Original Article

Dydrogesterone Use and Pregnancy-Associated Urinary Tract Infection: Associations with Hormonal, Cytokine, Renal and Bacterial Profiles

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ABSTRACT

Objective: To examine the association between dydrogesterone use and UTI in pregnant women, with attention to reproductive hormones, the cytokine markers Inter Leukin-17 (IL-17) and Matrix Metalloproteinase-1 (MMP-1), renal indices, bacterial etiology, and antimicrobial susceptibility.

Study Design: Experimental study.

Place and Duration of Study: This study was conducted at the Department of Microbiology, College of Science, Tikrit University, Salah al-Din, Iraq, from 12th May 2025 to 30th August 2025.

Methods: In this experimental study at Tikrit University and Tikrit Teaching Hospital, pregnant women were grouped by UTI status and dydrogesterone exposure. Serum estrogen. The levels of progesterone, IL-17, MMP-1, urea and creatinine were measured with ELISA. Urine from UTI Positive women was cultured, the isolates identified with the VITEK 2 system and susceptibility data was obtained. Was interpreted according to CLSI guidelines.

Results: Results: Estrogen was significantly elevated in the dydrogesterone group, especially when considering the UTI group. This difference remained after taking account of maternal age and pregnancy into the positive sub-group. stage. No significant difference was found for the other five metabolites: progesterone, IL-17, MMP-1, urea, and creatinine. UTI The occurrence and distribution of bacteria were not significantly related to susceptibility patterns. exposure.

Conclusion: The use of dydrogesterone was not significantly associated with UTI or renal, immune, or other complications. or microbiological change. The immune-endocrine profile is most likely to be high because of the increased oestrogen level of this type of profile. The interaction is not as a direct effect of the drug, but as an interaction occurring while the baby is in the mother's womb.

Key Words: Dydrogesterone, Duphaston, UTI, Pregnancy, IL-17, MMP-1, estrogen.

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INTRODUCTION

One of the most common bacterial complications of pregnancy is urinary tract infection or UTI. has clinical significance as undetected asymptomatic bacteriuria may lead to cystitis or Pyelonephritis and fetal and maternal effects. Pregnancy makes one more vulnerable: urinary: In the presence of stasis, dilatation of the ureters, incomplete bladder emptying and host defense changes in pregnancy. bacterial persistence.

The focus of UTI here is not just an issue that happened locally but is a result of the virulence of the bacteria, susceptibility to antimicrobial agents, immune regulation, endocrine status, and renal function adaptation.[1-3] Escherichia coli remains the predominant uropathogen, but Staphylococcus aureus, Streptococcus agalactiae, Klebsiella spp., and other organisms occur at frequencies varying by local epidemiology and prior antibiotic exposure.

Because agent choice is constrained by fetal safety, gestational age, and regional resistance, culture-based identification and susceptibility testing remain indispensable.[3-5] The oral synthetic progestogen, dydrogesterone (Duphaston), is used in early. Threatened miscarriage, recurrent pregnancy loss, and luteal support are all pregnancy indications for which

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CM is indicated. [6-8] Its biological reach may go further than supplementation: reproductive immunology has placed it. As a candidate immunomodulator via cytokine controls and tolerization of the mother-fetal axis.[9-13] Successful gestation is achieved by finely-tuned immune regulation, not by general However, hormones, cytokines, and immune cells maintain fetal tolerance, and suppression is what is needed to avoid it. Preserving antimicrobial defense.[14] Most of such evidence, however, is from reproductive immunology cohorts (not infection) and a direct link between dydrogesterone and UTI. It has not been determined if it has been established.

To assess whether dydrogesterone exposure occurs at a time of inflammation, measurements of IL-17 and MMP-1 were taken. or tissue-remodeling activity. In contrast, IL-17 promotes recruitment and mucosal defence of neutrophils but in, when considering the use of pregnancy, maternal-fetal tolerance must be taken into account.[13,14] MMP-1, an interstitial collagenase, involved in matrix turnover, placental remodeling, and inflammation, and cervical remodeling. Both the intrauterine cytokine levels are associated with metalloproteinase activity.[15-17] Estrogen Progesterone and androstenedione, in addition to their reproductive functions, also affect immune function and are interconverted. Signaling by cytokines during gestation.[14,18] The present study, therefore, evaluated the association of dydrogesterone with the bacteria in UTI is not known in pregnant women, and antimicrobial resistance is not known. Susceptibility, IL-17, MMP-1, urea, creatinine, estrogen, and progesterone.

