

1 **ASSESSMENT OF THE EFFECT OF HORMONAL CONTRACEPTIVES ON URINARY**
2 **TRACT INFECTION IN WOMEN IN PORT HARCOURT**

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4
5 **ABSTRACT**

6 Increasing trend in unwanted pregnancy, economic factor, maternal-child and other health
7 conditions are the rationales for fertility regulation and family planning; hence, an essential
8 element of preventive care. However, contraception has been implicated with risk of Urinary
9 Tract Infection (UTI) which is a cause of morbidity, mortality and great economic loss. This
10 observational, cross-sectional study investigated the bacteria associated with UTI in women on
11 hormonal contraceptives in Rivers State. A total of 250 subjects grouped as contraceptive users
12 and controls were recruited excluding those who did not consent, less than 18 years of age as
13 well as those pregnant or on treatment for UTI using well-structured questionnaire. Blood and
14 urine specimens were collected and analyzed following standard microbiological methods.
15 Estimation of the hormonal indices was done using Enzyme Linked Immunosorbent Assay
16 method. The result obtained in this study revealed prevalences of 80% and 20% for contraceptive
17 users and control subjects respectively. The predominant uropathogens isolated include;
18 *Esherichia. coli* (55.6%), *Klebsiella* spp (17.6%), *Staphylococcus auerus* (3.2%), *Pseudomonas*
19 spp (2.0%) and *Staphylococcus* Spp (1.6%). *E. coli* was the most prevalent and *Staph* Spp the
20 least prevalent pathogen. UTI was significantly correlated with the use of contraceptives. The
21 study therefore suggests that contraceptive users be routinely checked for urinary tract infection.

22 Keywords: Contraceptives, Hormones, Urinary tract infection, Bacteria.

23
24 **Introduction**

25 The negative effect of high fertility rate on women and their children, and the benefits of fertility
26 control are well known. Too many or too closely spaced pregnancies, pregnancies of a woman at
27 too young or too old an age, give rise to health risks with associated higher maternal and
28 neonatal mortality rates to both mothers and the infants (1). These factors, among others provide
29 health rationale for fertility regulation and family planning, which is now considered an essential
30 element of preventive health care. The benefits from fertility regulation relate to the broader
31 issue of the status of women. The ability of a woman to control her own fertility is one of her

32 basic and important rights. It is presumed that a better regulated sexuality and fertility affects the
33 status of the women socially and economically. This is perceived to be reflected in their
34 educational, health, and economic status coupled with independence to take decisions on their
35 role and be responsible for the total well-being (1).

36 Among the most common infectious diseases, urinary tract infections (UTIs) are commonly
37 encountered diseases in developing countries which are estimated to affect at least 250 million
38 all around the world each year (2). UTIs refer to the presence of microbial pathogens within the
39 urinary tract and it is usually classified by the infection site:-bladder (cystitis), kidney
40 (pyelonephritis), or urine (bacteriuria) and also can be asymptomatic or symptomatic, UTIs that
41 occur in a normal genitourinary tract with no prior instrumentation are considered as
42 “uncomplicated,” whereas “complicated” infections are diagnosed in genitourinary tracts that
43 have structural or functional abnormalities, including instrumentation such as indwelling urethral
44 catheters, and are frequently asymptomatic (3). It has been estimated that globally symptomatic
45 UTIs result in as many as 7 million visits to outpatient clinics, one million visits to emergency
46 departments, and 100,000 hospitalizations every year (4). Urinary tract infections have been
47 linked to several predisposing factors. The effect of hormonal contraceptive as one of the factors
48 is scarcely documented. There is therefore the need to scientifically establish the relationship
49 between hormonal contraception and UTI. The information from this study will aid individuals
50 and health care givers on better ways of managing women on hormonal contraceptive to avoid
51 the inherent risk associated with such infections. It will also assist in shaping government
52 policies and guidelines in treatment, prevention and control of urogenital infections among
53 women using contraceptives in Port Harcourt, and beyond. The aim of this study was to

54 determine the effect of hormonal contraceptives on urinary tract infection in women in Port
55 Harcourt, Nigeria.

