Heliyon 11 (2025) e41021

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Hypertensive disorders of pregnancy affected thyroid hormone synthesis via endoplasmic reticulum stress in preterm infant rats

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ARTICLE INFO

Keywords:
Preterm infants
Congenital hypothyroidism
Hypertensive disorders of pregnancy
Endoplasmic reticulum stress

ABSTRACT

Background: Maternal hypertensive disorders of pregnancy (HDP) was associated with increased risk of congenital hypothyroidism in preterm infants, but its underlying mechanisms remain unclear.
Objective: To investigate the possible mechanisms by which intrauterine exposure to HDP affects thyroid hormone synthesis in preterm infant rats.
Methods: preterm infant rats were obtained by Caesarean section delivery from the L-NAME group and Control groups which was induced by L-NAME and saline, respectively. Thyroid hormone levels of preterm infant rats were detected by ELISA, and morphology structure were observed by H&E staining and electron microscopy, and the expression of key factors of thyroid hormone synthesis and endoplasmic reticulum stress indicators were analyzed by RT-qPCR and Western blotting.
Results: Compared with the Control group, significantly higher serum TSH concentration was observed in the L-NAME group ($p < 0.05$), while T3 and T4 levels showed no noticeable change. The L-NAME group revealed a reduction in the size and number of thyroid follicles, with the emergence of thyroid follicular epithelial hyperplasia. While electron microscopy revealed that the endoplasmic reticulum of thyroid follicular epithelial cells was marked swollen within L-NAME group. Additionally, the mRNA expression of *Ttf1*, *Pax8* and *Tshr* was down-regulated in thyroid tissues of L-NAME group. Furthermore, the protein levels of Tg, NIS and TSHR were reduced, while the protein level of p-IRE1α, ATF6α, XBP1s and Bip were increased in the L-NAME group.
Conclusion: The results indicated that HDP may reduce the expression of key molecules involved in thyroid synthesis through endoplasmic reticulum stress which could ultimately result in the development of congenital hypothyroidism.

1. Introduction

Epidemiological research has shown that the incidence of congenital hypothyroidism is 1/3000-1/2000, which is much higher in preterm infants than that in term infants [1,2]. Without timely intervention, congenital hypothyroidism may have adverse effects on

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https://doi.org/10.1016/j.heliyon.2024.e41021
Received 16 April 2024; Received in revised form 14 November 2024; Accepted 5 December 2024
Available online 11 December 2024

neonatal growth, development and even cause irreversible damage to neurological development [3–5]. Our research team found that the smaller the gestational age and the lower birth weight of extremely preterm infants, the higher the incidence of congenital hypothyroidism. In addition, we also found that the correlation between maternal hypertensive disorders of pregnancy (HDP) and congenital hypothyroidism was particularly prominent [6].

HDP is a vascular disease of the placenta in pregnancy that involves multiple organ functions, and is an important cause of maternal and neonatal deaths, complications, and medically induced preterm labor worldwide, seriously jeopardizing the health of mothers and infants [7–9]. Numerous studies have demonstrated that HDP is closely related to thyroid dysfunction in pregnancy [10,11]. Our prospective study had reported that HDP was an independent risk factor for congenital hypothyroidism in preterm infants, as the incidence of congenital hypothyroidism in preterm infants that were born with maternal HDP was reached up to15.7 %, which is about 2.2 times higher than that of non-HDP infants [6].

The clinical manifestations of congenital hypothyroidism in preterm infants are characterized by markedly elevated thyroid stimulating hormone (TSH), with or without a concomitant reduction in free triiodothyronine (T3) and/or free thyroxine (T4) levels, which is similar to that of subclinical hypothyroidism in adults [12,13]. The rapid return to normal TSH level after the replacement therapy suggests deficiency in thyroid hormone synthesis. Thus, a relative deficiency of thyroid hormones may be one of the mechanisms of congenital hypothyroidism in preterm infants [14]. In vitro studies show that subclinical hypothyroidism is an endoplasmic reticulum storage disease [15]. Previous experiments by our research team found that HDP caused abnormal endoplasmic reticulum morphology in the preterm infant rats of different gestational ages [16]. As such, it is presumed that HDP may affect thyroid hormone synthesis by interfering with endoplasmic reticulum homeostasis.

