

The Impact of Combined Oral Contraceptive Pills on *Staphylococcus aureus* Nasal Carriage State

Asmaa kadhim Gatea¹, Suhaila F.M.H Al-Shaikh^{1*}

1. University of Babylon, College of Medicine, Department of Obstetrics and Gynecology, Iraq

*Corresponding author

Suhaila F.M.H Al-Shaikh 2

drsuhaila_alshaikh@uobabylon.edu.iq

Abstract

Background: Up to 20% of human population is asymptomatic carriers for *Staphylococcus aureus*. Human nares colonized with *Staphylococcus aureus* are the most important reservoir of this pathogen and the carrier state affected by different variables. **Aim:** To investigate the influence of using oral hormonal contraceptive pills on *Staphylococcus aureus* nasal carriage state. **Method:** A cross sectional studies involved 125 Healthy woman who divided into two groups as users of hormonal contraceptives (60 women) and none or ever users (65 women). Cotton swab obtain from anterior nares of each woman and subjected to culture to identify the *Staphylococcus aureus*. The results were compared between the two groups. Pregnant woman and those who are immune-compromised, having chronic diseases and currently on antibiotic therapy were excluded from this study. **Results:** *Staphylococcus aureus* nasal carriage state was doubled in woman using oral hormonal contraceptives. This was correlated with the duration of use of this contraceptives, the longer the duration the more the carriers. **Conclusion:** Hormonal contraceptive pill may boost the risk of *Staphylococcus aureus* nasal carriage in healthy women

Keywords: *Staphylococcus aureus*, combined oral contraceptives, nasal carrier

How to cite this article: Gatea AK, Al-Shaikh SFMH (2020): The impact of combined oral contraceptive pills on *Staphylococcus aureus* nasal carriage state, *Ann Trop Med & Public Health*; 23(S14): SP231420. DOI: <http://doi.org/10.36295/ASRO.2020.231420>

Introduction

One of the most important sites in human body to carry *Staphylococcus aureus* is human nares. (1) The incidence of chronic nasal carrier of this bacteria in human may exceed 20%, therefore being a carrier means that more liability to get infection. (2) So the nasal carriage of *Staphylococcus aureus* has important public health relevancies. (3) There are many risk factor that make the human susceptible to carry this microorganism although there is limited evidence about the link between some of these factors especially modifiable one to carrier state. (4) Of these modifiable risk factors, it has been found that raised blood glucose and using hormonal contraceptives may up regulate the risk of being a nasal carrier (5). While smoking on the other hand found to be a protective factor. (6) The observed association between nasal carrier state and human age and gender suggest a possible role for reproductive hormone via regulation and modifications of immune response. This has been proved by Zanger Pand winklers and their colleagues who suggest that both endogenous and exogenous reproductive hormones positively linked with carrier state (1, 7) Winkler et al also reported in their epidemiological study that the more the level of blood estrogen the more the risk of *Staphylococcus aureus* nasal carriage in women. (7) In healthy peoples 20% never carry *staphylococcus* in their nares while 80% are carrier, 60% of them are intermittent and the rest 20% are persistent carrier. So carriage of this bacteria play a vital role in the pathogenesis and epidemiology of this infection which make preventive strategy fundamental especially when the treatment become difficult because of increasing incidence of infection caused by methicillin resistant *Staphylococcus aureus*. (8) The effect of reproductive hormones on *Staphylococcus aureus* carriage need to be proved by large epidemiological studies especially if their effect proved to increase the risk which could have the important effect on the overall burden of this bacteria in population.

Aim

To assess the association between using of combined oral contraceptive pills and nasal carriage state of *Staphylococcus aureus*

Subjects and methods

A case control study. Approved by the Medical Ethical and Scientific Committees of the College of Medicine/University of Babylon, all women enrolled in this study signed informed consent before their participation. The study involved 125 healthy women divided into two groups according to whether they use combined oral contraceptive pills or not. The user group (60 women) by whom COCP type {Microgynon} Ethinyl Estradiol 30 microgram and Levonorgestril 150 microgram was used for 6 months and more. Non-user group (65 women): Is the healthy control group who never used hormonal pills for contraception. A cotton swab obtained from both anterior nares of each participant and subjected to bacteriological culture.

Exclusion criteria: menopause state, pregnant, diabetics, on immune suppressant drugs, steroid therapy or on antibiotics, health care providers and those who use any form of hormonal containing medications within previous six months all were excluded from this study.

Study groups data (age, residence, educational level, fertility, parity and history of abortion, type and duration of pills use) was collected by a standard questionnaire.

