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Ibtihal Kadhim Mazyed, Fatima Aziz Mahdi Al-badry

Functional and structural kidney alterations associated with fertility drug administration in rats

Department of Biology, College of Education for Pure Sciences, University of Thi-Qar, Thi-Qar, Iraq

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Abstract. *Fertility stimulants are medications used to enhance reproductive fertility in both men and women. Clomiphene citrate (Clomid), Duphaston, and Procreation V are commonly used fertility drugs. However, their prolonged use has been associated with adverse effects, including histological and biochemical changes in the liver and kidney. This study aimed to evaluate renal changes in structure and function following infertility drug administration.*

Methods. Forty-two adult female rats were divided into seven groups, including a control group and six experimental groups receiving Clomid (50 mg), Duphaston (10 mg), or Procreation V (500 mg) for one or two months. Kidney function was assessed by measuring urea, creatinine, and uric acid levels in sera. Ion levels (potassium, sodium, and calcium) were also analyzed. Histopathological examinations were conducted to identify tissue injuries.

Results Renal function markers (urea, creatinine, and uric acid) significantly increased in rats treated with Clomid and Duphaston for two months compared to controls ($p < 0.05$). Procreation V caused mild, non-significant changes. Ion analysis showed significant increases in potassium and sodium levels ($p < 0.05$), while calcium levels declined across all drug-treated groups. Histopathological findings revealed hemorrhage, necrosis, congestion, fibrosis, inflammation, and glomerular structural alterations, with more severe damage observed in Clomid and Duphaston groups following prolonged exposure.

Conclusions. Prolonged use of Clomid and Duphaston leads to significant kidney function impairment and structural damage, while Procreation V showed milder effects. These findings suggest potential renal risks associated with long-term fertility drug use, necessitating caution in clinical applications.

Keywords: *rats, kidney function, urea, histological changes, Clomid, Duphaston.*

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Correspondence should be addressed to Ibtihal Kadhim Mazyed: ibtihalkazem.bio@utq.edu.iq

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Ібтіхал Кадхім Мазієд, Фатіма Азіз Махді Аль-Бадрі

Функціональні та структурні зміни нирок, асоційовані з прийомом лікарських засобів для лікування безпліддя у щурів

Факультет біології, Освітній коледж природничих наук, Університет Ті-Кар, Ті-Кар, Ірак

Резюме. *Стимулятори фертильності – це лікарські засоби, які використовуються для підвищення репродуктивної здатності як у чоловіків, так і у жінок. До найбільш поширених препаратів для стимуляції фертильності відносяться кломіфенцитрат (Кломід), Дюфастон та Прокацеяція V. Однак їх тривале застосування асоціюється з негативними ефектами, включаючи гістологічні та біохімічні зміни в печінці та нирках. Метою цього дослідження було оцінити структурні та функціональні зміни в нирках після застосування препаратів для лікування безпліддя.*

Методи. Сорок дві дорослі самки щурів були розподілені на сім груп, включаючи контрольну групу та шість експериментальних груп, які отримували Кломід (50 мг), Дюфастон (10 мг) або Прокацеяція V (500 мг) протягом одного або двох місяців. Функція нирок оцінювалася за рівнями сечовини, креатиніну та сечової кислоти в сироватці крові. Також були проаналізовані рівні іонів (калію, натрію та кальцію). Проведені гістопатологічні дослідження для виявлення ушкоджень тканин.

Результати. Маркери функції нирок (сечовина, креатинін та сечова кислота) значно збільшилися у щурів, які отримували Кломід та Дюфастон протягом двох місяців, порівняно з контролем ($p < 0,05$). Прокацеяція V спричинила незначні зміни, що не були статистично значущими. Аналіз іонів показав значне підвищення рівнів калію та натрію ($p < 0,05$), тоді як рівні кальцію знижувалися в усіх групах, які отримували препарати. Гістопатологічні результати виявили геморагії, некроз, конгестію, фіброз, запалення та зміни структури клубочків, при цьому більш важкі пошкодження спостерігалися в групах Кломіду та Дюфастону після тривалого застосування.

