Prenatal and Postnatal Effects of Hypothyroidism and Thyroxin Replacement on the Development of Rat Testis

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Abstract: Objectives: To evaluate the impact of hypothyroidism during pregnancy on newborn rats and their testicular development till age of maturity and role of postnatal thyroxin (T4) replacement therapy in regeneration of normal testicular architecture and maturation. Material & Methods: The study included 60 offspring of pregnant rats, divided into 3 equal groups: Control group received neither 6-propyl-2-thiouracil (PTU) nor T4 replacement therapy (Group I), PTU-treated group received PTU (Group II) and T4-treated group (Group III) included rats that were pretreated with PTU and received T4 every second day from 21th to 60th day post-partum (dpp). Blood samples were collected on the 20th dpp for estimation of plasma levels of T3, T4 and thyroid stimulating hormone (TSH). Both body weight (BW) and testicular weight (TW) were determined at the 20th and 60th dpp and testicular weight/body weight ratio was calculated. Histological studies of testis included Hx & E and Masson’s trichrome stain and electron microscopy (EM). Results: At 20 dpp, all studied rats showed significantly lower plasma total T4 and T3 and significantly higher plasma TSH. Mean BW and TW were significantly lower in group II compared to group I. At 60 dpp, both BW and TW of group III animals were non-significantly lower compared to group I and non-significantly higher compared to group II. At 60 dpp, Hx & E stained group II sections showed semineferous tubules of smaller diameter than group I with no sperms, disruption of spermatogonia and the tubules were filled with degenerated cells and shrunken primary spermatocytes. Group III testis showed semineferous tubules of normal sizes, outline and lumen filled with sperms, spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms. At 60 dpp, Masson’s Trichrome stained sections showed some semineferous tube containing disrupted spermatogenic cells and the tubules were filled with degenerated cells with markedly thickened basal lamina in group II, while group III showed semineferous tubules containing spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms with normal thickness basal lamina. EM examination of testicular sections of group II showed ovoid-shaped semineferous tubules with heterochromatic patches and elongated mitochondria and degenerated cells in the cytoplasm. Group III showed the irregular nucleus of Sertoli cells with large nucleoli, spermatogonia resting on the basement membrane and rounded mitochondria in the cytoplasm. Conclusion: Prenatal exposure to antithyroid drugs deleteriously affects the constitutional and testicular growth with concomitant changes of testicular architecture and these effects could be reversed by postnatal administration of thyroxin.

Keywords: Antithyroid drugs, Prenatal exposure, Toxic effects, Thyroxin replacement therapy

1.Introduction

Adequate maternal thyroid function during pregnancy is an important determinant of early fetal development; it plays a critical role for at least the first 12–14 weeks of gestation when fetal thyroxin supply comes exclusively from placental transfer of maternal hormones (Lazarus, 2012).

The role of the thyroid gland in testicular development and function is still unclear in many vertebrates. Contrasting reports and differences between sexes and among species in their dependence on the thyroid for gonadal development and function have made it difficult to formulate a generalized relationship. Furthermore, the apparent multiple effects of thyroid hormones on the reproductive physiology including effects on developing Sertoli cells has added to the complexity (Maran et al., 2000 & 2001).

Kala et al. (2002) found that persistent hypothyroidism diminishes the bioavailability of androgens and estrogens, indicating the importance of euthyroidism during fetal and neonatal period towards the maintenance of optimal hormonal status in the epididymis required for its maturation. Moreover, Karimov et al. (2003) reported that common features to be seen in the wake of hypothyroidism include a decline in the locomotor activity of spermatozoa and abnormalities in maturation of cells of spermatogenesis, which facts necessitate restoration of the thyroid function to prevent disorders of spermatogenesis in the fully-developed organism.

Sakai et al. (2004) conducted a morphological analysis on the testes of rats with congenital hypothyroidism and reported a prolonged proliferation of Sertoli cells during postnatal development; a developmental delay
in the appearance of spermatocytes and spermatid; direct contact with each other for both spermatocytes and spermatid, without Sertoli cell cytoplasm completely intervening between adjacent germ cells; subsequent apoptosis of germ cells after maturation; reduction in the height of the seminiferous epithelium; and lower testosterone levels and concluded that the thyroid hormone plays an important role in developing and maintaining normal function of testes.