Nasal swab technique:

Nasal swab samples were collected by circulating a cotton-tipped swab 4 times with gentle pressure against the inner wall of both anterior nares. Disposable rubber gloves were used to prevent cross-contamination. Specimens were put in transport media, swabs were inoculated and spread on to blood and mannitol salt agar. All plates were aerobically incubated at 37 c for 24 hours.

Golden yellow hemolytic colonies on blood agar and yellow mannitol fermenting colonies on mannitol agar were regarded as presumptive *Staphylococcus aureus* which then confirmed by Gram stain reaction.

The primary outcomes measured is the incidence of *Staphylococcus aureus* nasal carriage among users of combined oral contraceptives pills.

Secondary outcomes measured were the relation between carriage state and women age and parity

Statistical analysis

Statistical Package for Social Science (SPSS) version to analyze data. Continuous variables expressed as mean ± standard deviation (SD), while categorical variables expressed as frequencies and percentages. Independent samples t-test and Chi square test utilized for continuous and categorical parameters respectively

P- Value of 0.05 and less considered statistically significant.

Results

Regarding characteristics of the study population It is clear from (table 1) that there are no differences from the statistical point of view between the pill user and the control groups regarding the age, number of parities and the number of abortions.

Table1

Comparison of demographic data of pill users and non-user groups (values are mean ± SD or percentages).

parameters	Non-user group N = 65	user group N = 60	Total N	P- value
Age (years)	26.42±5.59	26.37± 5.98		0.963
Parity N %	1-2 (37) 56.9%	(32) 53.3%	69	0.922
	3-4 (20) 30.8%	(20) 33.3%	40	
	≥ 5 (8) 12.3%	(8) 13.3%	16	
Miscarriage N %	0 (44) 67.7%	(42) 70%	86	0.781
	≥ 1 (21) 32.3%	(18) 30%	39	

The *Staphylococcus aureus* carriage state was detected in 48% of the pill user group while only 20% were positive cultures for *Staphylococcus Aureus* in the non-user group with p value = 0.001. Table (2)

Table 2: *Staphylococcus aureus* carrier state among the study groups

Staphylococcus Aureus Carrier state	Non-user group N = 65	User group N = 60	Total N %	P- value
(- ve)	52(80%)	31(51.7%)	83(66.4%)	0.001
(+ ve)	13(20%)	29 (48.3%)	42(33.6)	

About the duration of using pills and its relation to carrier state it has been found that 81.48 % of women using pills for more than 24 months while 21.21% using pills from 6-23 months (table 3)

Table 3: *Staphylococcus aureus* carrier state among the pill user group according to duration of use

Pills use duration (months)	Staphylococcus Aureus (+ ve) N=29	Staphylococcus Aureus (- ve) N=31	Total N %	P- value
6-23	(7) 21.21%	(26) 78.791%	(33) 55%	0.000003
≥24	(22) 81.48%	(5) 18.52%	(27) 45%	
Total	(29) 48.3%	(31) 51.7%	(60)100%	

The current study also revealed that the mean age of *staphylococcus aureus* carrier women was higher than that of non carriers 30.33±5.608 vs 24.40±4.7 respectively with a very highly significant p value, and the same was true in the view of the number of parities, it is clear that the higher the parity the higher the carrier state of *Staphylococcus aureus* with a p value of 0.0001, while the number of miscarriages, is not significantly different between the two groups. Table (4) , figure (1)

Table (4) Women mean age, number of parity and miscarriage among the study group according to *Staphylococcus aureus* carrier state:

parameters		<i>Staphylococcus aureus</i> (+ ve) N = 42	<i>Staphylococcus aureus</i> (- ve) N = 83	Total N	P- value
Age (years±SD)		30.33±5.608	24.40±4.7	125	<0.000001
Parity N %	1-2	(13) 31%	(56) 67.5%	69	0.0001
	3-4	(18) 42.8%	(22) 26.5%	40	
	≥ 5	(11) 26.2	(5) 6%	16	
Miscarriage N %	0	(26) 61.9%	(60) 72.3%	86	0.237
	≥ 1	(16) 38.1%	(23) 27.7%	39	