Висновки. Тривале застосування Кломіду та Дюфастону призводить до значних порушень функції нирок та структурних ушкоджень, в той час як Прокацеяція V має м'якші ефекти. Ці результати свідчать про потенційні ризики для нирок, пов'язані з тривалим використанням препаратів для стимуляції фертильності, що вимагає обережності при клінічному застосуванні.

Ключові слова: *щури, функція нирок, сечовина, гістологічні зміни, Кломід, Дюфастон.*

Introduction. Introduction. Fertility stimulants are medications that help enhance fertility levels in women and men. They enhance reproductive fertility for women by stimulating the growth of ovarian follicles [1]. Clomiphene citrate (CC) or Clomid, Duphaston, and Procreation V are examples of these drugs. Clomid is a selective modulator of estrogen receptors and is the most widely used fertility drug [2]. It stimulates ovulation by inhibiting the endogenous negative estrogen feedback on the hypothalamic-pituitary axis, leading to an increase in FSH [3]. Duphaston contains the active ingredient dydrogesterone, which is a synthetic chemical compound similar to the natural female progesterone hormone. It performs the same function by binding to progesterone receptors in the uterus and does not affect the progesterone hormone naturally secreted by the body [4].

Ibtihal Kadhim Mazyed
ibtihalkazem.bio@utq.edu.iq

Procreation V is a fertility supplement that improves reproductive function based on its natural components of herbs, vitamins, minerals, and antioxidants. These ingredients work to enhance ovarian function and fertility, as well as support uterine health and fetal development in the early stages of pregnancy. Studies have shown that consuming high oral doses of these drugs causes ovarian dysfunction, enlargement, vasomotor flashes, nausea, vomiting, weight gain, and shortness of breath [5], as well as histological and biochemical changes in the liver and kidneys [6]. Additionally, Procreation V affects the digestive system, causing flatulence, diarrhea, and temporary colic [7].

Despite the known side effects of these drugs on various organs, the long-term impact of fertility stimulants on kidney structure and function remains insufficiently explored. While existing studies have focused on ovarian and liver effects, the renal consequences of these treatments have not been extensively studied, especially in terms of chronic use and associated structural damage. The current study aims to fill this knowledge gap by determining renal changes in both the structure and function of the kidney following infertility drug administration.

Materials and Methods. Drugs of infertility. In this study, three infertility drugs were utilized: clomiphene citrate (50 mg, France), Duphaston (10 mg, Netherlands), and Procreation V (500 mg, USA). The drugs were administered orally via stomach tube to the experimental groups as outlined below.

Ethical statement. The study was approved by the Ethical Committee Board of the Department of Biology, College of Education for Pure Sciences, University of Thi-Qar (Protocol No. 6110, Date: 09/06/2022).

Animals. Forty-two adult female rats (Rattus norvegicus), aged 11-13 weeks and weighing between 215 and 225 grams, were selected for this experiment. The rats were sourced from the animal facility of the University of Thi-Qar, College of Education for Pure Sciences, and were housed under controlled laboratory conditions with a 12-hour light/dark cycle and a room temperature of 21 ± 3°C.

Experimental design. The rats were randomly divided into seven experimental groups, with six animals per group. The groups were as follows:

Control Group: Animals received distilled water and standard feed.

Clomid Groups:

Group 2: Animals received Clomid (50 mg) for one month.

Group 3: Animals received Clomid (50 mg) for two months.

Duphaston Groups:

Group 4: Animals received Duphaston (10 mg) for one month.

Group 5: Animals received Duphaston (10 mg) for two months.

Procreation V Groups:

Group 6: Animals received Procreation V (500 mg) for one month.

Group 7: Animals received Procreation V (500 mg) for two months.

All drugs were administered orally via stomach tube at a consistent dose throughout the experiment.

Kidney function assessment. To evaluate kidney function, blood samples were collected from the rats and centrifuged at 2000 rpm for 20 minutes to separate the serum. The concentrations of urea, creatinine, and uric acid were determined using commercially available kits (Biolabo, Biomerieux, France) according to the manufacturer's instructions [8]. The levels of electrolytes, including potassium, sodium, and calcium, were measured using an OPTILION analyzer. The analyzer utilized refrigerated cassettes, which were equilibrated at room temperature (18-30°C) for 14 days before use. Ion concentrations were calculated using the calibration curve, with the final results printed automatically by the device.

