International Journal of Pharmaceutical and Bio-Medical Science

ISSN(print): 2767-827X, ISSN(online): 2767-830X

Volume 06 Issue 02 February 2026

Page No : 677-684

DOI: https://doi.org/10.47191/ijpbms/v6-i2-02, Impact Factor: 8.163

Cleavage and Blastocyst Formation Rates and Their Correlation with Fertilization Outcomes in Natural Versus Programmed IVF Cycles: A Randomized Clinical Trial

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ABSTRACT

Background: Early embryo developmental milestones, particularly cleavage and blastocyst formation, are important indicators of embryo competence in in-vitro fertilization (IVF). Whether menstrual cycle programming with combined oral contraceptive pills (OCPs) alters these embryological outcomes compared with natural cycles remains a subject of debate, especially in low- and middle-income settings.

Objective: To compare cleavage and blastocyst formation rates in natural versus OCP-programmed IVF cycles and to evaluate their relationship with fertilization outcomes.

Methods: This single-center, open-label randomized clinical trial enrolled 86 women undergoing IVF at a tertiary fertility center in Nigeria. Participants were randomized equally to undergo controlled ovarian stimulation either in a natural cycle or following OCP pretreatment. Standardized stimulation, fertilization (IVF or ICSI), and embryo culture protocols were used in both groups. Cleavage rate and blastocyst formation rate were the primary outcomes, while correlations between fertilization rate and subsequent embryo development were secondary outcomes. Data were analyzed using intention-to-treat principles.

Results: There was no statistically significant difference between the OCP-programmed and natural cycle groups in mean cleavage rate (70.7% vs. 67.2%, $p = 0.438$) or blastocyst formation rate (52.4% vs. 45.2%, $p = 0.122$). Fertilization rate demonstrated a strong positive correlation with cleavage rate ($r = 0.758$, $p < 0.001$) and a moderate correlation with blastocyst formation rate ($r = 0.659$, $p < 0.001$). Cleavage rate was also moderately correlated with blastocyst development ($r = 0.515$, $p < 0.001$).

Conclusion: Cycle programming with combined oral contraceptive pills does not adversely affect cleavage or blastocyst formation in IVF. Fertilization success strongly influences subsequent embryo development irrespective of cycle type. These findings support the use of OCP pretreatment for scheduling flexibility without compromising early embryological outcomes.

ARTICLE DETAILS

Published On:
09 February 2026

KEYWORDS: In-vitro fertilization; Oral contraceptive pills; Cleavage rate; Blastocyst formation; Fertilization rate; Embryo development.

Available on:
https://ijpbms.com/

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INTRODUCTION

In-vitro fertilization (IVF) constitutes a major modality within assisted reproductive technology (ART) for the treatment of infertility, a condition estimated to affect 10–15% of couples of reproductive age worldwide.[1,2] Although substantial progress has been made in controlled ovarian stimulation protocols, embryology laboratory practices, and embryo transfer techniques, overall IVF success rates remain suboptimal, underscoring the need for ongoing appraisal of factors that impact treatment efficacy.[3]

The developmental potential of embryos is a critical predictor of IVF outcomes and is routinely evaluated using fertilization rates, cleavage rates, and progression to the blastocyst stage.[4] Appropriate cleavage patterns reflect satisfactory oocyte competence, sperm integrity, and favorable in-vitro culture conditions, while attainment of the blastocyst stage has been consistently associated with improved implantation, clinical pregnancy, and live birth rates.[5,6] Consequently, cleavage and blastocyst formation rates are widely accepted surrogate markers of embryo viability and laboratory performance.[7]

Pre-treatment menstrual cycle modulation before controlled ovarian stimulation may influence oocyte quality, embryo development, and endometrial receptivity. Programmed cycles employing combined oral contraceptive pills (OCPs) are commonly utilized to achieve follicular synchronization, minimize the occurrence of functional ovarian cysts, and allow for predictable cycle scheduling. [8] Nevertheless, concerns persist regarding potential adverse effects of OCP pretreatment on follicular recruitment, oocyte competence, and subsequent embryological development. [9, 10]