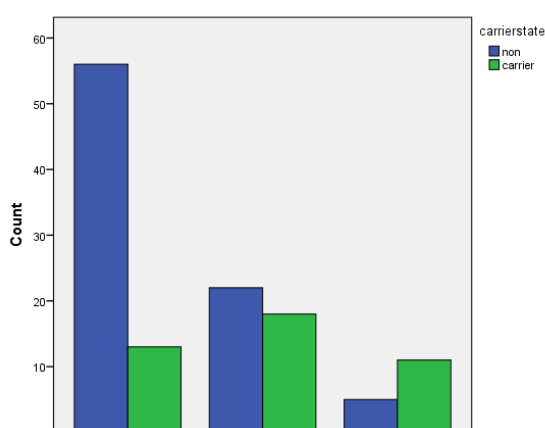


Figure 1: number of parity according to *Staphylococcus aureus* carrier state among the women in the study groups

Discussion

Carrying *Staphylococcus aureus* in human nares thought to be a subclinical inflammatory state that result from decline in the innate immune reaction (9) which is affected by many factors as sex, reproductive state (10)

In this study we try to assess whether using combined oral contraceptives (containing estrogen and progesterone) influence the *Staphylococcus aureus* nasal carriage state or not.

We found that women using these contraceptives were more prone to carry *Staphylococcus aureus* in their nares 48.3% in users compared to 20% of non-user group.

This result supposed to be due to immune-modulation effects of reproductive hormones especially production of immunoglobulin although there is conflict about this associations as shown by previous studies (11-13).

Klinger and his college who study the effect of hormonal contraceptives on human immune system conclude that using estrogen and progesterone associated with reduction in the immunoglobulin level.(13) which support the explanations of our result.

Other possible explanation is what have been found in the study done at 2018 by Nurjadi and his colleagues who found that Toll-like receptor 9 (TLR9) transcription level was higher in people who not carry *Staphylococcus aureus* in their nares (14), in addition, they observed that both TLR 9 transcription and genotype level was varied between male and female which confirm the role of sex hormones in immune response to *Staphylococcus aureus* which may explain the higher carriers state of this bacteria in hormonal contraceptives users.(14)

Other possible immunological effect of hormonal contraceptives is that they associated with lower serum level of interleukin 8 and Gamma interferons. This was observed by Mohammed Al.saadi and his college when they study the effect of using hormonal contraceptives on vaginal lactobacilli and serum interleukins(15)

Our study also revealed that carrier state was more in those using hormonal contraceptives for longer duration.

More recent study in 2019 done by Dina B et al who study the effect of hormonal contraceptives in form of combine one (which contain estrogen and progesterone) and that containing progesterone alone on *Staphylococcus aureus* throat and nasal carriage state, they found that *Staphylococcus aureus* nasal carriage prevalence were 34%, 42%, and 61% among progestin-only users, non-users, and progestin-estrogen combination contraceptive users, respectively (P<0.001), Use of oral combined pills doubled the odds of nasal carriage (non-users reference; OR = 2.31, 95%CI = 1.43–3.74). (16)

Regarding women mean age it was observed that the older the women the more the carrier state risk whether they were pills user or not, this was opposite to what have been found in previous studies by B.J.Chen at 2017 (17) and Fabiano at 2014 (18) who found inverse relationship between the age and *Staphylococcus aureus* nasal carriage state.

Carrying *Staphylococcus aureus* in human consider as a major source for infection with these microorganisms, so different strategies tried to eradicate the bacteria from carriers, some suggest using topical antibiotics as mupirocin intranasal which is tested and found to be effective by Heimanet al (19).

On the other hand treating carriers had advantages and disadvantages. This was assessed by Adriana et al who observed that The advantages were less infection and less spread of microorganism. The observed disadvantages were possibility of raising bacterial resistance to the antibiotics and absence of strong evidence regarding the effectiveness of the elimination of the colonizing bacteria, as well as limiting infection rates.

Thus routine treatment of carriers was discouraged and should be limited for those patients at risk and during attacks of outbreaks (20)

Conclusions

Using hormonal contraceptives in form of combined estrogen and progesterone increase liability of women to be a *Staphylococcus aureus* nasal carriers and the incidence increased as the duration of using these contraceptives increased.