Histopathological examination. Following the experimental period, kidneys from all groups were harvested, fixed in 10% formalin, and processed for histopathological examination. The tissue samples were dehydrated in a graded ethanol series, cleared in xylene, and embedded in paraffin wax. Sections of 4 µm thickness were cut from each tissue block and stained with hematoxylin and eosin for microscopic evaluation [9].

Statistical analysis. Data were expressed as mean ± standard deviation (S.D.). Statistical analysis was performed using SPSS software (Version 25). Differences between groups were considered statistically significant at a p-value of ≤ 0.05.

Results. Table 1 reports elevated kidney function parameters (urea, creatinine, and uric acid) following infertility drug administration compared to the control group.

Table 1

Effect of infertility drugs on kidney functions of female rats

Groups	Uric acid (g/dl)	Creatinine (mg/dl)	Urea (mg/dl)
Control groups	4.28±0.34d	0.61±0.07b	46.50±6.28d
Clomid group for one month	6.96±0.66b	0.68±0.24b	54.00±5.40c
Clomid group for two months	9.73±0.58a	0.88±0.07a	77.00±1.89a
Duphaston group for one month	5.73±0.70c	0.66±0.17b	51.61±4.53cd
Duphaston group for two months	7.50±0.50b	0.86±0.08a	68.33±1.96b
Procreation V for one month	5.58±0.67c	0.61±0.07b	50.33±1.63cd
Procreation V for two months	5.93±0.74c	0.66±0.18b	50.83±3.81cd

Notes: Different letters indicate differences significantly (P≤ 0.05).

Urea concentration was significantly increased (P ≤ 0.05) in the Clomid and Duphaston 2-month groups, while this increase was not significant in the Duphaston 1-month and Procreation V groups (both 1 and 2 months) compared to the control group. Additionally, a significant increase (P ≤ 0.05) in urea levels was observed in the Clomid and Duphaston 2-month groups compared to their respective 1-month groups. In contrast, the Procreation V 2-month group showed no significant difference in urea concentration when

compared to the 1-month group. The Clomid 2-month group exhibited the highest increase in urea levels, while the Procreation V 1-month group had the lowest.

Creatinine concentration significantly increased ($P \leq 0.05$) after Clomid and Duphaston treatment for two months compared to the control group, while no significant changes were observed in the other drug groups. Treatment with Clomid and Duphaston for two months led to a significant increase ($P \leq 0.05$) in creatinine levels compared to the 1-month treatment with these drugs. However, no significant increase was observed in the Procreation V 2-month group compared to the Procreation V 1-month group. When comparing across drug groups, a higher increase in creatinine levels was found after two months of treatment compared to one month.

Regarding uric acid, a significant increase ($P \leq 0.05$) was observed in all drug-treated groups compared to the control group. Comparison between the 2-month and 1-month treatments with Clomid and Duphaston showed a significant increase, except in the Procreation V 2-month group, which did not show a significant change compared to the Procreation V 1-month group. When comparing across drug groups, the Clomid 2-month group exhibited the highest elevation in uric acid levels, while the Procreation V 1-month group had the lowest concentration.

Table 2 shows a significant increase ($P \leq 0.05$) in potassium levels in the Clomid and Duphaston treatment groups compared to the control group.

Table 2

Effect of infertility drugs on the level of ions of female rats

Groups	Calcium (mg/dl)	Sodium mMol / L	Potassium mMol / L
Control group	9.49±0.48a	131.80±0.81g	4.55±0.48e
Clomid group for one month	7.87±0.75b	145.24±0.72c	5.93±0.38bc
Clomid group for 2 months	3.78±0.41d	165.52±0.94a	6.66±0.54a
Duphaston group for one month	8.40±0.45b	143.46±1.02d	5.60±0.30bcd
Duphaston group for 2 months	5.03±0.64c	151.95±0.85b	6.17±0.58ab
Procreation V for one month	8.32±0.81b	135.68±1.56f	5.13±0.62de
Procreation V for 2 months	8.51±0.29b	140.88±1.18e	5.39±0.16cd

Notes: Different letters indicate differences significantly ($P \leq 0.05$).

