

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

37 Among the most common infectious diseases, urinary tract infections (UTIs) are commonly
38 encountered diseases in developing countries which are estimated to affect at least 250 million
39 all around the world each year (2). UTIs refer to the presence of microbial pathogens within the
40 urinary tract and it is usually classified by the infection site:-bladder (cystitis), kidney
41 (pyelonephritis), or urine (bacteriuria) and also can be asymptomatic or symptomatic, UTIs that
42 occur in a normal genitourinary tract with no prior instrumentation are considered as
43 “uncomplicated,” whereas “complicated” infections are diagnosed in genitourinary tracts that
44 have basic or practical irregularities, including instrumentation, for example, inhabiting urethral
45 catheters, and are much of the time asymptomatic (3). It has been estimated that globally
46 symptomatic UTIs result in as many as 7 million visits to outpatient clinics, one million visits to
47 emergency departments, and 100,000 hospitalizations every year (4). Urinary tract infections
48 have been linked to several predisposing factors. The effect of hormonal contraceptive as one of
49 the factors is scarcely documented. Hormonal contraceptives are compelling at counteracting
50 unintended pregnancy (4b). Between zero to nine in each hundred individuals depending on
51 these will get pregnant through the span of a year, contingent upon which type of hormonal
52 prophylactic they use (4b). This number is lower in individuals who utilize hormonal
53 contraceptives superbly. In examination, 18 of every 100 individuals depending on male
54 condoms will get pregnant through the span of a year (4b). The implantable bar, or simply the
55 embed, is the best type of hormonal preventative (4b) and is normally put in your arm by your
56 social insurance supplier. Under one of every hundred individuals utilizing this strategy will get
57 pregnant throughout a year (4b).

58 Strategies for contraception can be named non-hormonal or hormonal. Non-hormonal types of
59 contraception, similar to condoms or the copper intrauterine gadget (IUD), don't change the
60 regular dimensions or elements of hormones inside the body.

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62 Notwithstanding, hormonal contraceptives change the ordinary dimensions of estrogen,
63 progesterone, just as different hormones.

Comment [ER6]: Better to describe about contraceptive relation with UTI and hormones. Even elaborate more on causative agent of UTI and its relation with contraceptive.

64 There is therefore the need to scientifically establish the relationship between hormonal
65 contraception and UTI. The information from this study will aid individuals and health care
66 givers on better ways of managing women on hormonal contraceptive to avoid the inherent risk
67 associated with such infections. It will also assist in shaping government policies and guidelines
68 in treatment, prevention and control of urogenital infections among women using contraceptives
69 in Port Harcourt, and beyond. The aim of this study was to determine the effect of hormonal
70 contraceptives on urinary tract infection in women in Port Harcourt, Nigeria.

71 **Materials and Methods**

72 **Study design:** The study was a (descriptive) study that employed a cross sectional approach,
73 blood and urine specimens were collected following standard microbiological methods, for the
74 assessment of the effect of hormonal contraceptives on urinary tract infection in women in Port
75 Harcourt. There were two groups of subjects; 200 of those using hormonal birth control
76 contraceptives (test subjects) and 50 of those not using birth control contraceptives at all
77 (control subjects) who have met the set inclusion criteria. . Women undergoing treatment for
78 urinary tract infection or pregnant as at the time of the study, were excluded from this study.
79 Diabetic patients, patients experiencing vaginal discharge, dysuria, lower abdominal pains, loin
80 pains; patients identifying with antimicrobial use during the previous 14 days; patients who have
81 participated in sexual intercourse within the last 24 hours and those hospitalized during the four
82 weeks before enrolment, were excluded from the study.

83 Ethical approval was obtained from the Rivers State Hospital Management Board, Rivers State
84 University Teaching Hospital and University of Port Harcourt Teaching Hospital ethical
85 committees before commencement of the study.

Comment [ER7]: Write UTI.

Comment [ER8]: Write these things under ethical approval heading .

86 Informed written consents were obtained from participants who met the inclusion criteria.

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

Comment [ER9]: Describe everything in detail. Blood collected were transported to laboratory for hormones estimation. Also about culture in chronological order.

