PHARMACIA

Pharmacia 71: 1–7
DOI 10.3897/pharmacia.71.e141047

Research Article

Levothyroxine therapy in pregnancy: Are we overtreating patients?

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Received 5 November 2024 ♦ **Accepted** 25 November 2024 ♦ **Published** 11 December 2024

Citation: Yanachkova V, Staynova R, Grekova-Kafalova D, Petkova V (2024) Levothyroxine therapy in pregnancy: Are we overtreating patients? Pharmacia 71: 1–7. https://doi.org/10.3897/pharmacia.71.e141047

Abstract

Background: Pregnancy imposes unique physiological requirements on the mother's thyroid gland to meet the thyroid hormone demands both for her and the fetus. A lack of consensus in current guidelines on diagnosing thyroid dysfunction during pregnancy and administering levothyroxine raises concerns regarding treatment efficacy. As hypothyroidism—subclinical or overt—is a recognized risk factor for an unfavorable pregnancy outcome, the administration of excessive or unneeded therapy can also lead to complications.

Objective: This study aims to evaluate the prevalence of levothyroxine replacement therapy among euthyroid pregnant women.

Materials and methods: A retrospective cohort study was conducted using the data from 6237 pregnant women who delivered at the OB/GYN Hospital "Dr. Shterev" in Sofia, Bulgaria, between January 2017 and December 2022. Thyroid function data were available for 1746 pregnant women meeting inclusion criteria: aged > 18 years, with singleton pregnancies, and thyroid hormone level tests conducted no later than mid-second trimester.

Results: According to pregnancy-specific thyroid disorder diagnostic criteria, patients were categorized into euthyroid (n = 1066), subclinical hypothyroidism (n = 421), overt hypothyroidism (n = 48), isolated maternal hypothyroxinemia (n = 160), gestational thyrotoxicosis (n = 46), and Graves' disease (n = 5). Analysis revealed that 37.7% (n = 401) of euthyroid pregnant women were prescribed levothyroxine. Only 22.9% (n = 92) of euthyroid women received hormone replacement therapy due to autoimmune thyroiditis.

Conclusion: Our findings prompt consideration regarding the appropriateness of levothyroxine therapy for euthyroid pregnant women. Clear guidance is warranted on the initiation of hormone replacement therapy during pregnancy.

Keywords

euthyroid women, hormone replacement therapy, hypothyroidism, levothyroxine, pregnancy, thyroid dysfunction

Introduction

The optimal function of the thyroid gland in pregnant women is essential for controlling metabolic processes, particularly in the regulation of glucose metabolism, water and sodium balance, and calcium-phosphorus exchange (Muller et al. 2018). These metabolic pathways are integral to sustaining energy homeostasis during pregnancy. In contrast, an adequate supply of maternal thyroid hormones is critical for the developing fetus, ensuring normal growth, maturation, and neurological development (Fotakis et al. 2022). In the early stages of pregnancy, fetal development and maturation depend entirely on maternal thyroid hormone levels, as fetal thyroid function begins only around 20 weeks of gestation (Korevaar et al. 2017; Zuñiga et al. 2022). Therefore, the complex regulatory mechanisms of thyroid function in pregnant women, which ensure the fulfillment of both maternal and fetal biological needs, are of significant importance (Park 2018).

Employing population norms for thyroid-stimulating hormone (TSH) levels in pregnant women, the prevalence of thyroid dysfunction showed no significant differences when compared to that observed in the general population (Yanachkova et al. 2024). However, when trimester-specific criteria for TSH levels are applied, subclinical hypothyroidism is detected in approximately 4.8% to 18% of pregnant women, while overt hypothyroidism is observed in about 0.2% to 1.0% of cases (Maraka et al. 2016; Dülek 2018). The leading cause of hypothyroidism is Hashimoto's autoimmune thyroiditis, which affects 5% to 20% of pregnant women who test positive for thyroid antibodies (Moleti et al. 2018). Autoimmune thyroiditis is observed in approximately 55% of women diagnosed with subclinical hypothyroidism and in over 80% of those with overt hypothyroidism. Among women with normal thyroid function, the estimated prevalence of positive antibody titers—anti-thyroid peroxidase (TPO) antibodies and anti-thyroglobulin (Tg-Ab) antibodies—stands at around 18%. Notably, approximately 16% of pregnant women who test positive for antibodies but maintain normal thyroid function in the first trimester exhibit a TSH level above 4.0 mIU/L by the third trimester (Urgatz and Poppe 2024).