56 **Materials and Methods**

57 **Study design:** The study was an observational study that employed a cross sectional approach,
58 blood and urine specimens were collected following standard microbiological methods, for the
59 assessment of the effect of hormonal contraceptives on urinary tract infection in women in Port
60 Harcourt. There were two groups of subjects; 200 of those using hormonal birth control
61 contraceptives (test subjects) and 50 of those not using birth control contraceptives at all
62 (control subjects) who have met the set inclusion criteria.

63 **Sample collection:** Blood and clean-catch mid-stream urine samples were obtained from
64 consenting subjects for analysis using standard laboratory methods. 3mls of venipuncture blood
65 was collected into plain (anti-coagulant-free) bottles. The site of the venipuncture was swabbed
66 with 70% alcohol. A tourniquet was tied on the forearm and a venipuncture was carried out.
67 Approximately 10 ml of urine was collected. Clinical data and laboratory values were collected
68 using the procedure as stated above with well-structured questionnaire.

69

70 Women undergoing treatment for urinary tract infection or pregnant as at the time of the study,
71 were excluded from this study. Diabetic patients, patients experiencing vaginal discharge,
72 dysuria, lower abdominal pains, loin pains; patients identifying with antimicrobial use during the
73 previous 14 days; patients who have participated in sexual intercourse within the last 24 hours
74 and those hospitalized during the four weeks before enrolment, were excluded from the study.

75 **Analytical procedures:** Urine culture in CLED, Gram staining, Biochemical tests, Estimation of
76 Estradiol (Perfemed ELISA), and Estimation of Progesterone (Perfemed ELISA) were
77 performed. The following materials were used: Enzyme Linked Immunosorbent Assay
78 Machines, Apdia Reader (AD Touch), Apdia washer (AD Wash), Apdia shaker/incubator,
79 Perfemed ELISA reagents (Lot No.: 118021403) for estradiol, Perfemed ELISA reagent (Lot
80 No.: 118020704) for progesterone, Capp pipette ,Agar and other culture materials and
81 Biochemical test kits.

82 **Statistical Analysis:** The data collected from this study was analyzed using predictive
83 Statistical Package for Social Sciences (SPSS IBM version 21). Prevalence rate, odd ratio, were
84 estimated. Discrete variables were expressed as percentages and proportions were compared
85 using the Chi-square test. Statistical significance difference were considered at value of $p < 0.05$
86 while quantitative data were analyzed using t-test and ANOVA, regression, following a
87 parametric test for normal distribution using S-K test with $p > 0.05$ as normally distributed.

88

89 **Results**

90 This study included a total of 250 female subjects categorized into two of which 80% were
91 contraceptive users test subjects and 20% non-contraceptive users (control subjects) respectively.
92 The study subjects had a mean age of 35.48 ± 5.237 and greater percentage of the study
93 participants were mainly married 233 (92%). Also, 139 (55.6%) were professionals/skilled in
94 terms of occupation with 167 (66.8%) tertiary level education; only 7 (2.8%) had no formal
95 education. In addition, the bacteria count showed that 181 (72.4%) had counts $< 10^5$ cfu/ml while

96 69 (27.6%) had count $\geq 10^5$ cfu/ml. Basically, five different species of bacteria were isolated
97 namely; *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp, *Staphylococcus* spp and
98 *Staphylococcus aureus* with a bacteria frequency of 169 (67.6%), 58 (23.2%), 6 (2.4%), 6
99 (2.4%) and 11 (4.4%).

100 Table 1 shows the prevalence of UTI among the study population. 65 (26.0%) subjects of the
101 contraceptive users were positive while the non-contraceptive users were 4 (1.6%) subjects. The
102 prevalence of 69 (28.0%) and 181 (72.4%) was recorded for positive and negative respectively.

103 Table 2 shows the prevalence of risk factor. Of all the subjects 24.0% were married, while 2.0%
104 were either separated or divorced. As regards to the occupation distribution, the highest
105 prevalence was recorded within the skilled/professional subjects which amounted to 14.8% for
106 users and 0 (0%) non-users. 19.2% of the study population for users and 1.6% for non users had
107 tertiary education.

108 Table 3 present age related occurrence of the study population. The study revealed that 44% of
109 the study population was between the age bracket of 30 - 39 years for both users and non-users,
110 while 7% of the population fell between the age brackets of 20-29 years respectively. The chi-
111 square distribution showed no evidence of statistical significant relationship.

