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Antifertility Potential of Isoniazid and Rifampicin in Adult Female Wistar Rats

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Abstract

The aim of this study was to investigate the effects of INH and RIF on the reproductive functions of adult female Wistar rats. Twenty-eight adult female Wistar rats weighing between 160 g and 170 g were divided into four groups. Group A served as the control. Group B was given 5 mg/kg body weight of INH. Group C animals was given 10 mg/kg body weight of RIF. Group D animals received a combination of 5 mg/kg body weight of INH and 10 mg/kg body weight of RIF. Duration of treatment was 90 days and via oral route. Histological findings showed that INH and RIF caused histopathologic changes in the ovary and uterus. Compared with the control, the ovarian SOD was significantly elevated in all the treated groups. Ovarian MDA, CAT and GPx activities were significantly elevated in INH-only treated group. FSH was significantly elevated in RIF-only and INH and RIF co-treated groups. LH was significantly elevated in all the groups. Progesterone level was significantly reduced in INH-only and INH and RIF co-treated groups. Estradiol level was significantly elevated in RIF-only and INH and RIF co-treated groups. Testosterone level was significantly elevated in INH-only treated group. Prolactin level was significantly reduced in all the groups while testosterone:estradiol ratio was significantly elevated in INH-only treated group but significantly reduced in INH and RIF co-treated group. In conclusion, administration of INH and RIF caused toxicity in the female reproductive system.

Keywords: Antitubercular agents, Rifampin, Isoniazid, Female, Reproductive health

Introduction

The broad viewpoints of Medical practitioners on tuberculosis (TB) in pregnancy reflects the Public Health significance of the condition, with the concern being two ways. One concern is about the effect of TB on pregnancy and the pattern of growth of the newborn, while the other is the effect of pregnancy on the progression of TB. TB not only accounts for a significant proportion of the global burden of disease, it is also a significant contributor to maternal mortality, with the disease being among the three leading causes of death among women aged 15-45 years (1).

The combination of rifampicin and isoniazid along with ethambutol and pyrazinamide has been adjudged best for efficacy and tolerability amongst the available TB drugs and is, therefore, the mainstay "first line" therapy (2, 3). There are historical and clinical proofs that these first-line anti-tuberculosis agents are the most potent oral anti-tuberculous medications (4-6). In addition, *in-vitro* and *in-vivo* clinical data support the use of such individual agents (7, 8). This may be because the combination has been found to be a beneficial and cost-effective treatment for TB (9), but, this is not without some systemic toxicity from the results from human data.

Since TB affects people in their productive and reproductive age group, there have been recent suggestions that anti-tuberculosis agents could produce adverse effects on reproductive health system (10-13). Available data on adverse reactions of antituberculous drugs in human and animal experiments particularly with respect to reproduction are limited (14). Most of the few available studies on effects of anti-tuberculosis agents on reproduction and/or fertility had focused on males (15, 16) but with scanty literature on female fertility (17, 18).

There is need to continuously review most drugs consumed by mankind including those generally considered as safe. For instance, rifampicin is said to belong to category C drugs and recommended for use even in pregnancy as there has not been any claim of its teratogenic effects (19-21). However, it has been shown that neonates born to mothers treated with isoniazid exhibit hemorrhage in the postpartum period (22). This study is intended to investigate and broaden the perspective of the effects anti-TB drugs on female reproductive parameters.

Materials and Method

Drugs

Rifampicin capsules (manufactured by Bond Chemicals Limited, Adesakin Layout, Awe, Oyo State, Nigeria) and isoniazid tablets (manufactured by Mancare Pharmaceutical Pvt Limited, Vasai West, Mumbai, India) were purchased from Flowell Pharmacy, 39 Ugbowo-Lagos Road, Benin City, Edo State, Nigeria.