METHODS

Study design and participants: This experimental study was conducted at Tikrit University and Tikrit City. Teaching Hospital was approved by the institutional ethics committee (Ref. SCITUH-0012, 05 - 1-2025) written informed consent was obtained from all participants. The study included 35 pregnant women classified by UTI status and dydrogesterone exposure. Dydrogesterone users included 20 UTI-positive women and 5 women with no bacterial growth; non-users included 6 UTI-positive women and 4 women with no bacterial growth. The UTI status has been created bacteriologically; dydrogesterone exposure was considered to be if the use was documented or reported. Maternal Adjusted analyses accounted for age and stage of pregnancy. Data on treatment indication, dose, duration, prior UTI, obstetric history, and recent antibiotics were incompletely available and considered when interpreting results.

Sample collection and assays: Peripheral venous blood was drawn aseptically, allowed to clot, and centrifuged to recover serum. Midstream clean-catch urine from women with suspected or confirmed UTI was processed promptly; the sediment was examined microscopically, and quantitative culture confirmed significant bacteriuria. Serum MMP-1, IL-17, estrogen, progesterone, urea, and creatinine were measured by enzyme-linked immunosorbent assay (ELISA) using kits from Sunlong Biotech Co., Ltd. following the manufacturer's instructions, with concentrations read from analyte-specific standard curves.

Bacterial identification and susceptibility: Isolates from UTI-positive women were identified with the VITEK 2 automated system. Susceptibility was classified as sensitive, intermediate, or resistant according to Clinical and Laboratory Standards Institute (CLSI) criteria. Susceptibility was tested against a 15-agent panel (detailed in figure 1).

Statistical analysis: Analyses were performed in SPSS version 26. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Groups were compared with independent-samples or Welch's t-tests, and categorical variables with chi-square or Fisher's exact tests. The dydrogesterone-UTI association was summarized as odds ratios (ORs) with 95% confidence intervals (CIs); multivariable logistic and linear regression adjusted for maternal age and pregnancy stage, and Hedges' g provided standardized mean differences. Given the exploratory design and small subgroups, P-values were interpreted alongside effect sizes and confidence intervals. All tests were two-tailed, with $P < 0.05$ regarded as significant.

RESULTS

Across the measured serum markers, dydrogesterone use was associated with a significantly higher estrogen concentration, whereas progesterone, IL-17, MMP-1, urea, and creatinine did not differ significantly between users and non-users. The nonsignificant immune and renal comparisons showed small effect sizes and wide confidence intervals, supporting cautious interpretation rather than evidence of a clear systemic inflammatory or renal shift.

Within the UTI-positive subgroup, the estrogen difference remained statistically significant in both unadjusted analysis and after adjustment for maternal age and pregnancy stage. This indicates that the estrogen signal was not fully explained by these two maternal characteristics, although residual confounding cannot be excluded.

Dydrogesterone use was not significantly associated with UTI occurrence, and the confidence interval around the odds ratio was wide. Among women with UTI, bacterial distribution also did not differ significantly by dydrogesterone use; Staphylococcus aureus was the most frequently recovered organism overall, followed by Escherichia coli and Streptococcus agalactiae.

Table No. 1: Hormonal, immune, and renal parameters according to dydrogesterone use.

Parameter	Dydrogesterone users (Mean ± SD)	Non-users (Mean ± SD)	Mean difference	95% CI	P-value	Hedges' g
Estrogen	203.04 ± 145.36	114.60 ± 92.78	88.44	3.53 to 173.35	0.042*	0.65
Progesterone	66.44 ± 33.67	54.20 ± 21.33	12.24	-7.35 to 31.83	0.210	0.39
MMP-1	29.39 ± 13.26	31.41 ± 18.79	-2.01	-16.10 to 12.07	0.762	-0.13
IL-17	90.24 ± 20.62	94.87 ± 17.37	-4.63	-18.97 to 9.72	0.508	-0.23
Urea	28.68 ± 4.31	27.90 ± 5.22	0.78	-3.21 to 4.77	0.681	0.17
Creatinine	0.62 ± 0.11	0.58 ± 0.15	0.04	-0.07 to 0.15	0.451	0.33

Values are presented as mean ± standard deviation unless otherwise indicated. CI, confidence interval. *P < 0.05.

Table No. 2: Unadjusted and adjusted association between dydrogesterone use and estrogen among UTI-positive women.