In this study, we used NG-Nitro-L-arginine-methylester (L-NAME) to establish a rat model of HDP and obtained preterm infant rats by Caesarean section delivery [17,18], to simulate the clinical signs of congenital hypothyroidism in preterm infant rats. The objective of this study was to explore the possible mechanisms of congenital hypothyroidism caused by intrauterine exposure to HDP in preterm infant rats. To this end, thyroid hormone levels were detected, the morphological structure of thyroid was observed, and the expression of key factors of thyroid hormone synthesis and endoplasmic reticulum stress indicators of preterm infant rats was analyzed.

2. Materials and methods

2.1. Experimental animals and experimental design

Twenty ten-week-old female SD rats and ten ten-week-old male SD rats were purchased from the Beijing Weitong Lihua Laboratory Animal Science and Technology Co. The rats were kept under standard laboratory conditions (temperature 21 ± 2 °C, relative humidity 38 %, 12 h of light/12 h of dark cycle) for one week, and were fed and watered ad libitum. All animal experiments were performed in accordance with internationally accepted principles for the use and care of laboratory animals, and all operations were in accordance with the ethical requirements for animal science experiments of Shandong Provincial Hospital (2022-067).

The female and male rats were mated, and the presence of spermatozoa in the vaginal smear was defined as the first day of gestation (GD1). Pregnant rats were then randomly divided into L-NAME (n = 10) and Control groups (n = 10). Rats in the L-NAME group were injected subcutaneously with L-NAME (N109211, Aladdin) at a dose of 250 mg/(kg·d) from GD 13–21, and rats in the Control group were injected with an equal amount of saline subcutaneously. Rats were anesthetized by GD21, and preterm infant rats were obtained by cesarean delivery. Liver and thyroid tissues were removed from premature rats and stored at −80 °C for subsequent thyroid function tests, WB and qPCR studies.2.2. Evaluation of blood pressure and urinary protein concentration.

Symptoms of HDP, blood pressure and proteinuria, were assessed on GD10, GD14, and GD20. Rat tail artery noninvasive blood pressure measurement: the tail set of method of measuring the pregnancy rats tail arterial blood pressure. Detailed steps: keep quiet environment, the rats in 40 °C preheat 15 min, then put in 37 °C temperature rat bag. Put pressure sensors in the rat tail roots and BP - 2010 - a host automatically monitor the change of blood flow to the rat tail pulse waveform, when entering a state of blood pressure can be measured, will show the ready signal, the rats into a stable state. The ready signal, pulse stability, BP - 2010 - a automatic pressure, began measuring the rat tail artery SBP, MBP, DBP. Each rat was measured 15 times in a row, and three times with a difference <10 mmHg were taken and averaged. The noninvasive tail-cuff method was employed to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MBP), modeling is considered successful when the blood pressure increases by more than 20 mmHg after injection of the molding drug [19]. While protein concentrations in urine were quantified on GD10 and GD20 using a BCA assay kit (BL521A, Beyotime).

2.2. Thyroid hormone analysis

It has been demonstrated that liver homogenate hormone levels exhibit a correlation with alterations in serum hormone levels [20]. The use of liver homogenates to ascertain thyroid function in preterm infant rats was deemed an optimal approach, given the inherent challenges associated with blood sampling from preterm infant rats. Liver tissue was cut into pieces and grinded on ice after cleaning and weighing. PBS was added into homogenate (Live tissue: PBS = 1:3). After centrifuged at 4 °C, 10000r/min for 20min, the supernatant was extracted. The concentration of TSH was determined by ELISA assays (CEA463Ra, Cloudcloning), while T4 and T3 levels was assessed based on chemiluminescence assays that were performed at the Department of Clinical Laboratory, Shandong Provincial Hospital Affiliated to Shandong First Medical University. All experiments were conducted strictly following the manufacturers guidelines.