It is imperative to approach the examination of isolated maternal hypothyroxinemia with specific scrutiny. This condition is characterized by normal TSH levels alongside decreased free thyroxine (FT4) levels (Ramezani Tehrani et al. 2021; Liu et al. 2022b). The prevalence of IMH exceeds that of subclinical hypothyroidism, clinical hypothyroidism, and autoimmune thyroiditis. Notably, the FT4 level at 12 weeks of gestation has been identified as a significant predictor of fetal cognitive development (Miranda and Sousa 2018). Therefore, it is recommended that FT4 testing be conducted during the first trimester (Ramezani Tehrani et al. 2021).

Within the past twenty years, a substantial body of research has been amassed about the adverse effects of subclinical hypothyroidism, isolated maternal hypothyroxinemia, and thyroid autoimmunity on both pregnancy outcomes and fetal development (Zhang et al. 2017; Chung 2020; Peng and Pearce 2022). However, it is crucial not to disregard the evidence from studies that demonstrate the negative consequences linked to excessive treatment of individuals who are in good health and have a normal thyroid function.

An association has been observed between thyroid dysfunction during pregnancy and the manifestation of several complications for both maternal and fetal health (Alemu et al. 2016). The conditions that can arise during pregnancy include microcytic anemia, cardiac dysfunction, spontaneous abortion, preterm birth, intrauterine growth restriction, gestational hypertension, and preeclampsia (Kumar et al. 2023). Additional complications may include postpartum hemorrhage, low birth weight, congenital anomalies, stillbirth, delayed development, impaired neurological development, and transient congenital hypothyroidism caused by thyroid-blocking antibodies (Ozon et al. 2019).

The presence of subclinical hypothyroidism, isolated maternal hypothyroxinemia, and hyperthyroidism has been found to potentially contribute to an elevated susceptibility to gestational diabetes mellitus (Chen et al. 2022; Sitoris et al. 2022). Hence, the presence of subclinical hypothyroidism in the mother is linked to impairments in the neurobehavioral development of the child (Thompson et al. 2018).

Treatment with levothyroxine replacement therapy during pregnancy demands close attention and proper management due to the fluctuating levels of thyroid hormones throughout gestation. Careful assessment of individual circumstances is necessary to ensure a healthy pregnancy and minimize potential risks to both the mother and fetus (Joshi et al. 2024). Distinguishing between women with thyroid dysfunction and those with normal thyroid function is crucial. However, the initial phase of treatment is challenging, as most countries lack trimester-specific reference intervals for TSH levels, leading to reliance on fixed, predetermined thresholds (Turkal et al. 2022).

Thyroid hormone replacement therapy is used to treat both subclinical and overt hypothyroidism, with TSH levels serving as the primary indicator of therapeutic success. Levothyroxine is often initiated when TSH levels are less than 2.5 mU/L or between 2 and 2.5 mU/L, in order to keep TSH levels below 1 mU/L (Ding et al. 2021). Even in cases where antithyroid antibodies are detected, this is not taken into account in any recommendations.

Given the rising prescription rates of levothyroxine in non-pregnant individuals, our objective was to evaluate the prevalence of levothyroxine replacement therapy among euthyroid pregnant women.

Material and methods

Study design, setting, and population

A retrospective cohort study was conducted using the data from 6237 pregnant women who delivered at the OB/GYN Hospital "Dr. Shterev" in Sofia, Bulgaria, between January 2017 and December 2022. Thyroid function data were available for 1746 pregnant women meeting inclusion criteria: 18 to 45 years of age, with singleton pregnancies, with thyroid hormone level tests assessed at least twice and no later than mid-second trimester. According to the diagnostic criteria established by the European Thyroid Association (ETA) guideline, women included in the study were classified based on their thyroid dysfunction status into the following groups: euthyroid, subclinical hypothyroidism, overt hypothyroidism, gestational thyrotoxicosis, isolated maternal hypothyroxinemia, and Graves' disease (Fig. 1). Euthyroid pregnant women (n = 1066) were classified into two distinct groups: those prescribed levothyroxine without pre-existing thyroid hypofunction (levothyroxine users, n = 401) and those who did not receive levothyroxine therapy until delivery (levothyroxine non-users, n = 665).