Apart from the well-established actions of gonadotropins, the role of the other hormones in the control of male reproductive organs is not well understood. Hypothyroidism is the most common disorder known to affect these organs, and has been shown to be associated with a wide range of reproductive abnormalities of ovarian functions in mammals, including humans (Jeong et al., 2006). In males, as hypothyroidism has hardly any effect on the adult testis and causes minimal effect on the testis morphology, the testis was long regarded as one of the least sensitive organs to thyroid hormone (NTP, 2006).

The present rat-model study was designed to evaluate the impact of hypothyroidism during pregnancy on the newborn rats and their testicular development till age of maturity and the possibility of a role of postnatal thyroid replacement therapy in regeneration of normal testicular architecture and maturation.

2. Material & Methods

The present comparative study was conducted at Anatomy Department, Faculty of Medicine, Benha University and included 60 Wistar female rats weighing 150-200 gm. Rats were acclimatized to standard laboratory conditions (12:12-h light-dark cycle, environmental temperature, free access to food and water).

**Induction of hypothyroidism**

Prenatal treatment was started 1 day post-coitum and stopped at birth, by giving pregnant rats a drinking water containing 0.025% (w:v) 6-propyl-2-thiouracil (PTU) and 0.075% saccharine-aspartam (Cologan, Lidl UK GmBH) to mask the bitter taste of PTU, control pregnant rats received water laced with 0.075% saccharine-aspartam. After birth, to maintain the hypothyroid conditions, lactating rats were provided with drinking water containing 0.025% PTU and 0.075% sweetener (PTU). Control mothers received sweetened water (C). Treatment has been maintained to day 20 (weaning) (Luiz Renato et al., 1995).

**Drugs:**

1. 6-propyl-2-thiouracil (PTU) was supplied as Thyrocil 50 mg tablets (Amoun Chemical Co., Egypt).
2. Thyroxin (T4) was supplied as Eltroxin 100 µg tablets (Glaxo Wellcome Co.) and was injected intraperitoneally after being dissolved in 2 NaOH and diluted with saline and administered as daily injection of 10 µg/100 gm body weight.

**Animal Grouping:**

Newly born rats were randomly divided into two broad groups according to age of decapitation: Group A animals were decapitated at the 20th dpp, while Group B animals were followed up until adulthood and decapitated 60 days after birth; time of complete testicular development (Reuhl et al., 2001). Each broad group was subdivided into the following subgroups:

- Group I (Control group): included 20 (10 of group A and 10 of group B) developing male rats of mothers that received neither PTU nor thyroid replacement therapy.
- Group II (PTU-treated group): included 20 (10 of group A and 10 of group B) developing male rats of mothers that received PTU and maintained till end of the study on the same conditions as Group I.
- Group III (T4-treated group): included 20 (10 of group A and 10 of group B) male rats of mothers that were pretreated with PTU and received thyroid replacement therapy every second day from 21st to 60th day post-partum (dpp).

**Evaluated Parameters**

**Laboratory Findings**

Blood samples were collected from all of the 60 offspring, on the 20th dpp, to assure hypothyroidism prior to categorization and start of the T4 replacement therapy. Blood samples were collected on 2% EDTA; plasma was separated by centrifugation and stored at -20°C for hormones measurements including plasma T3 (Vermaak et al., 1986), T4 (Kaptein et al., 1981) and TSH (Wada et al., 1982) were measured by semiautomatic analyzer IMX (Abbott, Chicago, IL) using the Clinical Assays GammaCoat RIA kit, manufactured by INCSTAR Corp, Stillwater, MN.

**Body and testicular weight changes**

For animals decapitated at the 20th dpp, both body weight and testicular weight were determined at the 20th, while for animals decapitated at the 60th dpp, body weight was determined at the 20th and 60th dpp and testicular weight was determined at 60th day after decapitation. Testicular weight/body weight ratio was calculated and the percentage of change of both body and testicular weights were determined according to the following equation: % of change= ((weight at 60 dpp- weight at 20 dpp)/ (weight at 60 dpp))(x(100).