A significant elevation ($P \leq 0.05$) in potassium levels was also observed when comparing the Clomid and Duphaston 2-month groups with their respective 1-month groups. However, no significant increase in potassium levels was found in the Procreation V 2-month group compared to the Procreation V 1-month group. The highest potassium level was observed in the Clomid 2-month group, while the lowest level was found in the Procreation V 1-month group.

Sodium levels were significantly increased ($P \leq 0.05$) in all infertility drug-treated groups compared to the control group. Additionally, a significant increase ($P \leq 0.05$) in sodium levels was noted when comparing the 2-month treatment groups with the 1-month treatment groups for all infertility drugs. The highest sodium level was found in the Clomid 2-month group, while the lowest level was observed in the Procreation V 1-month group.

Furthermore, a significant decrease ($P \leq 0.05$) in calcium levels was observed in all drug-treated groups compared to the control group. A significant decrease ($P \leq 0.05$) was also noted in the Clomid and Duphaston 2-month groups compared to their respective 1-month groups, while no significant decrease was observed in the Procreation V 2-month group compared to the Procreation V 1-month group. The smallest decrease in calcium was found in the Clomid 2-month group, while the greatest decrease was observed in the Procreation V 1-month group.

There is histopathological tissue injury in the kidney that happens after drugs of infertility treatment. Normal structures of the kidney are shown in Figure 1.

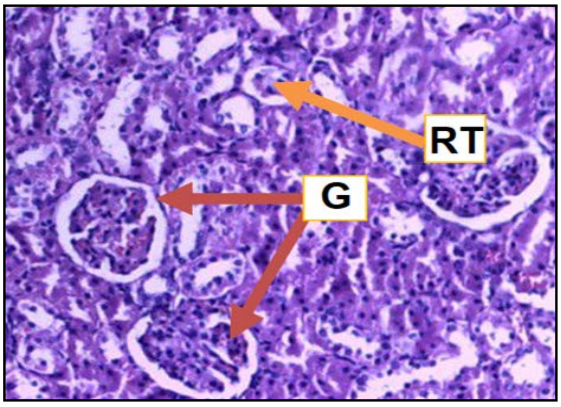

Fig. 1. Normal kidney structure in the control group. The figure shows the normal structure of the kidney in the control group, including glomeruli (G) and renal tubules (RT) (H&E, 100X).

Tissue damage observed includes hemorrhage, necrosis, congestion, fibrosis, inflammation, edema, and structural changes in the glomeruli, such as breakdown, absence, death, and bleeding. The histopathological findings for each treatment group are shown in Fig. 2-6.

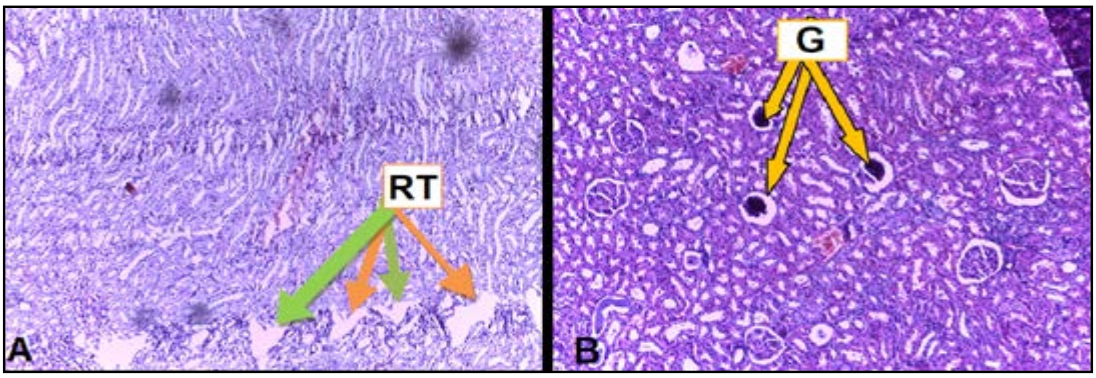

Fig. 2. Histopathological tissue injury in the Clomid 1-month Group.
A) Necrosis of renal tubules (RT) in the Clomid 1-month group.
B) Glomerular degeneration (G) in the Clomid 1-month group (H&E, 100X).

