Cochrane Database Syst Rev 2015 (9): CD011263. doi:10.1002/14651858.CD011263.pub2

[22] Runkle I, Paz de Miguel M, Barabash A et al. Early Levothyroxine Treatment for Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy: The St Carlos Gestational and Thyroid Protocol. Front Endocrinol 2021; 12: 743057. doi:10.3389/fendo.2021.743057

[23] Hamza A, Schlembach D, Schild RL et al. Recommendations of the AGG (Working Group for Obstetrics, Department of Maternal Diseases) on How to Treat Thyroid Function Disorders in Pregnancy. Geburtshilfe Frauenheilkd 2023; 83: 504–516. doi:10.1055/a-1967-1653

[24] Korevaar TIM, Tiemeier H, Peeters RP. Clinical associations of maternal thyroid function with foetal brain development: Epidemiological interpretation and overview of available evidence. Clin Endocrinol (Oxf) 2018; 89: 129–138. doi:10.1111/cen.13724

[25] Korevaar TI, de Rijke YB, Chaker L et al. Stimulation of Thyroid Function by Human Chorionic Gonadotropin During Pregnancy: A Risk Factor for Thyroid Disease and a Mechanism for Known Risk Factors. Thyroid 2017; 27: 440–450. doi:10.1089/thy.2016.0527

[26] Torremante P. Die Schilddrüse in der gynäkologischen Sprechstunde. Menopause & Contraception 2012; 1: 1–11

[27] Vinturache A, McKeating A, Daly N et al. Maternal body mass index and the prevalence of spontaneous and elective preterm deliveries in an Irish obstetric population: a retrospective cohort study. BMJ Open 2017; 7: e015258. doi:10.1136/bmjopen-2016-015258

[28] Sua XJ, Huangb SJ, Li X et al. Prepregnancy Overweight and Obesity Are Associated with an Increased Risk of Preterm Birth in Chinese Women. Obes Facts 2020; 13: 237–244. doi:10.1159/000506688

[29] Silva FP, Souza RT, Cecatti JG et al. Role of Body Mass Index and gestational weight gain on preterm birth and adverse perinatal outcomes. Sci Rep 2019; 9: 13093. doi:10.1038/s41598-019-49704-x

[30] Dudenhausen JW, Kunze M, Wittwer-Backofen U et al. The relationship between maternal age, body mass index, and the rate of preterm birth. J Turk Ger Gynecol Assoc 2018; 19: 182–186. doi:10.4274/jtgga.2018.0057

[31] Jung YM, Oh GC, Noh E et al. Pre-pregnancy blood pressure and pregnancy outcomes: a nationwide population-based study. BMC Pregnancy Childbirth 2022; 22: 226. doi:10.1186/s12884-022-04573-7