112 Table 4 illustrates the percentage occurrence of isolates in the study population. *E.coli* had the
113 highest occurrences for both (contraceptive users and non -users) groups with 69.57% while
114 *staph aureus* had the lowest of 1.45%.

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117 Table 1: Prevalence of Urinary Tract Infection among Study Population

	Population	Number Positive (%)	Number Negative (%)	X ² value	DF	P-value
120						
121	Contraceptive users	200	65 (26.0%)	135		
122	Non-contraceptive Users	50	4 (1.6%)	46	12.016	1 0.00
124	Total	250	69	181		

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126

127 Table 2: Prevalence of Risk Factors

128	Variables	Classification (N=250)	Contraceptive users Prevalence (%)	Non-contraceptive prevalence (%)
129	users			
130				
131		Single	0.0	0.0
132	Marital status	Married	24.0	1.6
133		Separated/ divorced	2.0	0.0
134		20 - 29 years	2.4	0.4
135		30 - 29 years	16.4	1.2
136	Age	40 - 49years	7.2	0.0
137		50 years and above	0	0.0
138				
139		Student/ Applicants	0.0	0.8
140		Public/ Civil servants	4.8	0.8
141	Occupation	Skilled/professional	14.8	0.0
142		Business	4.4	0.0
143		Unskilled	2.0	
144				
145		No formal education	0.4	0.0
146	Education	Primary	0.4	0.0
147		Secondary	6.0	0.0
148		Tertiary	19.2	1.6

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151 Table 3: Age Related Occurrence

152	Age group	Control	contraceptive	Total	X ² value	DF	P-value	
153	remarks			Users	Occurrence			
154	20 - 29 years	1 (14.29%)	6(85.71)	7(100%)				
155	30 - 39years	3 (6.82%)	41(93.18%)	44(100%)				
156	40 - 49 years	0 (0.0%)	18(100%)	18(100%)	1.037	3	0.59	N/S
157	50 years & above	0(0.0%)	0(0.0%)	0(0.0%)				
158	Total	4(5.79%)	65(94.20%)	69(100%)				

159

160 Table 4: Percentage Occurrence of Isolate among Study Population

161	S/N	Isolates	Contraceptive Users	Non-contraceptive	Total
162			(%)	Users (%)	
163	1	<i>E .coil</i>	46 (66.67%)	2 (2.89%)	48 (69.57%)
164	2	<i>Kleb.spp</i>	14 (20.29%)	1 (1.45%)	15 (21.74%)
165	3	<i>Pseudo.spp</i>	1 (1.45%)	0 (0.0%)	1 (1.45%)
166	4	<i>Staph.spp</i>	3 (4.35%)	1(1.45%)	4(5.79%)
167	5	<i>Staph. auerus</i>	1(1.45%)	0(0.0%)	1(1.45%)
168		Total	65(94.21%)	4(5.79%)	69(100%)

169 E.coli= *Escherichia coli*

170 Kleb spp = *Klebsiella pneumoniae*

171 Pseudo spp = *Pseudomonas aeruginosa*

172 Staph spp = coagulase negative Staphylococcus

173 Staph aureus = *Staphylococcus aureus*

174 **Discussion**

175 Urinary tract infection among women has been a subject of revolving research interest over the
176 past decade because of its high prevalence (3). This research was centered on investigating the
177 urinary tract infection in relationship with hormonal estrogen and progesterone levels in women
178 using such as birth controls. This result had shown, however, that there is high incidence of
179 Gram negative enterobacterial infection among women using hormonal contraceptives compared
180 to those that do not use hormonal contraceptives. There was also an observed high incidence of
181 *Escherichia coli* infection among this study group compared to the control group. This is in
182 consonance with the report of Takasashi and Loveland (2014) (5) but there was an observed five
183 percent (5%) increased rate to that study. Also, this may have been the case due to the fact that,
184 the use of hormonal contraceptives according to Walter, (2011) (6), has made the lower vaginal
185 and periurethral areas vulnerable to infection due to the exacerbating effect of these
186 contraceptives.