93 **Analytical procedures:** Urine culture in CLED, Gram staining, Biochemical tests, Estimation of Estradiol
94 (Perfemed ELISA), and Estimation of Progesterone (Perfemed ELISA) were performed. The following
95 materials were used: Enzyme Linked Immunosorbent Assay Machines, Apdia Reader (AD Touch), Apdia
96 washer (AD Wash), Apdia shaker/incubator, Perfemed ELISA reagents (Lot No.: 118021403) for estradiol,
97 Perfemed ELISA reagent (Lot No.: 118020704) for progesterone, Capp pipette ,Agar and other culture
98 materials and Biochemical test kits. All urine samples were cultured on Cystein Lactose Electrolyte
99 Deficient Agar (CLED) and incubated at 37°C for 24 hours. Pure cultures of all isolates were obtained and
100 biochemical tests done to identify the isolates.

Comment [ER10]: Rewrite the paragraph orderly, like sample collection then sample processing-culture, hormone estimation.

101

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

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109 **Results**

110 This study included a total of 250 female subjects categorized into two of which 80% were
111 contraceptive users test subjects and 20% non-contraceptive users (control subjects) respectively.
112 The study subjects had a mean age of 35.48±5.237 and greater percentage of the study
113 participants were mainly married 233 (92%). Also, 139 (55.6%) were professionals/skilled in
114 terms of occupation with 167 (66.8%) tertiary level education; only 7 (2.8%) had no formal
115 education. In addition, the bacteria count showed that 181 (72.4%) had counts <105 cfu/ml while
116 69 (27.6%) had count ≥105cfu/ml respectively. Basically, five different species of bacteria were
117 isolated namely; *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp, *Staphylococcus* spp and
118 *Staphylococcus aureus* with a bacteria frequency of 169 (67.6%), 58 (23.2%), 6 (2.4%), 6
119 (2.4%) and 11 (4.4%).

Comment [ER11]: No need to explain in result.

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

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

124	Population	Number	Number	X ² value	DF	P-value
125		Positive (%)	Negative (%)			
126						
127	Contraceptive users	200	65 (26.0%)	135		
128	Non-contraceptive	50	4 (1.6%)	46	12.016	1 0.00
129	Users					
130	Total	250	69	181		

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

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149 Table 2: Prevalence of Risk Factors

150 Variables	151 Classification (N=250)	152 Contraceptive users	153 Non-contraceptive
		Prevalence (%)	prevalence (%)
	Single	0.0	0.0
154 Marital status	Married	24.0	1.6
	Separated/ divorced	2.0	0.0
156	20 - 29 years	2.4	0.4
157	30 - 39 years	16.4	1.2
158 Age	40 - 49years	7.2	0.0
159	50 years and above	0	0.0

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	Student/ Applicants	0.0	0.8
	Public/ Civil servants	4.8	0.8
Occupation	Skilled/professional	14.8	0.0
	Business	4.4	0.0
	Unskilled	2.0	
	No formal education	0.4	0.0
Education	Primary	0.4	0.0
	Secondary	6.0	0.0
	Tertiary	19.2	1.6

UNDER PEER REVIEW

173

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

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180 Table 3: Age Related Occurrence

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

Comment [ER12]: Why this in different table. It has already been explain in table 2.

188

189 Table 4 illustrates the percentage occurrence of isolates in the study population. *E.coil* had the
190 highest occurrences for both (contraceptive users and non -users) groups with 69.57% while
191 *staph auerus* had the lowest of 1.45%.

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194 Table 4: Percentage Occurrence of Isolate among Study Population

195 196	S/N	Isolates	Contraceptive Users (%)	Non-contraceptive Users (%)	Total
197	1	<i>E .coil</i>	46 (66.67%)	2 (2.89%)	48 (69.57%)
198	2	<i>Kleb.spp</i>	14 (20.29%)	1 (1.45%)	15 (21.74%)
199	3	<i>Pseudo.spp</i>	1 (1.45%)	0 (0.0%)	1 (1.45%)
200	4	<i>Staph.spp</i>	3 (4.35%)	1(1.45%)	4(5.79%)
201	5	<i>Staph. auerus</i>	1(1.45%)	0(0.0%)	1(1.45%)
202	Total	65(94.21%)	4(5.79%)	69(100%)	