2.3. Histological analyses and electron microscopy

Thyroid lobes were collected and fixed with 4 % paraformaldehyde for 24 h. The samples were then subjected to gradient dehydration, and after being embedded in paraffin, they were cut into 4-μm thick sections. The samples were eventually stained with hematoxylin and eosin (H&E) examination under a light microscope. Using ImageJ, the thyroid follicular size and number in the thyroid gland was measured. The thyroid follicular size was defined as the average area (mm^2) of the individual follicles in the histological section.

2.4. Electron microscopy

Some thyroid lobes were preserved in 3 % glutaraldehyde within 2 min of ex-vivo, trimmed into 1 mm × 1 mm x 2 mm strips, fixed at 4 °C overnight. Then, sent to the electron microscope room of Shandong Institute of Otolaryngology for electron microscopic analysis.

2.5. RT-qPCR

Total RNA was isolated from thyroid tissue of premature rats in both groups using Trizol reagent (AG21102, AG), and the corresponding cDNA was obtained by reverse transcription using Evo M-MLV RT Mix kit (AG11728, AG). The cDNA was then amplified by qPCR using SYBR Green PCR Master Mix (AG11701, AG) on a Light Cycler 480 instrument (Roche, Germany). The primer sequences used in this case are shown in Supplementary Table 1. Levels of gene expression were eventually determined after normalization against β-actin.

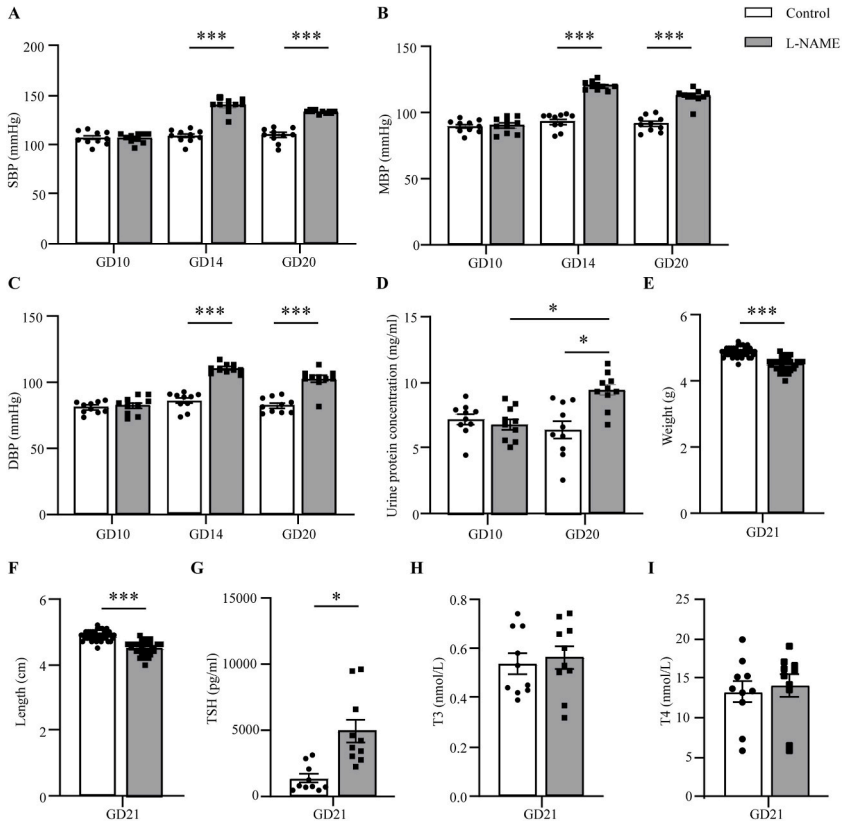

Fig. 1. Congenital hypothyroidism in L-NAME group preterm infant rats. Control and L-NAME group pregnancy rats GD13-21 were injected subcutaneously with saline and L-NAME at a dose of 250 mg/(kg·d), respectively, preterm infant rats were obtained by Caesarean section delivery on GD21. (A) SBP on GD10, GD14 and GD20 (N = 10); (B) MBP on GD10, GD14 and GD20 (N = 10); (C) DBP on GD10, GD14 and GD20 (N = 10); (D) Protein concentrations in urine on GD10 and GD20 (N = 10); (E) Body weight of preterm infant rats (n = 42); (F) Body length of preterm infant rats (n = 42); (G) Liver homogenized levels of TSH (n = 10); (H) Liver homogenized levels of T3 (n = 10); (I) Liver homogenized levels of T4 (n = 10). Error bars represent the mean ± SEM. *p < 0.05 ***p < 0.001.