Analysis	Comparison	Group 1 value	Group 2 value	Difference	95% CI	P-value	Hedges' g
Unadjusted	UTI + dydrogesterone (n=20) vs UTI + no dydrogesterone (n=6)	210.45 ± 156.41	99.33 ± 64.67	111.12	19.98 to 202.26	0.019*	0.76
Adjusted	UTI + dydrogesterone vs UTI + no dydrogesterone	-	-	139.75	20.55 to 258.95	0.022*	-

The adjusted model included maternal age and pregnancy stage. Welch's t-test was used for the unadjusted comparison. CI, confidence interval. *P < 0.05.

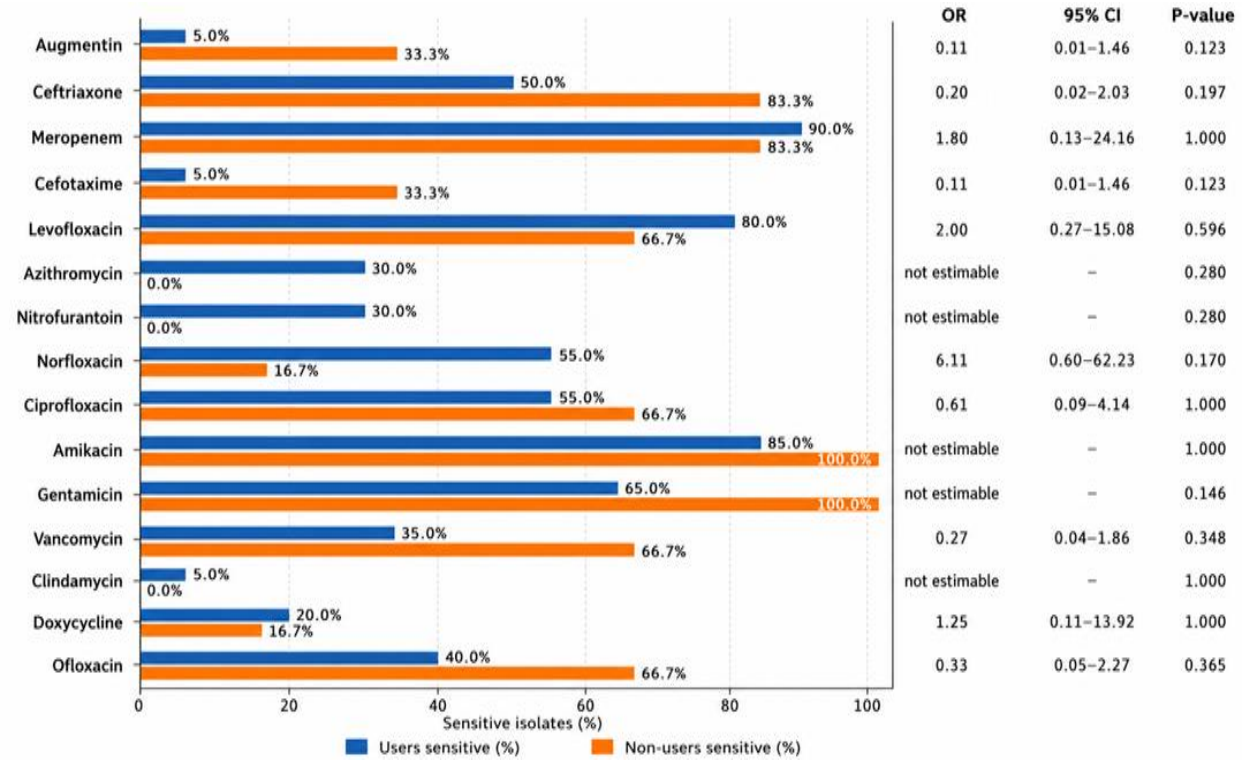

Figure 1: Antimicrobial susceptibility according to Duphaston use (UTI-positive)

Fisher's exact test; some ORs not estimable (zero cells).

No statistically significant between-group difference in antimicrobial susceptibility was observed for any tested agent. The highest sensitivity proportions among dydrogesterone users were observed for meropenem, amikacin, and levofloxacin, whereas the small number of non-users produced several zero-cell comparisons and imprecise odds ratios.

Table No.3: Association between dydrogesterone use, UTI occurrence, and bacterial isolate distribution.