Conversely, commencing ovarian stimulation in a natural menstrual cycle avoids hormonal suppression and preserves a more physiological endocrine milieu, which may favor oocyte maturation and early embryo development.[11] Although prior studies have compared natural and programmed IVF cycles with respect to oocyte yield, pregnancy rates, and live birth outcomes, findings remain heterogeneous.[12–14] Furthermore, limited evidence specifically addresses early embryological outcomes such as cleavage and blastocyst formation rates and their relationship with fertilization particularly in low- and middle-income settings where clinical characteristics and IVF practices may vary.[15]

This study aimed to compare cleavage and blastocyst formation rates between natural and programmed IVF cycles and to assess their association with fertilization outcomes. Elucidating the impact of cycle programming on early embryonic development may inform optimization of IVF protocols and contribute to improved reproductive outcomes.

MATERIALS AND METHODS

This study was designed as a single-center, open-label randomized controlled trial comparing outcomes between two intervention groups. Eligible participants were assigned in a 1:1 ratio to either study arm using simple randomization. The study population comprised women with a diagnosis of primary or secondary infertility who presented to the In-Vitro Fertilization (IVF) clinic of the Federal Medical Centre, Abuja, a tertiary referral institution offering assisted reproductive services.

The trial was conducted in compliance with the ethical standards of the 2013 Declaration of Helsinki for research involving human participants. Ethical clearance for the study protocol was obtained from the Research and Ethics Committee of the Federal Medical Centre, Abuja. All participants provided written informed consent prior to enrollment, and strict measures were taken to ensure the confidentiality and privacy of participant data throughout the study.

Participants were excluded if they had contraindications to combined oral contraceptive pill use, including thromboembolic disease, hormone-sensitive malignancies, or significant hepatic dysfunction. Further exclusion criteria included women aged 21–38 years with clinical or biochemical evidence of diminished ovarian reserve or ovarian failure, as well as individuals who declined participation or withdrew consent at any stage of the study.

INTERVENTIONS

Eligible participants were randomized in a 1:1 ratio to two study arms using sealed opaque envelopes, each containing a unique identifier corresponding to a pre-generated randomization sequence, allocating participants to either Group A (control) or Group B (intervention).

Group A – Natural Cycle (Control)

Participants in Group A underwent controlled ovarian stimulation (COS) during their natural menstrual cycle without prior hormonal pre-treatment. Stimulation followed a short GnRH agonist protocol, initiated regardless of cycle day. Buserelin acetate (Suprefact® 1 mg/mL; Sanofi, France) was administered subcutaneously at 0.5 mL daily from cycle day 2. Recombinant or urinary FSH (Humog®, Bharat Pharmaceuticals, India) was started on cycle day 2 or 3, with doses individualized based on age, body mass index (BMI), antral follicle count, and baseline serum FSH. Adjustments included a 75 IU reduction for women with polycystic ovarian morphology and incremental 75 IU increases per 5 kg/m² above standard dosing.

Group B – OCP-Programmed Cycle (Intervention)

Participants in Group B received combined oral contraceptive pills (OCPs) to program the menstrual cycle prior to COS. Microgynon® (150 µg levonorgestrel + 30 µg ethinyl estradiol; 28-tablet pack, 21 active and 7 placebo) was administered

orally once daily at a fixed time for a minimum of two weeks. The OCP regimen was initiated between cycle days 10 and 30 of the pre-IVF month, with the last active tablet taken the day before COS initiation. Withdrawal bleeding was expected within the first week of the subsequent month. COS then proceeded using the same short GnRH agonist protocol as in Group A.