2.6. Western blotting

Thyroid tissues were first lysed using RIPA buffer (P0013B, Beyotime) supplemented with proteases (P1010-1, Beyotime) and phosphatase inhibitors (01385/16121, CWBIO). We used the JESS Ultra Micro multifunctional automatic protein expression quantitative analysis system, proteins were diluted to 2.0 mg/mL and separated by a 12–230 kDa capillary cartridge (ProteinSimple) according to the manufacturers guidelines. Protein expression was measured by chemiluminescence and quantified as area under the curve using the Compass for Simple Western program (ProteinSimple). Proteins were detected with the following primary antibodies: Tg, TPO, NIS, TSHR, IRE1α, p-IRE1α, XBP1s, ATF6α, PERK, p-PERK, ATF4, eIF2α, p-eIF2α, antibody concentration was explained in Supplementary Table 2.

2.7. Statistical analysis

All data were analyzed using SPSS version 26.0, with the results presented as means ± standard error of means (SEM). The results of the two groups were compared using the Student's T-test. The blood pressure of the pregnant rats from the two groups on different gestational days was analyzed using repeated measures analysis of variance. The level of statistical significance was set at $p < 0.05$.

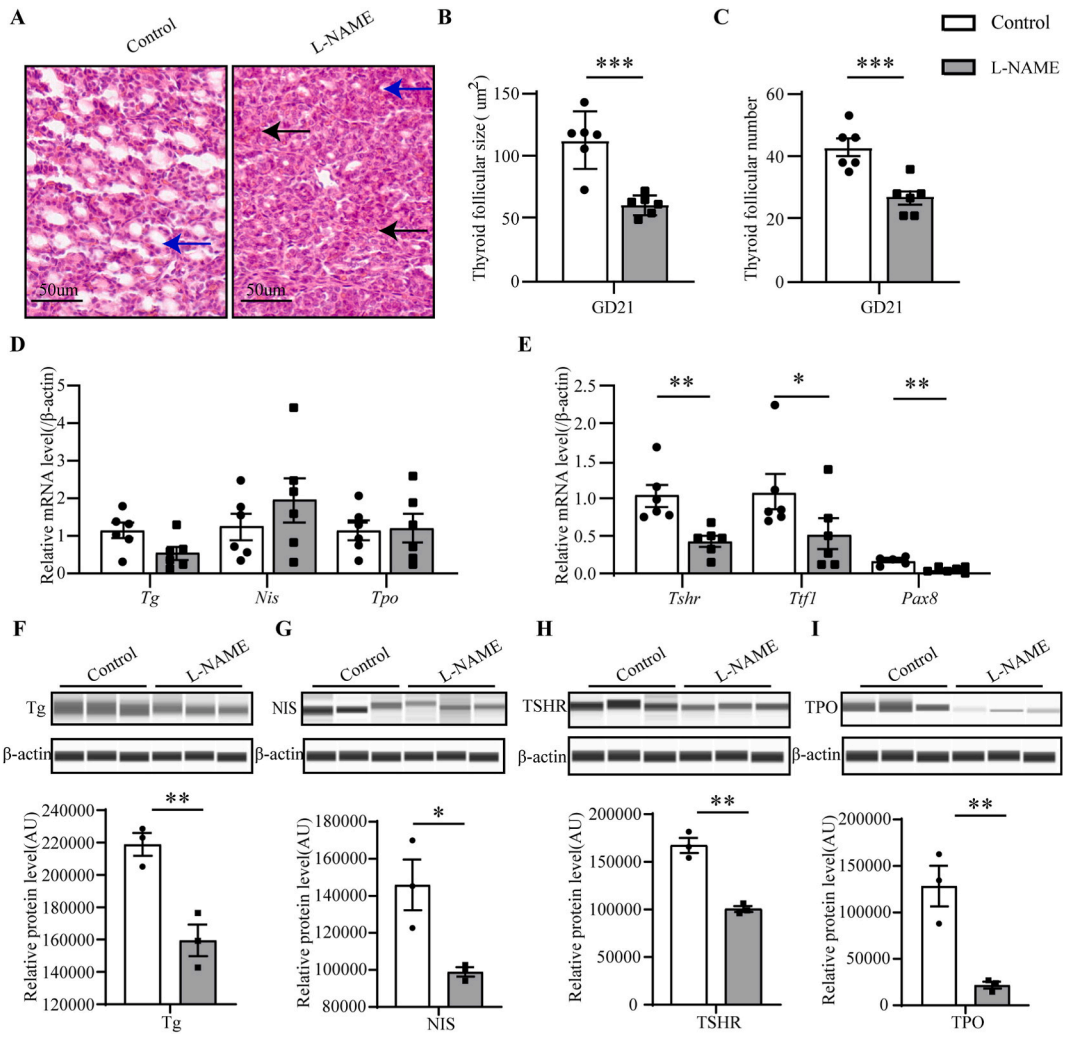

Fig. 2. HDP caused impairment of thyroid hormone synthesis in preterm infant rats. (A) Representative microphotographs of thyroid glands from the Control and L-NAME groups, blue arrows point to thyroid follicular, black arrows point to cell masses (20× objective, bar = 50 μm); Thyroid follicular size (B) and number (C) from preterm infant rats of the Control and HDP groups (n = 6); The mRNA levels of *Tg*, *Tpo, Nis* (D) and *Tshr*, *Ttf1*, *Pax8* (E) in the thyroid glands of preterm infant rats from the Control and L-NAME groups (n = 6); Western blot analysis showing the level of Tg (F), NIS (G), TSHR (H) and TPO (I) in preterm infant rats from the Control and L-NAME groups (n = 3). Values were quantified as area under the curve using the Compass for Simple Western program, and normalized against β-actin as reference; Error bars represent the mean ± SEM. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

3. Results

3.1. Congenital hypothyroidism in L-NAME group preterm infant rats

At GD10, SBP, MBP, and DBP were not noticeably different between the two cohorts. However, following the subcutaneous administration of L-NAME, the three values increased significantly for the L-NAME group on GD14 and GD20 ($p < 0.001$) (Fig. 1A–C). In addition, the protein concentration in urine was higher for the L-NAME group in comparison with the Control group on GD20 ($p < 0.001$) (Fig. 1D). The results of thyroid function of pregnant rats showed that there was no difference in serum TSH, free T3 and free T4 between the two groups (Supplementary Figs. 1A–C). Intrauterine exposure to HDP lead to lower body weight and length of preterm infant rats ($P < 0.001$) (Fig. 1E and F). Meanwhile, the TSH level in the L-NAME group was significantly higher than that in the control group ($P < 0.05$) (Fig. 1G), while T3 and T4 levels showed no noticeable change between the two groups (Fig. 1H and I).

3.2. HDP caused impairment of thyroid hormone synthesis in preterm infant rats

In order to further confirm the cause of thyroid function abnormality in preterm infant rats of the L-NAME group, the