Levothyroxine therapy was initiated for various reasons, including a family history of thyroiditis, the presence of positive TPO-Ab and/or Tg-Ab antibodies, conception via assisted reproductive technology (ART), being overweight, or having a TSH level of 2.5 mU/L. Detailed information regarding demographics, medical and obstetric history, and thyroid function tests was obtained from patient records. The two cohorts were compared based on age, family history of thyroid dysfunction, body mass index (BMI), parity, mean levels of TSH, FT4, antibody status, method of conception, as well as pregnancy complications and neonatal outcomes.

Ethics approval

The study was reviewed and approved by the Institutional Review Board of the Specialized Obstetrics and Gynecology Hospital "Dr Shterev," Sofia, Bulgaria (protocol No. 466/2018).

Laboratory measurements

TSH levels were measured using the immuno-chemiluminescence method (Roche Cobas 8000, Switzerland), and the TSH reference interval for the respective laboratory was 0.27–4.20 mUI/L. For FT4 levels, an immuno-chemiluminescence method (Roche Cobas 8000, Switzerland) was used (reference range for the laboratory: 12–22 pmol/L). Anti-thyroid antibody levels were determined by the electro-chemiluminescence method, ECLIA (Roche Cobas 8000, Switzerland). The TSH intraassay coefficients of variation were 1.8; for FT4, it was 1.6, and for anti-TPO and TAT, < 13%. The lower range of detection for TSH was 0.005 mIU/L. In all patients, whose data were used for the analysis, information for ultrasound of the thyroid gland was available.