Outcome / isolate	Dydrogesterone users n/N (%)	Non-users n/N (%)	Total n (%)	Effect / statistic	95% CI	P-value
UTI positive	20/25 (80.0%)	6/10 (60.0%)	26/35 (74.3%)	OR 2.67	0.54-13.21	0.393
Control / no growth	5/25 (20.0%)	4/10 (40.0%)	9/35 (25.7%)	Reference	-	-
Escherichia coli	5 (25.0%)	0 (0.0%)	5 (19.2%)	-	-	-
Staphylococcus aureus	14 (70.0%)	6 (100.0%)	20 (76.9%)	Overall distribution	-	0.310
Streptococcus agalactiae	1 (5.0%)	0 (0.0%)	1 (3.8%)	-	-	-
Total UTI-positive isolates	20 (100%)	6 (100%)	26 (100%)	-	-	-

The UTI association is presented as an odds ratio (OR) with 95% CI. Bacterial distribution was compared among UTI-positive women only.

DISCUSSION

The main finding is that estrogen levels are increased among dydrogesterone consumers, particularly in the central observation. Women with UTI's had a similar increase in white blood cell counts, but this was not the case for progesterone levels, immune markers, renal function or renal clearance. Indices, UTI occurrence, Bacterial distribution, or susceptibility. The most prevalent signal was thus Not endocrine, renal or in general inflammatory in nature. It is important to note that this estrogen finding is best interpreted as an association with endocrine activity, and not as a direct estrogenic effect of dydrogesterone. It may be caused by a different hormonal environment, the indication for treatment, Even after adjustment for placental activity or residual confounding, it was still present, suggesting that age; This is not just accounted for by and pregnancy stage. The reproductive hormones are strongly intertwined with Immune regulation, and hormone regulation of humoral and cytokine mediated immune responses. Responses.[14,18] Monteiro et al. found that pregnancy level estrogen and progesterone bolster humoral immunity via the TFH/B-cell axis.[18] Here, however, it was the estrogen rise that was not mirrored by increases in IL-17/MMP-1, no detectable systemic cytokine or tissue remodeling response.

The fact that there is not a progestogenic difference does not rule out being progestogenic, as routine Specific progesterone immunoassays are able to identify endogenous progesterone, but not dydrogesterone or its metabolites; and this is not a measure of the serum progesterone effects of the drug, but of the serum progesterone level. Likewise, Serum IL-17 is serum IL-17 together with the stable IL-17 and MMP-1 levels, which do not support a dramatic systemic shift towards Th17. may not reflect mucosal immunity in the urinary tract. Reported cytokine modulation by hormones. The majority of their data come from reproductive-immunology rather than culture-confirmed UTI cohorts.[9, 13, 20]

Urea and creatinine were comparable suggesting no renal disturbance; renal indices were also comparable. Detect subtle injury from infection, rather than exclude established renal involvement. biomarkers might be more sensitive. There was no association between dydrogesterone and UTI, and the range of confidence is broad which does not allow a definitive conclusion. UTI during pregnancy is multifactorial, Influenced by urinary stasis, gestational physiology, previous infection, exposure to antimicrobial agents and other factors. These data indicate that dydrogesterone is not an independent risk factor for bacterial virulence. [2,3]

Key strengths include the small, unevenly distributed groups, the case-control design, reliance, all limitations, which limit the ability to draw causal conclusions, from being based on serum markers instead of local markers, and from incomplete dose-duration information. Susceptibility did not demonstrate resistance to any of the drugs; were very sensitive to meropenem and amikacin, and moderately resistant to tobramycin and imipenem. These are locally informative and should be interpreted in conjunction with the types of bacteria, previous exposure, and pregnancy susceptibility.[3,19] Larger prospective cohorts. Balanced exposure groups, standardized culture criteria and detailed dose-duration information are available on them. This estrogen profile had to be verified to see if it is repeatable.

CONCLUSION

The use of dydrogesterone was not significantly correlated with the occurrence of UTI, the distribution of bacteria, and the presence of pyuria, and This cohort did not have a change in antimicrobial susceptibility, immune-marker alteration or renal biomarker change. It had the most consistent association with an elevated estrogen profile, especially in UTI-positive. These effects persisted, statistically, after taking into account the age and pregnancy stage of the women. The following should be looked at as an is an exploratory endocrine association and not evidence of causality and should be confirmed through the following steps larger, prospective studies.