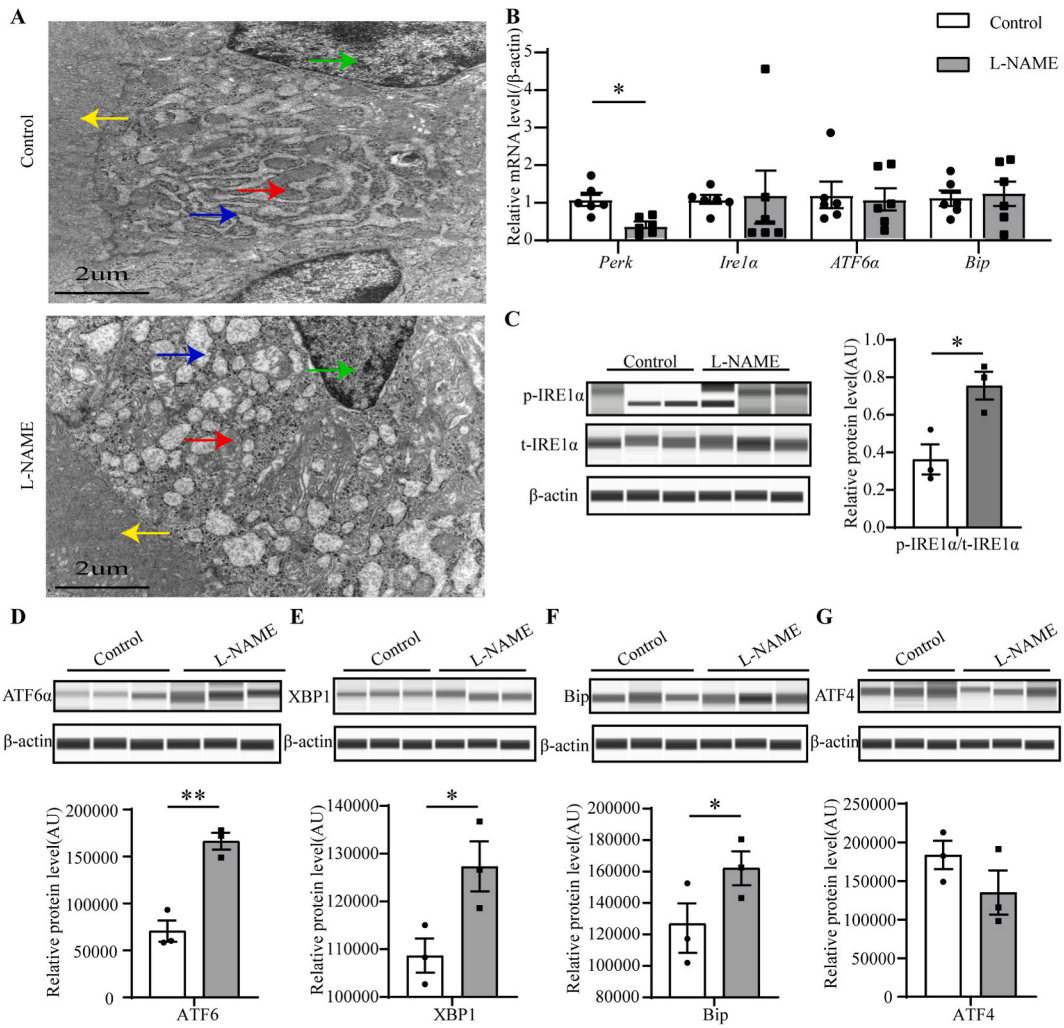

Fig. 3. HDP induced endoplasmic reticulum stress in the thyroid gland of preterm infant rats. (A) Representative electron micrographs of thyroid glands from rats of the Control and L-NAME groups. Yellow arrows point to follicular lumen (including microvilli), blue arrows point to rough endoplasmic reticulum, green arrows point to nucleus, red arrows point to mitochondrion. (B) The mRNA levels of *Perk, Ire1α, Atf6α* and *Bip* in the thyroid glands of preterm infant rats from the Control and L-NAME groups (n = 6); Western blot analysis showing the level of p-IRE1α (C), ATF6α (D), XBP1s (E), Bip (F) and AFT4 (G) in preterm infant rats from the Control and L-NAME groups (n = 3). Values were quantified as area under the curve using the Compass for Simple Western program. p-IRE1α was normalized against total proteins, while ATF6α, XBP1s, Bip and ATF4 was normalized against β-actin. Error bars represent the mean ± SEM. *p < 0.05.