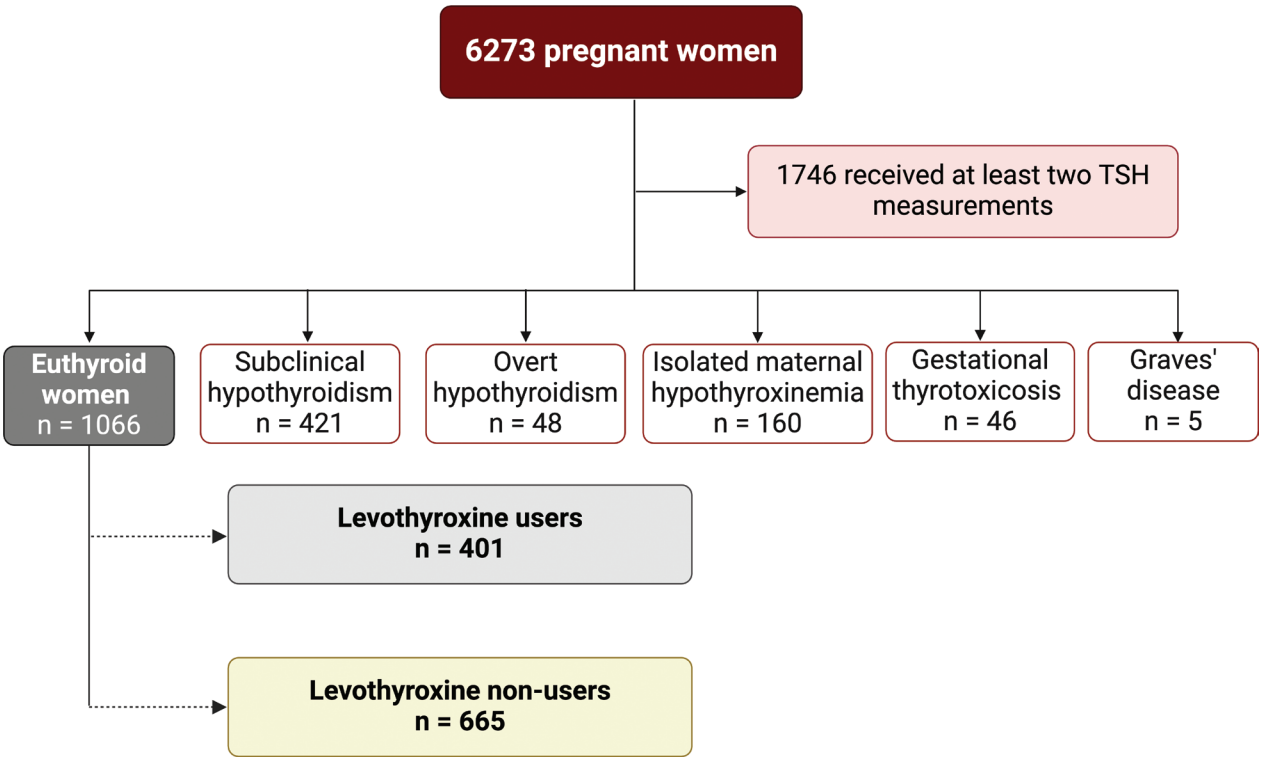

Figure 1. Flowchart for cohort selection.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM Corp, Armonk, NY, USA). The normality of the data distribution was assessed through the Kolmogorov-Smirnov test. Continuous data were expressed with mean and standard deviation. Categorical data were presented as numbers and percentages. The Mann-Whitney U test was used to assess the differences between continuous variables. Categorical variables were analyzed by a chi-square test. $P < 0.05$ was considered significant.

Results

Data from 1066 women were included in the final analysis. All participants were initially euthyroid, with no underlying abnormalities in thyroid function. The cohort was divided into two groups: euthyroid women prescribed levothyroxine therapy (levothyroxine users) and those who did not receive any treatment (levothyroxine non-users). No statistically significant differences regarding age or BMI were observed between the two groups. Levothyroxine users had higher mean TSH levels (2.65 ± 0.75 vs. 1.73 ± 0.64; p = 0.001) but lower mean FT4 levels (14.49 ± 2.33 vs. 16.36 ± 13.11; p = 0.001). Additionally, levothyroxine users had a higher incidence of family history of thyroid disease, positive anti-thyroid antibodies, and pregnancies achieved through assisted reproductive technology (ART). Neonatal weight monitoring revealed no significant differences between the two groups (Table 1).

There was a statistically significant difference in the incidence of complications during pregnancy among euthyroid patients on levothyroxine treatment (p = 0.001). A higher incidence of gestational hypertension (GHT) was observed among euthyroid patients treated with levothyroxine (Table 2).

Table 1. Main characteristics of the observed women.

Characteristics	Levothyroxine users N = 401	Levothyroxine non-users N = 665	p-value
Age (years)	32.3 ± 4.3	31.9 ± 4.6	0.160
BMI (kg/m²)	23.7 ± 4.9	23.6 ± 4.0	0.529
TSH (mIU/L)	2.65 ± 0.75	1.73 ± 0.64	**0.001**
FT4 (pmol/L)	14.49 ± 2.33	16.36 ± 13.11	**0.001**
Family history of thyroid dysfunction			**0.001**
Yes	183 (45.6%)	104 (15.6%)	
No	218 (54.4%)	561 (84.4%)	
Parity			**0.001**
Primipara	294 (73.3%)	543 (81.7%)	
Multipara	107 (26.7%)	122 (18.3%)	
Mode of conception			**0.001**
Spontaneous	328 (81.8%)	608 (91.4%)	
ART	73 (18.2%)	57 (8.6%)	
Thyroid autoimmunity			**0.001**
Yes	92 (22.9%)	51 (7.7%)	
No	309 (77.1%)	614 (92.3%)	
Thyroid nodules			0.821
Yes	14 (3.5%)	25 (3.8%)	
No	387 (96.5%)	640 (96.2%)	
Pregnancy complications			**0.001**
Yes	87 (21.7%)	81 (12.2%)	
No	314 (78.3%)	584 (87.8%)	
Delivery mode			0.470
Vaginal	222 (55.4%)	353 (53.1%)	
Cesarean section	179 (44.6%)	312 (46.9%)	
Birthweight, g	3324.36 ± 400.27	3299.82 ± 385.03	0.392

Abbreviations: ART: assisted reproductive technology; BMI: body mass index; TSH: thyroid-stimulating hormone; FT4: free thyroxin. Data are presented as numbers (percentages) or mean ± SD.

Table 2. Pregnancy complications associated with thyroid dysfunction.