Animals

Wistar rats used for the study were bred at the Animal House, Department of Anatomy, School of Basic Medical Sciences, College of Medical Sciences, University of Benin, Benin City Edo State Nigeria. They were kept in polypropylene cages under room temperature, with 12-hour light and 12-hour dark cycle photoperiodicity. They were allowed to acclimatize for two weeks before the commencement of the experiment. The animals were fed with pelleted feed (manufactured by Grand Cereals and Oil Mills Ltd, Bukuru, Jos, Nigeria) and clean tap water *ad libitum*. They were weighed daily before the commencement and throughout the duration of the experiment. Protocols for these experiments were in accordance with the guide for the care and use of laboratory animals (23).

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The research proposal was approved by the Research and Ethics Committee, College of Medical Sciences, University of Benin, Benin City Edo State Nigeria, with REC approval number CMS/REC/2018/034.

Research design

A total of twenty-eight (28) adult female Wistar rats weighing between 160 g and 170 g were used for this study. They were divided into four groups (A, B, C and D) of seven rats per group. Group A served as the control group administered with only water orally and feeds for ninety days. Group B animals, in addition to normal feeds, were administered 5 mg/kg body weight of isoniazid orally for ninety days. Group C animals, in addition to feed, were administered 10 mg/kg body weight of rifampicin orally for ninety days. Group D animals, in addition to normal feed, were orally administered 5 mg/kg body weight of isoniazid and 10 mg/kg body weight of rifampicin for ninety days.

The dosages of rifampicin and isoniazid used in this study are consistent with the recommended daily dosages for humans which are 5 mg/kg body weight/day for isoniazid and 10 mg/kg body weight/day for rifampicin (17, 27).

After ninety days of administration, the animals were humanely sacrificed under ketamine anesthesia. The ventral abdominal wall was opened and blood samples were collected via the abdominal aorta for hormone analyses while the ovaries and uterus were harvested for oxidative stress analyses and histological studies.

The hormones were assayed according to the principle of competitive enzyme immunoassay using AccuBind ELISA Microwells manufactured by Monobind Inc. Lake Forest, CA 92630, USA). The procedure for the enzyme immunoassay was followed according to the manufacturer's guidelines.

The ovaries were, immediately after harvesting, blotted free of blood and weighed immediately using an electronic weighing balance (manufactured by Kern & Sohn GmbH, D-72336 Balingen, Germany) calibrated in milligram and recorded to the nearest two decimal places. The relative ovarian weight was evaluated as the percentage of absolute ovarian weight divided by body weight while the relative uterine weight was evaluated as the percentage of absolute uterine horn weight divided by body weight.

One of the ovaries was then washed twice in cold phosphate buffered saline (PBS) after which it was homogenized using acid-washed sand and PBS in porcelain mortar and pestle. The tissue homogenate was centrifuged at 10000 rpm for 10 minutes at 4^{o}C. The supernatant was immediately processed for analysis of endogenous antioxidants. Superoxide dismutase activity was determined according the method of Misra and Fridovich (24). Catalase activity was determined according the method of Cohen *et al.,* (25). Glutathione peroxidase activity was determined according the method of Nyman (26).

The second ovary and uterus were preserved in 10 % phosphate buffered formalin for histopathology. The tissues were processed via paraffin wax embedding method of Drury and Wallington (28). Procedures of Haematoxylin and Eosin adopted on the sections were as described by Drury and Wallington (28) and Scheehan and Hrapchak (29).

Statistical Analysis

The data were analyzed using IBM Statistical Package for Social Sciences, Version 23 (manufactured by International Business Corporations {IBM}; released in 2015). Results were presented as mean $\pm$ standard error of mean (mean $\pm$ SEM). The parameters for all the experimental groups were compared with the control group using students' t-test. Differences in means were considered significant at 95 % confidence level (that is when probability was less than 0.05 {$P < 0.05$})

Results

Table 1 shows the initial and final body weight, body weight changes, ovarian weight, relative ovarian weight, uterine horn weight and relative uterine weight of all the experimental groups. From the Table, there was no significant difference ($P>0.05$) in the initial body weight (body weight before the commencement of the experiment) in all the experimental groups. Comparison between initial and final body weights in each group showed that there was significant increase ($P<0.05$) in body weight in all the groups. There was no significant difference ($P>0.05$) in the mean weight changes in all the experimental groups, compared with the control (Table 1).