morphological structure of thyroid tissue was observed. In both groups, the thyroid follicular epithelial cells were observed to surround the follicular lumen, with a small amount of colloid distributed within the follicular lumen. The L-NAME group revealed a emergence of thyroid follicular epithelial hyperplasia in comparison to the Control group. (Fig. 2A). Moreover, thyroid follicular size and number were also decreased compared to Control group ($p < 0.05$) (Fig. 2B and C). Next, the expression of key genes for thyroid hormone synthesis and thyroid transcription factors were detected by RT-qPCR. Three key genes related to thyroid hormone synthesis (*Tpo*, *Tg*, and *Nis*) showed no significant difference in the gene expression between the two groups (Fig. 2D). However, *Ttf1*, *Pax8* and *Tshr* were down-regulated in the L-NAME group ($P < 0.05$) (Fig. 2E). The expression of Ttf1 was found to be positively correlated with that of Tg [21], indicating that the synthesis of Tg may be reduced in the L-NAME group. Although there was no difference in the mRNA level of the key factors of thyroid hormone synthesis, was there any abnormality in the protein level? Western blotting analysis showed that the protein level of Tg, NIS, and TSHR, was significantly reduced in the L-NAME group compared with Control group ($P < 0.05$) (Fig. 2F–H), and there was unchanged in the level of TPO in the two groups (Fig. 2I).

3.3. HDP induced endoplasmic reticulum stress in the thyroid gland of preterm infant rats

The endoplasmic reticulum is the central intracellular organelle that is responsible for the synthesis, quality control, and degradation of proteins [22]. To investigate the reasons for the reduced expression of key factor for thyroid hormone synthesis, the ultrastructure of the thyroid gland was observed. Electron microscopy revealed a strong expansion of endoplasmic reticulum accompanied with the accumulation of lower electron density in them and swollen mitochondria with severe broken cristae in the L-NAME group compared with the Control group (Fig. 3A), which is direct morphological evidence of endoplasmic reticulum stress. Subsequently, sensitive markers of endoplasmic reticulum stress were detected to assess the level of endoplasmic reticulum stress. Bip mRNA expression was found to be slightly up-regulated, and Perk, Ire1α, and Atf6α were down-regulated after intrauterine exposure to HDP, but differences are all statistically non-significant except Perk (Fig. 3B). Western blotting analysis showed that the expression of p-IRE1α, XBP1s, ATF6α and Bip was higher in L-NAME group than that in Control group ($P < 0.05$) (Fig. 3C–F), and there was no difference in ATF4 expression between two groups (Fig. 3G).

4. Discussion

In this experiment, the HDP rat model was established by injection of L-NAME, and the preterm infant rats were obtained by Caesarean section delivery. The preterm infant rats in the L-NAME group showed obvious intrauterine growth restriction, which was consistent with the results of the clinical data analysis. The thyroid function test of the preterm infant rats in the L-NAME group exhibited elevated TSH, and the levels of T3 and T4 showed no noticeable change. Therefore, the preterm infant rats successfully simulated the clinical signs of congenital hypothyroidism after intrauterine exposure to HDP.