187 Furthermore, the high incidence of urinary tract infection among women using hormonal
188 contraceptive may have been facilitated by the underlying mechanism of contraception which
189 was described by Johnson *et al.* (2017)(7) to contribute to the process of vulnerability since there
190 is repressive ovulation, thickening of cervical mucus, variation in muscle tone and cervical
191 endometrium. This position was also held by Remis *et al.* (2007) (8) with significant correlation
192 established between urinary tract infection and contraceptives usage. Foxman and Frerichs
193 (2015)(9) had also held strongly that there is association between UTI & contraceptive use
194 Nevertheless, despite the above correlation, this phenomenon could be also be attributed to some
195 socio-demographic statistics like history of contraceptive usage, antibiotic usage as a method of

196 contraception as well as age and progesterone levels. The risk estimates obtained from this study
197 which reportedly did not attribute individual disparities like demographics with urinary tract
198 infection.

199 Age distribution of infection among the studied population was observed to have no significant
200 difference with $p>0.05$ while the highest prevalence was seen among the young and mid-adult
201 (30-39years & 40-49years) population. This was comparable with the reports of Kazi (10).
202 Although, in contract to this present study that had *Escherichia coli* as the most prevalent
203 pathogen, Kazi (10) reported *Lactobacillus fermentum* as the most population prevalent pathogen
204 among their studied population. However, this study is in conformity with the conclusion which
205 affirmed that the infection rate was related to the use of contraceptive and age (11).

206 Similarly, an attempt to evaluate hormonal relationships with the isolates showed that in this
207 study, there was observed a significant marked disparity in the prevalence of each isolated
208 pathogen among contraceptive users and the control subjects. Similarly there was observed a five
209 increase in the risk of contracting urinary tract infection for those exposed to contraceptive usage
210 compared with non - contraceptive users (controls) (12,9).

211 Vaginal colonization with *Escherichia coli* was significantly higher in contraceptive users (13),
212 this is evident in the high rate of *E.coli* isolated in this study. In the same way, another study (14)
213 observed *E.coli* as the most predominantly isolated uropathogen in their study despite the fact
214 that the prevalence rate of *E.coli* is less than the one noted in this study. Another study also
215 showed high colonization of the vagina with bacteria and a marked prevalence of *E.coli* similar
216 to what was observed in this study (15).

217 In addition, this present study is contrary to another study which reported a low prevalence (5),
218 this could however be due to the selection and diagnostic criteria that backed the study.

219 Nonetheless, Takahashi & Loveland (2014) share agreement in the type of organisms isolated
220 revealing *Escherichia coli* and the absence of effect of period/duration of contraceptive on risk of
221 urinary tract infection among contraceptive users. This present study reported a higher
222 prevalence of urinary tract infections than a previous work done in same region for both
223 contraceptive users and control subjects (16).

224 Gram positive bacteria isolated in this study had low prevalence and mainly *Staphylococcus*
225 species (*Staphylococcus aureus* and other *Staphylococcus* spp). The prevalence of Gram positive
226 organisms, as well as *Staphylococcus aureus* and other *Staphylococcus* spp obtained in this study
227 showed less than ten percent as opposed to the account of Seifu and colleague (2018)(14) which
228 is about twenty percent. Different study also reported similar isolates (*E.coli* and *Staph.* spp)
229 with high frequency in their study (10).

230 The high infection rate and prevalence of urinary tract infections seen in this study can be
231 explained by the susceptibility of female reproductive system to microorganisms thus, a good
232 pointer apart from the use of contraceptives. On the other hand, the use of contraceptive has
233 made the lower vaginal and peri urethral areas vulnerable to infection due to the exacerbating
234 effect of these contraceptives (6). The underlying mechanism of contraception on causation of
235 urinary tract infection shows that repressive ovulation, thickening of cervical mucus, variation in
236 muscle tone and cervical endometrium all contributes to the process of vulnerability to microbes
237 as published by one of the researchers in this area of study (7). This biological plausibility
238 established the rationale behind increased risk of urinary tract infections among contraceptive
239 user with a considerable indication.

240 Further investigation revealed an association of UTI (measured using the bacteria count) with
241 contraceptive use was statistically significant with the exception of the type of pathogens
242 isolated, this association is synonymous to the study of Paul and Precious (2011)(16) which
243 reported contraception as a predisposing factor of urinary tract infection. Similarly, there was a
244 report of an extensive association between urinary tract infections with contraception even after
245 controlling for confounders (8).

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