The ovarian weight was significantly lower in the isoniazid treated group ($P<0.05$) and in the rifampicin treated group ($P<0.05$), compared with the control. However, there was no significant difference ($P>0.05$) in the ovarian weight between the rifampicin-isoniazid co-treated group and the control. There was no significant difference ($P>0.05$) in relative ovarian weight when all the experimental groups were compared with the control (Table 1).

There was no significant difference in the uterine horn weight between the isoniazid treated group ($P>0.05$) and the control but the uterine horn weight was significantly lower in the rifampicin treated group ($P = 0.022$) and isoniazid-rifampicin co-treated group ($P = 0.043$), compared with the control (Table 1).

There was no significant difference ($P>0.05$) in the relative uterine weight between the isoniazid treated group and the control. However, relative uterine weight was significantly lower in the rifampicin treated ($P<0.05$) and isoniazid-rifampicin co-treated groups ($P<0.05$), compared with the control (Table 1).

Table 2 shows the mean ovarian oxidative stress parameters of all the experimental groups. From the Table, there was significant increase ($P<0.05$) in superoxide dismutase activity in all the experimental groups compared with the control. There was significant increase ($P<0.05$) in malondialdehyde activity in isoniazid treated group, compared with the control but there was no significant difference in malondialdehyde activity of the rifampicin treated group ($P>0.05$) and isoniazid-rifampicin co-treated group ($P>0.05$), compared with the control. There was a significant increase ($P<0.05$) in catalase activity in isoniazid treated group, compared with the control but there was no significant difference in catalase activity of the rifampicin treated group ($P>0.05$) and isoniazid-rifampicin co-treated group ($P>0.05$), compared with the control. There was significant increase ($P<0.05$) in glutathione peroxidase activity in isoniazid treated group, compared with the control but there was no significant difference in glutathione peroxidase activity of the rifampicin treated group ($P>0.05$) and isoniazid and rifampicin co-treated group ($P>0.05$), compared with the control.

Table 3 shows the results of treatments on the hormonal profile of all the experimental groups. From the Table, there was no significant difference ($P>0.05$) in follicle stimulating hormone level between the isoniazid treated group and the control group but the follicle stimulating hormone level was significantly lower in the rifampicin treated group ($P<0.05$) and in the isoniazid-rifampicin co-treated group ($P<0.05$), compared with the control. The luteinizing hormone levels

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were significantly higher (P<0.05) in all the experimental groups compared with the control. The progesterone levels were significantly lower in isoniazid treated group (P<0.05) and in isoniazid-rifampicin co-treated group (P<0.05), compared with the control but there was no significant difference (P>0.05) in progesterone level between the rifampicin treated group and the control. The estradiol levels were significantly higher in rifampicin treated group (P<0.05) and in isoniazid and rifampicin co-treated group (P<0.05), compared with the control but there was no significant difference (P>0.05) in estradiol level between the isoniazid treated group and the control. The testosterone level was significantly higher (P<0.05) in isoniazid treated group, compared with the control but there were no significant differences in testosterone level between the rifampicin treated group and the control (P>0.05) and between the isoniazid and rifampicin co-treated group and the control (P>0.05). The prolactin levels were significantly lower (P<0.05) in all the experimental groups compared with the control. The testosterone:estradiol ratio was significantly higher (P<0.05) in isoniazid treated group when compared with the control group and significantly lower (P<0.05) in isoniazid and rifampicin co-treated group, compared with the control but there were no significant differences in testosterone:estradiol ratio between the rifampicin treated group and the control group(P>0.05).