Pregnancy complication	Levothyroxine users N = 87	Levothyroxine non-users N = 81
GDM, n (%)	24 (27.6)	29 (35.8)
PE, n (%)	14 (16.1)	14 (17.3)
Preterm delievery, n (%)	21 (24.1)	23 (28.4)
GHT, n (%)	28 (32.2)	15 (18.5)

Abbreviations: GDM: gestational diabetes mellitus; PE: preeclampsia; GHT: gestational hypertension. Data are presented as numbers (percentages).

Discussion

Our study aimed to determine the percentage of euthyroid pregnant women receiving levothyroxine therapy according to trimester-specific reference intervals for thyroid function in pregnancy and to analyze the therapeutic benefits in patients without evidence of thyroid dysfunction. The increased demand for thyroid hormones during pregnancy is well-documented, as sufficient hormone levels and appropriate maternal thyroid adaptation are essential for a healthy pregnancy course. This need underscores the importance of establishing trimester-specific reference intervals for thyroid hormone levels in pregnant women.

A precise definition of subclinical and overt hypothyroidism is critical for establishing criteria to initiate thyroid hormone replacement therapy. The primary goal of treatment is to prevent maternal and fetal complications. However, there is ongoing debate regarding the threshold TSH values that warrant the initiation of levothyroxine therapy or adjustments to existing dosages (Lazarus et al. 2014). The role of anti-thyroid antibodies is also of significant concern (Korevaar et al. 2017). Even in euthyroid patients, the presence of anti-thyroid antibodies is associated with an elevated risk of complications, including increased incidence of spontaneous abortion and preterm delivery (Lazarus et al. 2014; Liu et al. 2022a).

The question of whether and when to initiate levothyroxine therapy in euthyroid pregnant women remains a topic of debate (Lazarus et al. 2014). According to the American Thyroid Association (ATA) guidelines, pregnant euthyroid women who are positive for thyroid antibodies and have TSH levels between 2.5 and 4.2 mU/L should receive levothyroxine therapy (Alexander et al. 2017). This recommendation is based on the understanding that autoimmune thyroiditis compromises the thyroid's capacity to meet the increased hormonal demands of pregnancy. Additional evidence is provided by the study conducted by Korevaar et al. (Korevaar et al. 2017). The use of levothyroxine in eu-

thyroid patients undergoing assisted reproductive technology is justified (Alexander et al. 2017; Korevaar et al. 2017). In contrast, there is currently insufficient evidence to recommend levothyroxine therapy for antibody-negative euthyroid pregnant women with TSH levels at or below 2.5 mU/L.

The effectiveness of levothyroxine therapy during pregnancy, the justification for its prescription, and the consideration of costs associated with frequent testing in this population remain open questions. While optimal thyroid hormone levels are recognized as essential for successful pregnancy outcomes, recent studies have highlighted potential adverse effects of thyroid hormone overtreatment on both maternal and neonatal health (Wiles et al. 2015; Korevaar 2020b, 2020a; Turunen et al. 2021).

In the present study, we conducted a comparative analysis of the immediate effects on maternal and fetal outcomes in pregnant women receiving levothyroxine therapy, based on trimester-specific reference intervals. Our findings suggest that the initiation of levothyroxine treatment in women with normal thyroid function, when compared to the trimester-specific reference intervals established for pregnant individuals, does not reduce the pregnancy-related complications. In fact, the results indicate a higher prevalence of GHT among euthyroid pregnant women who are administered additional levothyroxine.

Various practice guidelines recommend a 20–30% increase in the levothyroxine dose for women with hypothyroidism as soon as pregnancy is confirmed. (Lazarus et al. 2014; Alexander et al. 2017; ACOG 2020; Chan et al. 2023). However, these empirically based adjustments do not consistently lead to favorable patient outcomes, and cases of overdose remain frequent. Data on dosage adjustments for subclinical hypothyroidism, defined by trimester-specific reference intervals, commonly with TSH levels above 2.5 mU/L, have become increasingly contradictory. Evidence suggests that, in some cases, overtreatment does not provide additional benefits for pregnancy outcomes (Hales et al. 2020; Mikołajczak et al. 2020; Turunen et al. 2021; Peng and Pearce 2022).