Meaning of Abbreviated Words:

- **MMP-1:** (Matrix Metalloproteinase-1) An enzyme also known as Interstitial collagenase and that break down collagen in the body.
- **VITEK-2 System:** An automated microbiology platform made by biomerieux used to quickly identify bacteria and test their resistance to antibiotics.
- **ELISA:** Enzyme linked Immunosorbent Assay) – a blood test used to detect antibodies and antigens.
- **CLSI:** Clinical and Laboratory Standards Institute

Author's Contribution:

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Agreement to accountable for all aspects of work:	All the above authors

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REFERENCES

1. Kalinderi K, Delkos D, Kalinderis M, Athanasiadis A, Kalogiannidis I. Urinary tract infection during pregnancy: current concepts on a common multifaceted problem. J Obstet Gynaecol 2018; 38(4):448-453.
2. Abdullah MM, AL-Rubaii BAL. Effect of Lactobacillus supernatant on swarming-related gene expression in Proteus mirabilis isolated from urinary tract infections. Ukr J Nephrol Dial 2024;4(84):39–48.
3. Ansaldi Y, Martinez de Tejada Weber B. Urinary tract infections in pregnancy. Clin Microbiol Infect 2023;29(10):1249-1253.
4. Dube R, Al-Zuheiri STS, Syed M, Harilal L, Zuhaira DAL, Kar SS. Prevalence, clinico-bacteriological profile, and antibiotic resistance of symptomatic urinary tract infections in pregnant women. Antibiotics 2023;12(1):33.
5. Taha AB. Bacteriological profile, antimicrobial susceptibility, and factors associated with urinary tract infection in pregnant women. J Infect Dev Ctries 2024;18(3):402-410.
6. Mirza FG, Patki A, Pexman-Fieth C. Dydrogesterone use in early pregnancy. Gynecol Endocrinol 2016;32(2):97-106.
7. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. J Steroid Biochem Mol Biol 2005; 97(5):421-425.
8. Walch K, Hefler L, Nagele F. Oral dydrogesterone treatment during the first trimester of pregnancy: the prevention of miscarriage study (PROMIS). J Matern Fetal Neonatal Med 2005;18(4):265-269.
9. Raghupathy R, Szekeres-Bartho J. Dydrogesterone and the immunology of pregnancy. Horm Mol Biol Clin Investig 2016;27(2):63-71.
10. Raghupathy R, Al Mutawa E, Makhseed M, Azizieh F, Szekeres-Bartho J. Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage. BJOG 2005;112(8):1096-1101.
11. Kalinka J, Radwan M. The impact of dydrogesterone supplementation on serum cytokine profile in women with threatened abortion. Am J Reprod Immunol 2006;55(2):115-121.
12. Raghupathy R, Al-Azemi M. Modulation of cytokine production by the dydrogesterone metabolite dihydrodydrogesterone. Am J Reprod Immunol 2015;74(5):419-426.
13. Abdul Hussain G, Azizieh F, Makhseed M, Raghupathy R. Effects of progesterone, dydrogesterone and estrogen on the production of Th1/Th2/Th17 cytokines by lymphocytes from women with recurrent spontaneous miscarriage. J Reprod Immunol 2020;140:103132.
14. Piccinni MP, Raghupathy R, Saito S, Szekeres-Bartho J. Cytokines, hormones and cellular regulatory mechanisms favoring successful reproduction. Front Immunol 2021;12:717808.
15. Vu TD, Feng Y, Placido J, Reznik SE. Placental matrix metalloproteinase-1 expression is increased in labor. Reprod Sci 2008;15(4):420-424.
16. Caritis SN, Venkataramanan R, Thom E, et al. Impact of pregnancy history and 17-hydroxyprogesterone caproate on cervical cytokines and matrix metalloproteinases. Am J Perinatol 2018;35(6):517-523.
17. Inagaki N, Stern C, McBain J, Lopata A, Kornman L, Wilkinson D. Analysis of intra-uterine cytokine concentration and matrix-metalloproteinase activity in women with recurrent failed embryo transfer. Hum Reprod 2003;18(3):608-615.
18. Monteiro C, Kasahara T, Sacramento PM, et al. Human pregnancy levels of estrogen and progesterone contribute to humoral immunity by activating TFH/B cell axis. Eur J Immunol 2021;51(1):167-179.
19. ACOG. Urinary tract infections in pregnant individuals. Obstet Gynecol 2023;142(2):435-445.
20. Garry DJ, Baker DA, Persad MD, et al. Progesterone effects on vaginal cytokines in women with a history of preterm birth. PLOS ONE 2018;13(12):e0209346.