The photomicrograph of the ovary of the control group (Figure 1, upper left) shows normal histological features of the ovary with primary follicles (1°), secondary follicles (2°), and corpora lutea (CL) present in the cortex; blood vessels (BV) and interstitial glands (IG) are present in the medulla (M); the ovary is enveloped by germinal epithelium (GE). The photomicrograph of the ovary of rats treated with isoniazid only (Figure 1, upper right) shows ovarian atrophy in the cortex with absence of interstitial glands and non-remarkable medulla, reduced number and growth of developing follicles (1°) compared to the control, atretic tertiary follicle (aTF) and degenerating corpora lutea (dCL). There is presence of interstitial stromal cell hyperplasia arranged in variably sized island and clusters (IC) and follicular cysts (FC). The photomicrograph of the ovary of rats treated with rifampicin only (Figure 1, lower left) shows atretic tertiary follicle (aTF), degenerating corpora lutea (dCL); follicular cysts (FC) and generalized haemorrhagic inflammation of the ovary (Hg). The photomicrographs of the ovary of rats treated with isoniazid and rifampicin (Figure 1, lower right) shows reduced number of developing follicles, presence of follicular cysts (FC) and petechial hemorrhage (Hg) in the ovarian stroma.

The photomicrograph of the uterine horn of the control group (Figure 2, upper left) shows normal histological features with a patent endometrial canal (ec), inner endometrium (En), middle myometrium (My) and outer perimetrium (Pe). The photomicrograph of the uterine horn of the isoniazid-only-treated group (Figure 2, upper right) showed cystically dilated glands (cg) in the endometrium. The photomicrograph of the uterine horn of the rifampicin-only-treated group (Figure 2, lower left) shows mildly congested blood vessels (BV) in the lamina propria (LP) and myometrium. The photomicrograph of the uterine horn of the isoniazid and rifampicin co-treated group (Figure 2, lower right) shows severe endometrial hyperplasia (EH) obliterating the uterine lumen.

Table 1: Body weight, ovarian weight and uterine horn weight in animals of different groups

	Initial weight	Final weight	Weight difference	Ovarian weight	Relative ovarian weight	Uterine horn weight	Relative uterine weight
Control	168.00±3.70[a]	213.86±13.89[b]	45.86±10.57	0.086±0.008	0.041±0.005	0.552±0.087	0.202±0.05
Isoniazid only	166.86±3.75[a]	211.43±4.26[b]	44.57±2.65	0.064±0.006*	0.030±0.005	0.417±0.059	0.201±0.03
Rifampicin only	165.43±3.19[a]	222.00±24.30[b]	56.57±21.15	0.061±0.004*	0.029±0.004	0.162±0.018*	0.114±0.01*
Isoniazid +rifampicin	169.14±4.43[a]	224.14± 8.03[b]	55.00±5.22	0.087±0.011*	0.038±0.004	0.336±0.028*	0.148±0.02*

Comparing initial and final weight within a group. Data are presented as mean + SEM. Unlike superscript means significant difference (P < 0.05). Comparing other parameters across the groups, '*' means significant difference (P < 0.05).

Table 2: Ovarian Oxidative Stress in animals of different groups

	GPX	Catalase	Malondialdehyde	SOD
Control	0.281±0.070[a]	0.060±0.011	0.000123±0.00002	0.440±0.038
Isoniazid only	0.577±0.336*	0.093±0.011*	0.000195±0.00002*	0.731±0.156*
Rifampicin only	0.336±0.079	0.076±0.010	0.000128±0.00002	0.611±0.040*
Isoniazid + rifampicin	0.423±0.076	0.069±0.021	0.000115±0.00002	0.705±0.057*

Comparing the parameters across the groups. Data are presented as mean + SEM. '*' means significant difference (P < 0.05).

Table 3: Hormone profile in animals of different groups

	FSH	LH	PRG	Estradiol	Testosterone	PRL	$T_2 : E_2$ ratio
Control	0.78±0.11	0.13±0.03	17.30±1.08	14.80±2.36	0.13±0.02	0.48±0.02	0.009±0.02
Isoniazid only	0.88±0.17	0.42±0.04*	8.82±0.62*	11.26±5.70	1.08±0.032*	0.30±0.03*	0.084±0.043*
Rifampicin only	0.44±0.05*	0.84±0.05*	14.62±1.68	20.28±0.76	0.14±0.024	0.16±0.04*	0.007±0.001
Isoniazid + rifampicin	0.42±0.04*	1.92±0.31*	3.42±0.18*	26.34±2.42*	0.12±0.020	0.22±0.02*	0.005±0.001*

Comparing the parameters across the groups. Data are presented as mean ± SEM. '*' means significant difference (P < 0.05).