203 *E.coli*= *Escherichia coli*

204 *Kleb spp* = *Klebsiella pneumoniae*

205 *Pseudo spp* = *Pseudomonas aeruginosa*

206 *Staph spp* = coagulase negative Staphylococcus

207 Staph aureus = *Staphylococcus aureus*

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209 **Discussion**

210 Urinary tract infection among women has been a subject of revolving research interest over the
 211 past decade because of its high prevalence (3). This research was centered on investigating the
 212 urinary tract infection in relationship with hormonal estrogen and progesterone levels in women
 213 using such as birth controls. This result had shown, however, that there is high incidence of
 214 Gram negative enterobacteria infection among women using hormonal contraceptives compared
 215 to those that do not use hormonal contraceptives. There was also an observed high incidence of

Comment [ER13]: Where is the table for hormones estimation.

Comment [ER14]: Rephrase discussion part and follow the guideline to write discussion.

Comment [ER15]: Write UTI in all place.

216 *Escherichia coli* infection among this study group compared to the control group. This is in
217 consonance with the report of Takasashi and Loveland (2014) (5) but there was an observed five
218 percent (5%) increased rate to that study. Also, this may have been the case due to the fact that,
219 the use of hormonal contraceptives according to Walter, (2011) (6), has made the lower vaginal
220 and periurethral areas vulnerable to infection due to the exacerbating effect of these
221 contraceptives.

222 Furthermore, the high incidence of urinary tract infection among women using hormonal
223 contraceptive may have been facilitated by the underlying mechanism of contraception which
224 was described by Johnson *et al.* (2017)(7) to contribute to the process of vulnerability since there
225 is repressive ovulation, thickening of cervical mucus, variation in muscle tone and cervical
226 endometrium. This position was also held by Remis *et al.* (2007) (8) with significant correlation
227 established between urinary tract infection and contraceptives usage. Foxman and Frerichs
228 (2015)(9) had also held strongly that there is association between UTI & contraceptive use
229 Nevertheless, despite the above correlation, this phenomenon could be also be attributed to some
230 socio-demographic statistics like history of contraceptive usage, antibiotic usage as a method of
231 contraception as well as age and progesterone levels. The risk estimates obtained from this study
232 which reportedly did not attribute individual disparities like demographics with urinary tract
233 infection.

234 Age distribution of infection among the studied population was observed to have no significant
235 difference with $p>0.05$ while the highest prevalence was seen among the young and mid-adult
236 (30-39years & 40-49years) population. This was comparable with the reports of Kazi (10).
237 Although, in contract to this present study that had *Escherichia coli* as the most prevalent

238 pathogen, Kazi (10) reported *Lactobacillus fermentum* as the most population prevalent pathogen
239 among their studied population. However, this study is in conformity with the conclusion which
240 affirmed that the infection rate was related to the use of contraceptive and age (11).

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

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

252 In addition, this present study is contrary to another study which reported a low prevalence (5),
253 this could however be due to the selection and diagnostic criteria that backed the study.
254 Nonetheless, Takahashi & Loveland (2014) share agreement in the type of organisms isolated
255 revealing *Escherichia coli* and the absence of effect of period/duration of contraceptive on risk of
256 urinary tract infection among contraceptive users. This present study reported a higher
257 prevalence of urinary tract infections than a previous work done in same region for both
258 contraceptive users and control subjects (16).

259 Gram positive bacteria isolated in this study had low prevalence and mainly *Staphylococcus*
260 species (*Staphylococcus arueus* and other *Staphylococcus* spp). The prevalence of Gram positive

Comment [ER16]: Short form in all part

261 organisms, as well as *Staphylococcus arueus* and other *Staphylococcus* spp obtained in this study
262 showed less than ten percent as opposed to the account of Seifu and colleague (2018)(14) which
263 is about twenty percent. Different study also reported similar isolates (*E.coli* and *Staph.* spp)
264 with high frequency in their study (10).

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

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

281 **Conclusion:** Contraception is beneficial with an inherent risk of urinary tract infections for users
282 as established in this study. Generally, urinary tract infections were highly prevalent in the study

283 population and more prevalent among contraceptives users. Age distribution had no influence on
284 the risk of urinary tract infections.

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