**Microscopic Examination**

a. Histological studies: included Hx & E (Drury & Wallington, 1980) and Masson’s trichrome stain (John et al., 1996); testis of treated and controls rats were fixed in an aqueous fixative, embedded in paraffin and 5 m sections were stained with Masson’s trichrome dyes solutions and studied in a Zeiss photomicroscope equipped with ocular grid.
b. For electron microscopy, the specimens were cut into small blocks <1 mm³, some of which were post-fixed in osmium tetra-oxide, dehydrated through gradual alcohols and embedded in epon. For orientation of tissues, semithin sections stained with toludine blue were done. Ultrathin sections were mounted on grids, stained with uranyl acetate and lead citrate and examined with Jeol transmission microscope (John et al., 1996).

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X² test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

Thyroid hormonal profile

Prior to the initiation of replacement therapy (at 20 dpp), the hypothyroid state was assured by the significantly lower plasma total T4 and T3 and significantly higher plasma TSH in offspring of PTU-treated rats during pregnancy. These offspring were divided into two study groups that showed non-significant difference concerning plasma hormonal levels, (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=20)</th>
<th>PTU-treated (n=20)</th>
<th>T4-treated (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma TT4 (ng/ml)</td>
<td>48.8±3.1</td>
<td>24.4±2.4*</td>
<td>25.6±3.4*</td>
</tr>
<tr>
<td>Plasma TT3 (pg/ml)</td>
<td>3.05±0.44</td>
<td>2.25±0.21*</td>
<td>2.29±0.35*</td>
</tr>
<tr>
<td>Plasma TSH (µU/ml)</td>
<td>0.49±0.12</td>
<td>1.81±0.15*</td>
<td>1.83±0.11*</td>
</tr>
</tbody>
</table>

*: significant versus control group; PTU: 6-propyl-2-thiouracil; T4: thyroxine; TT4: total thyroxine; TT3: total tri-iodothyronine; TSH: thyroid stimulating hormone

Body and testicular weight changes

A) Body weight

- PTU-treated group: at 20 dpp mean body weight was significantly lower compared to control rats and despite the significantly higher percentage of weight gain at 60 dpp, BW was still significantly lower compared to control group.
- T4-treated group: at 20 dpp mean BW was significantly lower compared to control, but non-significantly higher compared to PTU-treated group. At 60 dpp, BW of T4-treated rats was non-significantly lower and non-significantly higher compared to control and PTU-treated rats, respectively with significantly higher percentage of BW gain compared to control, but non-significantly lower percentage of BW gain compared to PTU-treated rats, (Table 2, Fig. 1 & 3).

B) Testicular weight

- PTU-treated group: mean testicular weight of PTU-treated rats was significantly lower compared to control rats at both the 20th and 60th dpp with significantly lower percentage of TW gain compared to control group.
- T4-treated group: at 20 dpp mean TW was significantly lower compared to control, but non-significantly lower compared to PTU-treated group. At 60 dpp, TW of T4-treated rats was non-significantly lower but significantly higher compared to control and PTU-treated rats, respectively with significantly higher percentage of TW gain compared to both control and PTU-treated rats, (Table 2, Fig. 2 & 3).