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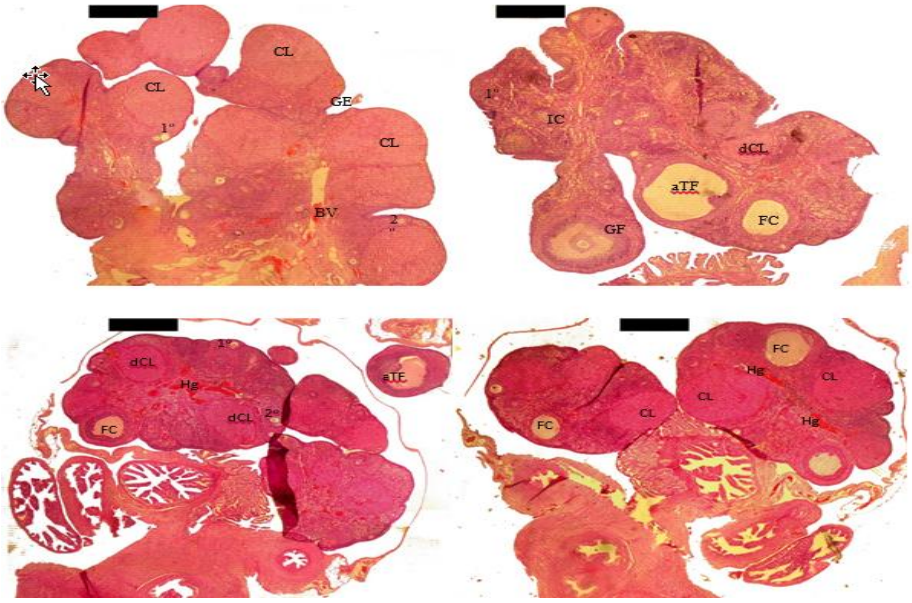

Figure 1: Photomicrograph of ovary of the control group (upper left) showing normal histological features. Photomicrograph of ovary of rat treated with isoniazid (upper right) showing ovarian atrophy in the cortex with absence of interstitial glands, non-remarkable medulla, reduced number of developing follicles. Photomicrograph of ovary of rat treated with rifampicin only (lower left) showing generalized haemorrhagic inflammation, reduced number of growing follicles, atresia of the follicles, cystic follicles and degeneration of the corpora lutea. Photomicrograph of ovary of rat treated with isoniazid and rifampicin (lower right) showing reduced number of developing follicles, follicular cysts, petechial hemorrhage in the ovarian stroma. [primary follicle (1º), secondary follicle (2º), graafian follicle (GF), atretic tertiary follicle (aTF), corpora lutea (CL), degenerating copora lutea (dCL), follicular cysts (FC), interstitial stromal cell (IC), blood vessels (BV), haemorhage (Hg), germinal epithelium (GE)]. (bar = 200 µm).