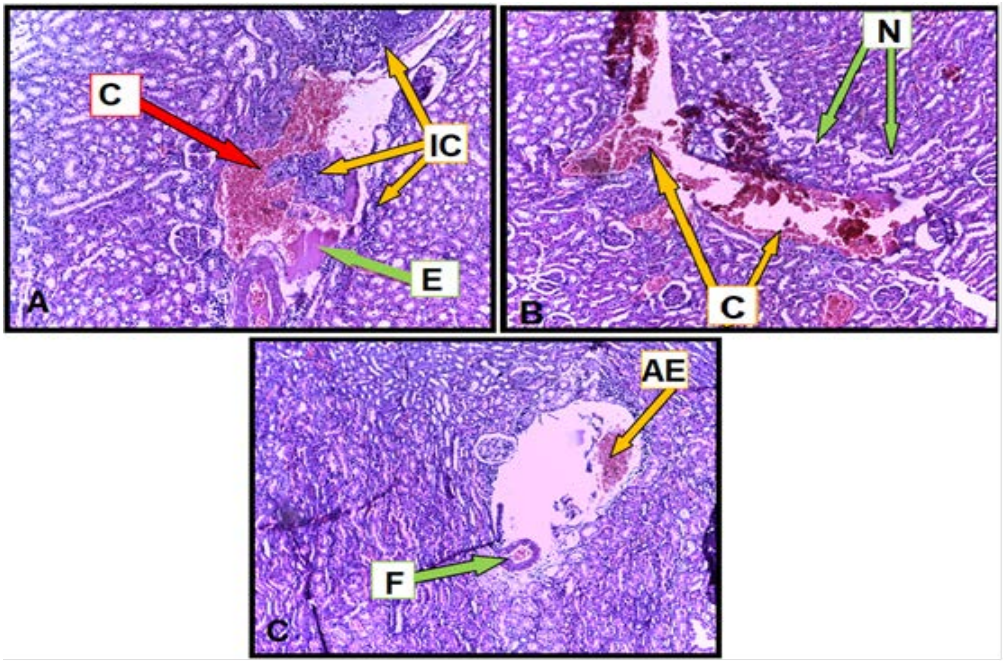

Fig. 3. Histopathological tissue injury in the Clomid 2-month Group.
A) Various tissue injuries, including congestion (C), edema (E), and infiltration of inflammatory cells (IC).
B) Severe congestion (C) and necrosis (N).
C) Aggregation of erythrocytes (AE) and fibrosis (F) in the Clomid 2-month group (H&E, 100X).

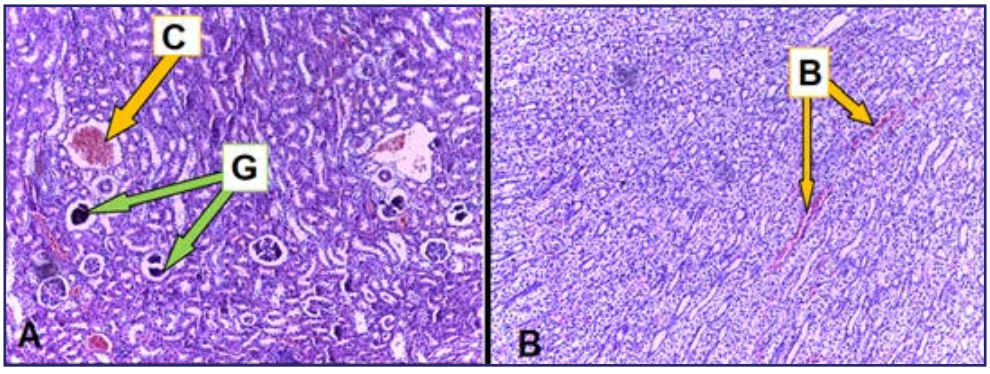

Fig. 4. Histopathological tissue injury in the Duphaston 1-month Group.
A) Glomerular degeneration (G) and congestion (C).
B) Bleeding in tubules (B) in the Duphaston 1-month group (H&E, 100X).