In the present study, we observed morphological and functional changes of thyroid gland in preterm infant rats after intrauterine exposure to HDP. We found that compared to Control group there was a reduction in the size and number of thyroid follicles, with the emergence of thyroid follicular epithelial hyperplasia which was consistent with the results of the previous observation on the effect of HDP on the morphology and structure of the thyroid gland of different gestational ages by this group [16]. Meanwhile, we found that the mRNA levels of thyroid transcription factors *Ttf1* and *Pax8* were down-regulated in the thyroid tissues of the L-NAME group, and the protein levels of Tg, NIS and TSHR were markedly reduced. In rodents, *Ttf1* and *Pax8* begin to regulate thyroid development from embryonic day 8.5 (E8.5), and promote the thyroid hormone synthesis [23]. Meanwhile, the down-regulation of *Ttf1* and *Pax8* also played an important role in the decreased protein levels of Tg, NIS, and TSHR. Additionally, TSH is involved in the regulation of thyroid hormone synthesis by binding its specific receptor TSHR from E16 [24]. However, HDP decreased the expression of Tg, NIS, and TSHR leading to insufficient synthesis of thyroid hormones, via negative feedback regulation to increase TSH secretion [25]. Thus, HDP reduced thyroid hormone synthesis in preterm infant rats by reducing the expression of key molecules, resulting in thyroid function abnormalities. The key factors involved in the synthesis of thyroid hormones (Tg, TPO, and NIS) are synthesized in the endoplasmic reticulum and play a crucial role in the steps of thyroid hormone production [26,27]. This study revealed that the swelling of the endoplasmic reticulum and deposition of low-density electron dense matter observed in the L-NAME group were morphological changes associated with protein accumulation and endoplasmic reticulum stress [28,29]. Additionally, there was a significant increase in the protein levels of ATF6α, XBP1s, and Bip, indicating activation of ATF6α and IRE1α pathways suggested that endoplasmic reticulum stress emerged in thyroid follicular epithelial cells. PERK, IRE1α, and ATF6α are responsible for mediating three classical pathways involved in endoplasmic reticulum stress. These pathways aim to restore endoplasmic reticulum homeostasis by reducing protein synthesis capacity, enhancing endoplasmic reticulum processing capacity and increasing endoplasmic reticulum associated degradation [30–32]. Upon activation of the ATF6 pathway by receiving signals related to protein toxicity through its cytoplasmic domain along with collaboration of IRE1α pathway regulating XBP1s expression level up-regulation as well as increasing Bip protein expression level which enhances protein processing ability within the endoplasmic reticulum. Meanwhile, its transmembrane domain mediates expansion of the endoplasmic reticulum [33,34]. However, under conditions where there is an accumulation of misfolded or unfolded proteins within the endoplasmic reticulum due to prolonged exposure to stress will affect the expression of key molecules involved in thyroid hormone synthesis [30,35]. Therefore, it indicated that HDP may induce endoplasmic reticulum stress on thyroid follicular epithelial cells resulting decreased expression levels of key factors involved in thyroid hormone synthesis, leading to congenital hypothyroidism ultimately.

In conclusion, the present study demonstrated that both endoplasmic reticulum stress and Ttf1 downregulation were responsible for the reduced synthesis of key molecules involved in thyroid hormone synthesis. The mRNA levels of key molecules were found to be

similar, whereas the protein levels were observed to be reduced. This indicated that the reduced expression of key molecules resulting from *Ttf1* down-regulation is not the primary factor. Furthermore, It has been evidenced that endoplasmic reticulum stress inhibits the expression of thyroid transcription factors. In light of these findings, it can be posited that the endoplasmic reticulum may serve as a pivotal mediator in the context of HDP-induced impairment of thyroid hormone synthesis.

5. Conclusion

In this study, we investigated the effects of HDP on thyroid morphology and thyroid hormone synthesis in preterm infant rats for the first time. We found that HDP reduced the expression level of key factor of thyroid hormone synthesis through endoplasmic reticulum stress, leading to thyroid hormone synthesis disorder, and causing congenital hypothyroidism in preterm infant rats ultimately. This will provide new insight into the mechanism of congenital hypothyroidism in preterm infants induced by maternal HDP.

CRediT authorship contribution statement

Maomao Sun: Writing – original draft, Methodology, Data curation. **Congrong Wu:** Writing – original draft, Methodology, Data curation. **Jie Jiang:** Writing – original draft, Methodology, Data curation. **Yue He:** Methodology. **Sha Zhu:** Data curation. **Yonghui Yu:** Writing – review & editing, Conceptualization.

Data availability statement

All data included in this study are available upon request by contact with the corresponding author.

Funding information

This work was supported by The Mechanism of Endoplasmic Reticulum Stress in Hypothyroidism Induced by Gestational Hypertension in Preterm Infants, Shandong Natural Science Foundation (Grant number: ZR2023MH175) and The Role of Ephx2/IRE1α-mediated endoplasmic reticulum homeostatic imbalance in HDP induced hypothyroidism in premature offspring, National Natural Science Foundation of China (No. 82470824).

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e41021.

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