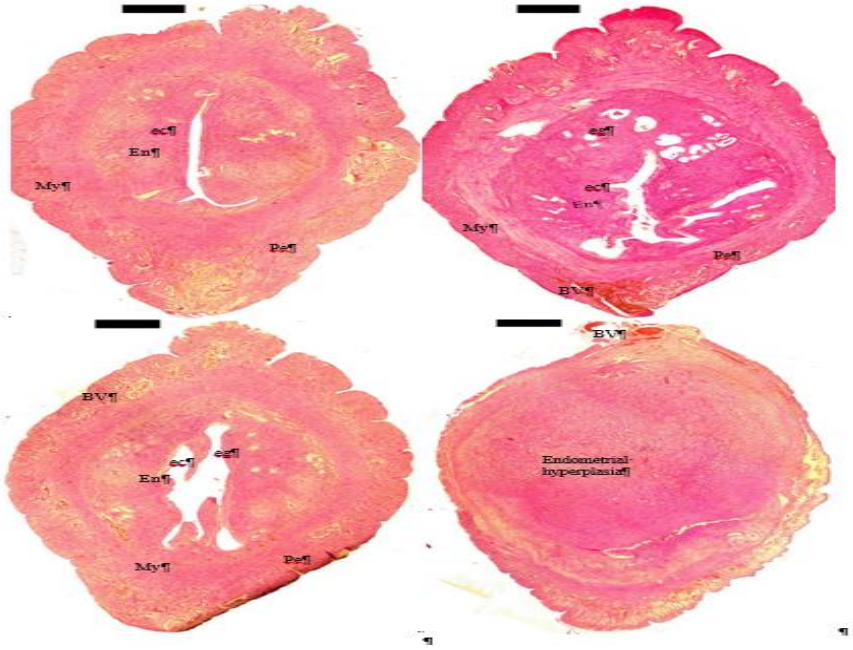

Figure 2: Photomicrograph of the uterus of the control group (upper left) showing normal histological features. Photomicrograph of the uterus of the isoniazid-only-treated group (upper right) showing cystically dilated endometrial glands and congested blood vessels. Photomicrograph of the uterus of the rifampicin-only-treated group (lower left) showing congested blood vessels in the lamina propria and myometrium. Photomicrograph of non-pregnant uterus of the isoniazid and rifampicin co-treated group (lower right) showing severe endometrial hyperplasia obliterating the uterine lumen. [Endometrial canal (ec), inner endometrium (En), endometrial glands (eg), blood vessels (BV), middle myometrium (My), endometrial glands (eg) and outer perimetrium (Pe)]. (bar = 200 µm).

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Discussion

Data on the effects of isoniazid and rifampicin on female reproductive system and fertility has remained scanty (17, 18). The present study investigated the effects of therapeutic doses of isoniazid and rifampicin individually and in combination daily for 90 days on the reproductive functions as well as on the ovarian, uterine and placental histomorphology of adult female Wistar rats.

The significant body weight increase in all the experimental groups in this study is consistent with earlier reports by several researchers of weight gain in tuberculosis patients following treatment with anti-tuberculosis agents been pointed as a marker for response to treatment (30, 31, 32, 33). The significant reduction in ovarian in the isoniazid-treated and rifampicin-treated groups is in agreement with Adebayo *et al*. and AL-Chalaby who found significant reduction in ovarian weight following administration of isoniazid and rifampicin(17, 34).

However, the study by AL-Chalaby showed significant reduction in relative ovarian weight following rifampicin and isoniazid administration (34). This is at variance with the findings of the present study which revealed no significant effect of the treatments on the relative ovarian weight between the experimental groups and the control. The noted variation in our findings might be attributed to the difference in the choice of dosages of the drugs as well as the durations of the treatment. These might have affected the final body weight of the animals and in turn influenced the relative ovarian weight.

The significant reductions in weight of the uterine horns and relative uterine weight in rifampicin-treated group and isoniazid and rifampicin co-treated groups is in agreement with Adebayo *et al*. who found significant decrease in uterine weight and relative uterine weight following administration of isoniazid and rifampicin (17).

One of the most studied mechanisms of isoniazid- and rifampicin-induced toxicities is their ability to induce oxidative stress. Adebayo *et al*. had shown the capacity of isoniazid and rifampicin to induce oxidative stress in the ovary (17). This is also confirmed in this study which revealed significant increase in ovarian superoxide dismutase, malondialdehyde, catalase and glutathione peroxidase activities in isoniazid-treated group. Furthermore, ovarian superoxide dismutase activity was significantly increased in rifampicin-treated group and in isoniazid and rifampicin co-treated group. Tamate *et al.* reported that high superoxide dismutase activity caused reduction in number of ova (35). This report supports the reduced number of follicles found in this study. Low SOD concentration has been shown to be associated with high progesterone concentration while high SOD concentration was associated with low progesterone concentration (36). This is consistent with the findings in this study where high SOD activity was found to be associated with low progesterone level in the isoniazid-treated group and in the isoniazid and rifampicin co-treated group. This suggests that isoniazid- and rifampicin-induced oxidative stress could have altered the progesterone level and possibly the levels of other female fertility hormones.