References

1. Zanger P, Nurjadi D, Guile M., Gabrysch S, Kremsner P.G. Hormonal contraceptives use and persistence *Staphylococcus aureus* nasal carriage. *clinical infectious disease*. 2012;55(12):1625-1632
2. K.Oslen.B.M. Falchfurberg. *Staphylococcus aureus* nasal carriage is associated with serum 25 hydroxy vitamins D level, gender and smoking status. *European journal of clinical microbiology and infectious disease* 2012; 31:465-473.
3. Shevertz RI, Bassetti S, Bassetti-Wyss B. "cloud" health workers. *Emerg infectious disease* 2001; 7: 241-4

4. Vanbelkum A, Melles DC, Nouwen J, van Leeuwenhoek WB, Van wamelW, Vos. MC, Wertheim HF, Verburg HA. co – evolutionary aspect of human colonization and infection by *Staphylococcus aureus*. *infect.Genet.Evol.* 2009; 9:32-47.
5. Nouwen J, Ott A, Boelens H et al. smoking pattern and fasting glucose level determine *Staphylococcus aureus* nasal carriage. Erasmus university and medical center. Rotterdam, the Netherlands PhD thesis 2004
6. Wang J, Liao C, Fang C, Chiew L, Liao D, Lee W, Guangzhou J, Chang S. prevalence of and risk factors for colonization by MRSA among adults in countries setting in Taiwan, *Journal of clinical microbiology* 2009;47:2957-2963
7. Winkler J, Block C, Leibovici L, Faktor J, Pitlik SD. Nasal carriage of *Staphylococcus aureus*: correlation with hormonal status in women. *J Infect Dis.* 1990;162(6):1400–2.
8. J Kluytmans, A van Belkum, and H Verbrugh. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. *Clinical microbiology review.* 1997;10(3):505–520.
9. Quinn GA, Cole AM. Suppression of innate immunity by a nasal carriage strain of *Staphylococcus aureus* increases its colonization on nasal epithelium. *Immunology.* 2007;122(1):80–9
10. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. *Hum Reprod Update.* 2005;11(4):411–23.
11. Bisset LR, Griffin JF. Humoral immunity in oral contraceptive users. II. In vitro immunoglobulin production. *Contraception.* 1988;38(5):573–8.
12. Lali P, Chandra L, Gupta RP. Serum immunoglobulin levels during contraceptive use of depot-medroxyprogesterone acetate in Indian women: a preliminary study. *Contraception.* 1996;53(6):363–5.
13. Klinger G, Graser T, Mellinger U, Moore C, Vogelsang H, Groh A, et al. A comparative study of the effects of two oral contraceptives containing dienogest or desogestrel on the human immune system. *GynecolEndocrinol.* 2000;14(1):15–24.
14. Nurjadi D, Heeg K, Weber ANR, Zanger P. Toll-like receptor 9 (TLR-9) promoter polymorphisms and gene expression are associated with persistent *Staphylococcus aureus* nasal carriage. *ClinMicrobiol Infect.* 2018;24(11):1210 e7–e12.
15. Mohammad A. K. Al-Saadi, Asmaa K. Gatea and Khedija A. Amran. Bacteriological and Cytokine Profiles for Women Using Hormonal Contraceptive Drugs. *British Journal of Medicine & Medical Research* 2016; 12(1):1-8. Article no. BJMMR.21391
16. Dina B. Stensen, Lars Småbrekke, and Anne-Sofie Furberg, hormonal contraceptive use and *Staphylococcus aureus* nasal and throat carriage in a Norwegian youth population. *PLoS One* 2019; 14(7):e0218511
17. B. J. Chen, X. Y. Xie, L. J. Ni, X. L. Dai, Y. Lu, X. Q. Wu, H. Y. Li, Y. D. Yao & S. Y. Huang. Factors associated with *Staphylococcus aureus* nasal carriage and molecular characteristics among the general population at a Medical College Campus in Guangzhou, South China. *Annals of clinical microbiology and antimicrobials* 2017;16: article number 20.
18. Fabiana Venegas Pires, Maria de Lourdes Ribeiro de Souza da Cunha, Lígia Maria Abraão, Patrícia Y. F. Martins, Carlos Henrique Camargo, Carlos Magno Castelo Branco Fortaleza. Nasal Carriage of *Staphylococcus aureus* in Botucatu, Brazil: A Population-Based Survey. *PLoS* 2014. <https://doi.org/10.1371/>
19. Heiman F. L. Wertheim, Jeroen Verveer, Hélène A. M. Boelens, Alex van Belkum, Henri A. Verbrugh, Magreet C. Vos. Effect of Mupirocin Treatment on Nasal, Pharyngeal, and Perineal Carriage of *Staphylococcus aureus* in Healthy Adults. 2005. doi: 10.1128/AAC.49.4.1465-1467.

20. Adriana Cristina de Oliveira; Adriana Oliveira de Paula. Decolonization of *Staphylococcus aureus* carriers: indications, advantages and limitations. *Textocontexto – enferm*2012;21(2)Florianópolis Apr./June.