C) Body/Testicular weight ratio showed

- At both the 20th and 60th dpp the body/testicular weight ratio showed non-significant difference among studied groups, (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>PTU-treated</th>
<th>T4-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (gm)</td>
<td>At 20 dpp (n=60)</td>
<td>55.4±1</td>
<td>44.7±1.15*</td>
</tr>
<tr>
<td></td>
<td>At 60 dpp (n=30)</td>
<td>155±2.2</td>
<td>150.2±2.3*</td>
</tr>
<tr>
<td>% of increase (n=30)</td>
<td>179.8%±5.3%</td>
<td>236.2%±11.1%*</td>
<td>232.4%±12.5%*</td>
</tr>
<tr>
<td>Testicular weight (gm)</td>
<td>At 20 dpp (n=30)</td>
<td>0.147±0.12</td>
<td>0.127±0.03*</td>
</tr>
<tr>
<td></td>
<td>At 60 dpp (n=30)</td>
<td>0.32±0.053</td>
<td>0.251±0.033*</td>
</tr>
<tr>
<td>% of increase (n=30)</td>
<td>120.3%±44.3%</td>
<td>98.1%±28.1%*</td>
<td>135.5%±47.6%†</td>
</tr>
<tr>
<td>Testicular/body weight</td>
<td>At 20 dpp (n=30)</td>
<td>0.0027±0.0002</td>
<td>0.0028±0.0001</td>
</tr>
<tr>
<td></td>
<td>At 60 dpp (n=30)</td>
<td>0.002±0.0004</td>
<td>0.0017±0.0002</td>
</tr>
</tbody>
</table>

*: significant versus control group; PTU: 6-propyl-2-thiouracil; †: significant versus PTU-treated group
Histological evaluation of outcome:
A) Hematoxyline & Eosin stained sections of testis

Control group: at 20 dpp testis showed normal seminiferous tubules showing both Sertoli cells and gonocytes with normal interstitial tissue in between Sertoli cells. Semineferous tubules containing spermatogonia. Clusters of Leydig cells are seen within normal interstitial tissue (Fig. 4). At 60 dpp, testis showed seminiferous tubules of normal sizes, outline and lumen filled with spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms. Leydig cells could be seen in the interstitial tissue (Fig. 5).

PTU-treated group: at 20 dpp testis showed normal seminiferous tubules containing spermatogonia on the basement membrane with crowding of Sertoli cells and some degenerated cells in the lumen. (Fig. 6). At 60 dpp, seminiferous tubules were of diameter smaller than that of control rats with no sperms. There

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was disruption of spermatogonia, the tubules were seen filled with degenerated cells and the primary spermatocytes appeared shrunken with markedly thickened basal lamina and wide interstitial tissue, (Fig. 7).

T4-treated group: at 60 dpp testis showed seminiferous tubules of normal sizes, outline and lumen filled with spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms. Clusters of Leydig cells were seen in the interstitial tissue, (Fig. 8).

B) Masson's Trichrome stained sections of testis

- Control group: at 60 dpp, testis showed seminiferous tubules filled with sperms with normal thickness basal lamina, (Fig. 9).
- PTU-treated group: at 60 dpp testis showed seminiferous tubules containing disrupted spermatogonia, Sertoli cells containing disrupted spermatogonic cells and the tubules were filled with degenerated cells. Basal lamina was markedly thickened, (Fig. 10).
- T4-treated group: at 60 dpp testis showed seminiferous tubules containing spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms with normal thickness basal lamina, (Fig. 11).
Fig. (9): A photomicrograph of section in testis of 60-days old control rat showing seminiferous tubules (T) filled with sperms (P). Basal lamina (BL) was normal in thickness, (Masson's Trichrome x1000).

Fig. (10): A photomicrograph of section in testis of 60-days old PTU-treated rat showing one seminiferous tubule and parts of others containing disrupted spermatogonic cells and the tubule was filled with degenerated cells (d). Basal lamina (BL) was markedly thickened, (Masson's Trichrome x1000).

Fig. (11): A photomicrograph of section in testis of 60-days old T4-treated rat showing seminiferous tubules containing spermatogonia (s), Sertoli cells (S), primary spermatocytes, spermatids (SP) and sperms (P). Basal lamina (BL) was normal in thickness, (Masson's Trichrome x1000).

C) **Electromicroscopic examination of testicular sections**

Fig. (12): Electromicrograph of section in testis of 20-days old control rat showing nucleus of Sertoli cells (N), spermatogonia (S) and rounded mitochondria (c). Spermatogonia were seen resting on the basement membrane (arrowed). Myoid cells (M) were seen in the basal lamina, (x8000).