The significant reduction of progesterone in isoniazid-treated group and in isoniazid and rifampicin co-treated group might be attributed to the atrophic effect of isoniazid on the corpora lutea. This submission is supported by the report of Majed and Samaneh as well as that of Samani *et al.* that implicated isoniazid in the regression of corpora lutea by induction of oxidative stress (37, 38). Riley and Behrman as well as Shimamura *et al*. had also shown that reactive oxygen species including superoxide radicals increase in the corpus luteum during regression, which in turn inhibits progesterone production in rats (39, 40).

High level of progesterone had been reported to act centrally and inhibit both the tonic and surge modes of gonadotrophin releasing hormone (GnRH) release (41). The reverse observation with low progesterone level seen in this study might be attributed to the inhibition of the negative feedback effect of progesterone on the gonadotropin releasing hormone, which might have led to the increased LH secretion seen in this study. This finding is also supported by the study of Robinson *et al.* where low progesterone level leading to high LH level was reported (41).

High LH level had been associated with polycystic ovarian syndrome (42). This possibly explains the presence of follicular cysts in the ovaries of all the experimental groups in this study.

Luteinizing hormone is responsible for androgen production and release during folliculogenesis and high level of luteinizing hormone (LH) in turn increases ovarian androgen secretion (42). In this study, although there was significant increase generally in LH in all the treatment groups compared with the control, significantly higher testosterone level was found in the group treated with only isoniazid. This group also has higher testosterone : estradiol ratio, compared with the control. High testosterone level and high testosterone : estradiol ratio had been implicated in polycystic ovarian syndrome (43). This might serve as possible explanation for the presence of follicular cysts seen in the ovaries following isoniazid administration in this study.

Shen *et al.* had implicated a potential role of FSH in suppressing oxidative stress-induced granulosa cell injury (44). Therefore, the low level of FSH in rifampicin-treated group and in isoniazid and rifampicin co-treated group possibly provides the observed evidence of oxidative stress as depicted by the increased superoxide dismutase.

High estradiol level had been associated with infertility (45, 46, 47), poor ovarian reserve (48) and endometriosis (49, 50, 51), with several authors hinting on the possibility of development of endometrial carcinoma as a result of high level of estradiol (52, 53). However, Miyamoto *et al*. showed that elevated estradiol levels suppress endometrial carcinogenesis, and also that relatively low estradiol levels might benefit the occurrence of this malignancy *in vivo* (54). Furthermore, a recent evidence has shown that high level of estradiol induced endometrial hyperplasia rather than carcinoma (55). This is supported by the findings from this study where hyperplasia of the uterine endometrium with associated elevation of estradiol level in the group treated with isoniazid and rifampicin was observed.

This study showed that there was significant reduction in prolactin level in all the treatment groups, compared to the control. The significant reduction in prolactin level found in all the experimental groups compared with the control is supported by previous report which demonstrated that isoniazid and rifampicin caused significant reduction in the prolactin level (17).

Prolactin is known to have inhibitory effect on the gonadotropin releasing hormone of the hypothalamus through which it inhibits secretion and release of luteinizing hormone (56). The low prolactin level might have potentiated non-inhibitory effect on the gonadotrophs leading to increased luteinizing hormone secretion. This might have accounted for the high LH level and low prolactin level seen in all the treatment groups, compared to the control. Furthermore,

because of its luteotropic effect, low prolactin level had been associated with infertility by inhibiting formation of corpus luteum with associated lowering of progesterone (57) which is consistent with the findings seen in the groups treated with isoniazid only or combination of isoniazid and rifampicin where the ovaries showed degeneration of corpora lutea.

Conclusion

In conclusion, administration of isoniazid and rifampicin singly and in combination at therapeutic doses showed varied degrees of toxicity in female rats, notably in the ovary and uterus through mechanisms that involved induction of oxidative stress and alterations in the female hormonal profile, histomorphology of the ovary and uterus, all of which are capable of impairing female fertility.

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