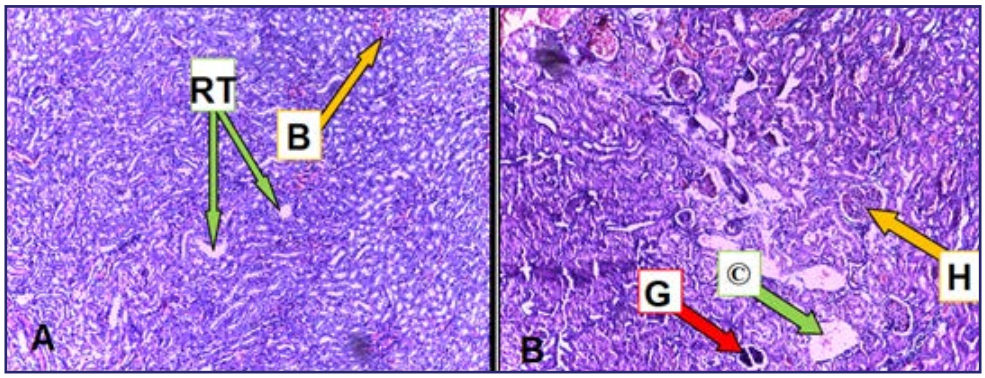

Fig. 5. Histopathological tissue injury in the Duphaston 2-month Group.
A) Dilation of renal tubules (RT) and bleeding (B).
B) Hemorrhage (H), absence (©), and glomerular degeneration (G) in the Duphaston 2-month group (H&E, 100X).

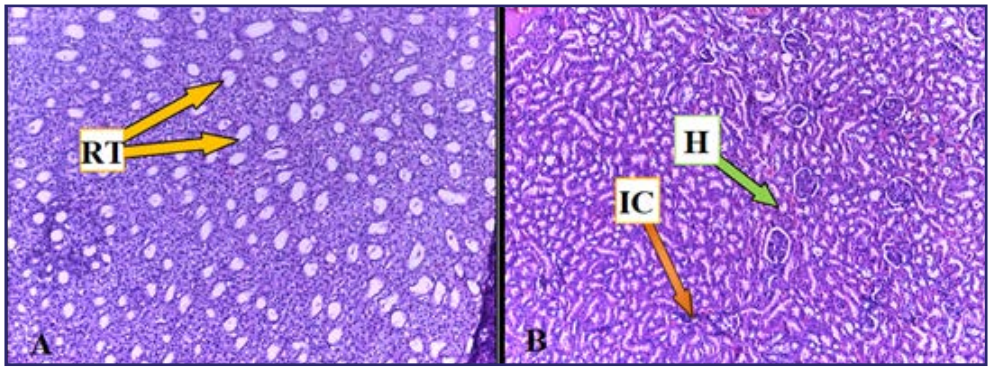

Fig. 6. Histopathological tissue injury in the Procreation V 1-month and 2-month Groups.
A) Normal tubules (RT) in the Procreation V 1-month group.
B) Hemorrhage (H) and mild infiltration of inflammatory cells (IC) in the Procreation V 2-month group (H&E, 100X).

Discussion. An increased number of kidney parameters were observed in all groups treated with infertility drugs compared to the control group. Notably, significant elevations in urea, creatinine, and uric acid were found, particularly in the groups treated with Clomid and Duphaston for an extended duration (two months). These increases are associated with the use of infertility drugs, which affect kidney function, leading to altered markers of kidney performance. This finding is consistent with the study by Gowda et al. [10], which highlighted that kidney disorders can lead to impaired function indicators such as creatinine and uric acid. The elevated levels of urea and uric acid may also be linked to increased blood glucose levels induced by infertility stimulants, as suggested by Dabala [11], who reported that renal failure could result from vasodilation and elevated glucose levels.