Fig. (13): Electromicrograph of section in testis of 20-days old PTU-treated rat showing nucleus of Sertoli cells (N) ovoid in shape with heterochromatic patches. Elongated mitochondria (c) and degenerated cells (d) could be seen in the cytoplasm. Spermatogonia (s) resting on the basement membrane (arrowed) and myoid cells (M) could be seen, (x4000).
Fig. (14): Electronmicrograph of section in testis of 60-days old T4-treated rat showing nucleus of Sertoli cells (N) with large nucleolus. Rounded mitochondria (c) were seen in the cytoplasm. Spermatogonia (s) were seen resting on the basement membrane (arrowed). Myoid cells (M) were seen in the basal lamina (B), (x8000).

- Control group: at 20 dpp testis showed the nucleus of Sertoli cells, spermatogonia resting on the basement membrane and rounded mitochondria. Myoid cells were seen in the basal lamina, (Fig. 12).
- PTU-treated group: at 20 dpp testis showed ovoid-shaped semineferous tubules with heterochromatic patches, and elongated mitochondria and degenerated cells in the cytoplasm. Spermatogonia resting on the basement membrane and myoid cells could be seen (Fig. 13).
- T4-treated group: at 60 dpp testis showed the irregular nucleus of Sertoli cells with large nucleoli, spermatogonia resting on the basement membrane with rounded mitochondria, spermatogonia in the cytoplasm and myoid cells in the basal lamina, (Fig. 14).
- Concerning intercellular junctions, sections of PTU treated rats showed wide separation between Sertoli cells, (Fig. 15) while sections of T4-treated rats showed normal junction between Sertoli cells (Fig. 16) in comparison to normal junction between Sertoli cells shown in sections of control rats, (Fig. 17).

Fig. (15): Electronmicrograph of section in testis of 20-days old PTU-treated rat showing wide separation between Sertoli cells (arrows), (x 30,000).

Fig. (16): Electronmicrograph of section in testis of 60-days old rat T4-treated showing normal junction between Sertoli cells (arrows), (x 30,000).
4. Discussion

Prenatal exposure to PTU resulted in hypothyroid offspring documented at 20th dpp by significantly lower plasma levels of thyroid hormones and high plasma TSH levels. These finding illustrated the deleterious effect of prenatal exposure to anti-thyroid drugs on the thyroid function of the embryo and newborn and go in hand with Weng et al. (2007) who found plasma concentrations of free and total T4 and free T3 were significantly decreased by 4 weeks after methimazole treatment. Also, de Oliveira et al. (2011) reported that thyroid function was affected by nicotine in both mothers and pups, suggesting a primary hypothyroidism and after nicotine withdrawal, pups recovered thyroid function probably due to the increased lactational transfer of T3 in relation with increased mammary gland deiodinase activities.

PTU-treated group showed significantly lower body and testicular weight compared to control rats. However, in T4-treated group, at 60 dpp both mean BW and TW were non-significantly lower and non-significantly higher compared to control and PTU-treated rats, respectively with significantly higher percentage of weight gain compared to control. In hand with these data, Jeong et al. (2006) reported that the absolute seminal vesicle weights were decreased in hypothyroid animals compared to control animals. Also, Shibutani et al. (2009) found offspring of pregnant rats administered PTU in drinking water from gestation day 10 to postnatal day 20 displayed evidence of growth retardation lasting into the adult stage, which was particularly prominent in males and that most of thyroid histopathological changes that appeared at the end of chemical exposure were related to growth retardation and reversed by the adult stage.

These reported growth retardations was attributed by Jana et al. (2006) to the effects of chronic exposure to toxins on hypothalamo-pituitary-testicular activities resulting in decreased paired testicular weights; epididymal sperm count; plasma LH, FSH, testosterone and testicular testosterone concentrations with an estrogenic effect. Cristovão et al. (2002) found severe neonatal hypothyroidism impairs testicular development and function. Also, Lisboa et al. (2008) attributed the effects of prenatal hypothyroidism to an effect on hepatic and skeletal muscle deiodinase activities.