Furthermore, euthyroid pregnant women who received levothyroxine treatment demonstrated notable disparities in overall health and comorbidities compared to those who did not receive treatment (Maraka et al. 2017). In clinical practice, it is often observed that women without pre-existing thyroid disorders or signs of autoimmune disease maintain TSH levels below 2.5 mU/L. Consequently, this frequently leads to the initiation of levothyroxine therapy in patients with TSH levels ranging from 2 to 2.5 mU/L, resulting in overtreatment and the potential development of iatrogenic hyperthyroidism in these women. This raises an important question: What benefits does this treatment provide for these women? It is essential to assess whether there are potential risks associated with administering this unwarranted therapy.

The Controlled Antenatal Thyroid Screening Study (CATS) was the first attempt to look at how treating a mother's subclinical hypothyroidism affects children's cognitive development (Lazarus et al. 2012). The study found no link between subclinical hypothyroidism in either treated or untreated women and the outcomes reported in questionnaires regarding children's behavior and autism spectrum disorders. However, children of overmedicated mothers have been observed to have greater autism spectrum symptoms and behavioral problems (Lazarus et al. 2012; Hales et al. 2020). The findings of this study suggest that levothyroxine treatment should be carefully monitored, and unnecessary therapy should be avoided. This highlights the complex balance between the benefits and risks of thyroid replacement therapy during pregnancy. This investigation has continued over the years in the CATS-II study, which also assessed long-term effects on anthropometric, bone, and cardiometabolic outcomes in both mothers and offspring, including a group of euthyroid individuals (Muller et al. 2020). The addition of levothyroxine for women with subclinical hypothyroidism did not significantly impact the long-term anthropometric, bone, or cardiometabolic parameters of their offspring. However, the lack of treatment was associated with sustained long-term increases in BMI and fat mass in these women (Muller et al. 2020). Mikolajczak et al. observed that levothyroxine overtreatment in pregnant women may decrease the volume of the thyroid gland of the offspring (Mikołajczak et al. 2020).

The evidence regarding therapeutic benefits for pregnant women who are euthyroid, antibody-positive, or have decreased thyroid function (based on trimester-specific reference ranges) is inconsistent (Korevaar 2020b). Similarly, the administration of levothyroxine has not demonstrated significant advantages for these women (Di Girolamo et al. 2022). In the absence of adverse effects, it is advisable to continue levothyroxine replacement treatment until the results of ongoing trials are available. However, it is important to consider the potential for excessive medical intervention during pregnancy. Therefore, close monitoring for iatrogenic hyperthyroidism is recommended, including follow-up TSH testing four to six weeks after any adjustments to levothyroxine dosage. Furthermore, it is important to recognize that the majority of these women are unlikely to require continued thyroid hormone replacement therapy following pregnancy (Wiles et al. 2015).

In our study, 37.6% of euthyroid pregnant women were receiving levothyroxine replacement therapy. In some cases, this therapy was not prescribed due to factors such as family history of thyroid disease, obesity, or multiple pregnancies. Our analysis shows that only 22.9% (n = 92) of euthyroid women received hormone replacement therapy due to thyroid autoimmunity.

Conclusion

Thyroid dysfunction in pregnant women presents a considerable risk for adverse outcomes during both the gestational and postpartum periods. Contemporary medical practice should prioritize preventive measures, particularly through early screening for thyroid abnormalities in the first trimester, which would enable timely detection, even among low-risk populations. Simultaneously, it is essential to critically assess diagnostic criteria and determine the specific cases and patient profiles in which hormone replacement therapy

initiation is appropriate. Mistimed or inadequate treatment administration can negatively impact pregnancy outcomes.

Over recent decades, levothyroxine has become one of the most commonly prescribed medications. However, the primary concern remains the extent to which therapeutic criteria for its use are met effectively. Pregnant women represent a distinct population requiring tailored therapeutic strategies. When proposing treatment interventions, it is crucial to consider that, while these may meet the needs of both mother and fetus, they may also carry potential adverse effects for both.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Specialized Hospital of Obstetrics and Gynecology "Doctor Shterev" Sofia, Bulgaria (Protocol No. 466/2018).

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Funding

No funding was reported.

Author contributions

Conceptualization, V.Y.; methodology, V.Y and R.S.; investigation, V.Y., and R.S.; data curation, V.Y.; Formal analysis, R.S.; visualization R.S.; writing—original draft preparation, V.Y. and R.S.; writing—review and editing, R.S. and D.G-K.; supervision, V.P.

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Data availability

All of the data that support the findings of this study are available in the main text.

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