Regarding the effect of infertility drugs on electrolytes, the current results indicate an increase in potassium and sodium levels following treatment. This may be related to elevated estrogen levels, which is consistent with the findings of Wong et al. [12], who demonstrated that steroid hormones like estrogen have differential effects on potassium channels. Additionally, changes in the permeability of cellular membranes due to estrogen disturbances may also explain the elevated ion levels. This observation aligns with the work of Carolyn and Peter [13], who noted that variations in estrogen levels influence the movement and passage of ions, particularly potassium, across membranes. The observed decline in calcium levels is likely due to ion imbalances induced by infertility drug treatment, which is in agreement with Wei et al. [14], who reported that reduced calcium levels can indirectly affect potassium levels.

Histopathological analysis revealed tissue injuries in the groups treated with infertility drugs, including inflammation, necrosis, congestion, hemorrhage, fibrosis, edema, and damage to the glomeruli, such as death, bleeding, absence, and breakdown. These injuries are likely linked to the use of infertility drugs. Mahimainthan et al. [15] reported glomerular hypertrophy due to hyperplasia of glomerular epithelial cells. The enlargement of glomeruli could be attributed to the infiltration of inflammatory cells, which is supported by the findings of Dervisoglu et al. [16], who observed that inflammation leads to hypertrophy, a process potentially induced by the use of infertility stimulants.

Necrosis observed in histological sections of the kidney may be linked to hyperglycemia resulting from the drug treatment, a finding consistent with Marcheix et al. [17], who reported that elevated blood glucose levels contribute to necrosis. Additionally, hyperglycemia can stimulate oxidation enzymes, as noted by Rabol et al. [18]. These pathological changes could also be a consequence of ovarian hyperstimulation syndrome, which is induced by infertility drugs. This is in agreement with Kobak et al. [19], who demonstrated that Clomiphene citrate can cause ovarian hyperstimulation syndrome, potentially leading to renal complications.

Clomid is widely prescribed to women with ovulatory issues, particularly in the case of polycystic ovary syndrome (PCOS), and is considered an affordable first-line treatment compared to more invasive fertility procedures. Clomid is also occasionally used in men to treat infertility by stimulating testosterone production. Duphaston is prescribed for conditions such as dysmenorrhea, irregular menstrual cycles, luteal phase deficiency, recurrent miscarriage, endometriosis, and hormone replacement therapy. Procreation V is utilized in advanced assisted reproductive technologies, including in vitro fertilization, intracytoplasmic sperm injection, and cryopreservation techniques. It is also used in genetic screening and editing through preimplantation genetic testing, personalized medicine in fertility, fertility preservation, and third-party reproduction.

Our study has several limitations. The primary limitations include the small sample size and the short duration of the study. Additionally, Clomid is associated with a low pregnancy success rate, limited effectiveness after 3-6 cycles, and potential side effects. Furthermore, all the agents used in this study are less effective in cases of severe ovulatory dysfunction or the presence of tubal or uterine factors.

Conclusions. The intake of infertility stimulants over two months led to impaired kidney function, evidenced by elevated levels of urea, creatinine, and uric acid, with more pronounced tissue damage. Additionally, these drugs caused an increase in potassium and sodium levels, alongside a decrease in calcium levels. Histopathological analysis revealed significant kidney tissue injuries, including edema, infiltration of inflammatory cells, necrosis, fibrosis, congestion, bleeding, and renal tubule dilation. Structural alterations in the glomeruli, such as shrinkage, cell death, bleeding, and breakdown, were also observed.

Conflicts of interest statement. The authors have no competing interests to declare.

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Author contributions:

Ibtihal Kadhim Mazyed: Conceptualization; data curation; investigation; methodology; project administration; software; supervision; visualization; writing – original draft and writing – review & editing;

Fatima Aziz Mahdi Al-badry: Conceptualization; investigation; methodology; project administration; resources; supervision; validation; visualization; writing – original draft and writing – review & editing.

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