Microscopically, at 60 dpp, semineferous tubules of PTU-treated group were smaller in diameter, filled with degenerated cells and the primary spermatocytes appeared shrunken but no sperms. EM examination showed ovoid-shaped semineferous tubules with heterochromatic patches and elongated mitochondria, and degenerated cells in the cytoplasm with wide separation between Sertoli cells. On contrary, T4-treated group showed semineferous tubules of normal sizes, outline and lumen filled with spermatogonia, Sertoli cells, primary spermatocytes, spermatids and sperms with normal interstitial tissue. EM showed Sertoli cells with large nucleolus and rounded mitochondria in the cytoplasm, spermatogonia and rounded mitochondria.

These findings were in line with Sahoo et al. (2008) who found hypothyroid rats showed decreased body weight and testicular germ cell counts with a significant reduction in the number of live sperms in epididymis. Rijntjes et al. (2009) reported that transient hypothyroidism induced by propyl-2-thiouracil blocks postpartum Leydig cell development.

The ameliorative effect of thyroxin on testicular architecture and subsequently on testicular functions supported the previously reported by Maran et al. (1999) who found plasma androgen binding protein was decreased irrespective of the duration of hypothyroidism and plasma FSH level was increased significantly in all hypothyroid groups and these results point out that suppression of T3 during the critical period of Sertoli cell proliferation affects their number.
and functional activity. **Tahmaz et al. (2000)** observed maturation arrest of spermatogenesis, reduced number of Sertoli and Leydig cells, decreased tubular diameter, interstitial edema, and thickening of basal membrane in hypothyroid testicles, and after treatment, testicular histology and spermatogenesis gradually recovered.

Also, **Jiang et al. (2000)** found thyroxin treatment markedly increased serum T4 levels and the weights of both epididymides and testes with partial reversion of the impaired sexual behavior and the percentage of epididymal sperm with cytoplasmic droplets was markedly decreased after T4 treatment. Moreover, fertility of epididymal sperm was completely reversed when determined both in vivo and in vitro, and homozygous embryos developed to term after transfer without loss of viability. **Jansen et al. (2007)** examined the influence of transient hypothyroidism on reproductive neuroendocrine in the male golden hamster and found that the severity of the effects induced by early hypothyroidism varies from transient to permanent and requires thyroid hormones during the early postnatal period. **Shibutani et al. (2009)** reported a delayed onset of puberty, being especially evident in males, and this effect might be related to gonadal growth suppression during exposure.

In trial to explain the mechanisms underlying the deleterious effect of prenatal exposure to antithyroid drugs on testicular developments; **Sahoo et al. (2008)** reported that mitochondrial lipid peroxidation and protein carbonylation levels in testes were elevated during hypothyroidism with reduced testicular antioxidant levels and suggested a direct regulatory role of thyroid hormone on testicular physiology and antioxidant defense system during development and maturation. **Mendis-Handagama & Ariyaratne (2008)** using immunocytochemistry found a positive but weak labeling of anti-Mullerian hormone in cytoplasm of some prepubertal Sertoli cell; but germ cells and testicular interstitial cells were negative for anti-Mullerian hormone at all tested ages. On the other hand, **Anbalagan et al. (2010)** attributed the deleterious effects of prenatal exposure to antithyroid drugs to subnormal androgens bioavailability, androgen receptor expression, and functional activity.

Recently, **Sahoo & Roy (2012)** reported that altered thyroid function during early stages of development adversely affect testicular growth, physiology, and antioxidant defense status and this compromised testicular antioxidant status might have contributed to poor growth and development by affecting the spermatogenesis and steroidogenesis in rats before puberty as indicated by reduced germ cell number, complete absence of round spermatids, decreased seminiferous tubule diameter, and decreased testosterone level.

It could be concluded that prenatal exposure to antithyroid drugs deleteriously affects both the constitutional and testicular growth with concomitant changes of testicular architecture and these effects could be reversed by postnatal administration of thyroxin. However, it is recommended to keep an eye on maternal thyroid function during pregnancy and to modulate therapeutic lines for thyrotoxicosis prior committing pregnancy.

**References**