Ovarian Stimulation and Monitoring (Both Groups)

All participants underwent COS using the short GnRH agonist protocol. Buserelin acetate (0.5 mL daily, subcutaneously) began on cycle day 2, and FSH stimulation (Humog®) was individualized based on BMI, age, and ovarian reserve. Subcutaneous injections were administered peri-umbilically. Dose modifications were made according to follicular response assessed via serial transvaginal ultrasound and serum hormone measurements, with monitoring every 48 hours from stimulation day 7 until leading follicles reached 18–21 mm and endometrial thickness measured 8–15 mm.

Ovulation Trigger and Oocyte Retrieval

Ovulation was triggered with intramuscular human chorionic gonadotropin (HCG) (Hucog®, 5,000 IU; Bharat Pharmaceuticals, India) 35–36 hours prior to oocyte retrieval. Retrieval was performed under transvaginal ultrasound guidance with conscious sedation (IV pethidine 100 mg and midazolam 5 mg). Follicular fluid was aspirated and immediately placed in a pre-warmed incubator at 37 °C for oocyte identification and counting by the embryologist.

Fertilization, Embryo Culture, and Transfer

Oocytes were fertilized either via conventional insemination or intracytoplasmic sperm injection (ICSI) based on semen parameters. Embryos were cultured in a closed, one-step medium under standard CO_2 incubator conditions (6% CO_2, ambient O_2). Fertilization was assessed 16–18 hours post-insemination. Cleavage-stage embryos were graded on day 2 based on cell number, symmetry, and fragmentation (Grades 1–4), while blastocyst assessment was performed on day 5. Embryo transfer was conducted under transabdominal ultrasound guidance using a Wallace® catheter, placing up to three top-quality embryos 0.5–1 cm below the fundus. Luteal support included vaginal progesterone (Cyclogest® 400 mg twice daily), intramuscular progesterone (Gestone® 100 mg every 48 hours), oral estradiol valerate (Progynova® 4 mg three times daily), oral acetylsalicylic acid (Vasoprim® 75 mg daily), and oral prednisolone (Perilon® 5 mg twice daily).

Pregnancy Assessment and Follow-Up

Biochemical pregnancy was evaluated 14 days post-transfer via serum β-HCG, with positive results confirmed by transvaginal ultrasound for intrauterine fetal viability. Follow-up continued for six weeks after confirmation, after which participants were referred for routine antenatal care. Those with negative results received counselling regarding subsequent treatment options, including repeat IVF cycles, alternative protocols, or donor gametes.

PRIMARY OUTCOME MEASURES

The primary outcomes of this study were the cleavage rate and blastocyst formation rate in participants undergoing natural versus OCP-programmed IVF cycles.

SECONDARY OUTCOME MEASURES

The secondary outcomes focused on the relationship between fertilization rate and subsequent embryo development.

SAMPLE SIZE DETERMINATION

The sample size for this study was determined using a standard formula for comparative studies designed to detect a clinically meaningful difference between two independent groups. The calculation was based on the expected difference in mean outcomes between the groups, the estimated population variability, a two-sided significance level of 5% ($\alpha = 0.05$), and a study power of 80% to detect the specified difference. To account for potential loss to follow-up and incomplete data, an attrition rate of 20% was included. Based on these assumptions, a total sample size of 86 participants was required, with 43 participants allocated to each study group.

RECRUITMENT

Participants were enrolled consecutively from the pool of eligible women attending the IVF clinic, based on their presentation and willingness to participate. All women diagnosed with infertility and scheduled for ovarian stimulation for IVF were approached by either the principal investigator or a trained research assistant. Eligibility and exclusion criteria were confirmed through medical record review and patient interviews. Women with contraindications to oral contraceptives, evidence of diminished ovarian reserve or ovarian failure, or those unwilling to participate were excluded. The study objectives, procedures, potential benefits, and risks were explained in clear, understandable language. Participants were assured of confidentiality and the safety of all procedures. Written informed consent was obtained only from women who demonstrated comprehension of the study and provided voluntary agreement to participate.

RANDOMIZATION AND ALLOCATION CONCEALMENT MECHANISM

Allocation Sequence Generation

Randomization was performed using WINPEPI software, which generated a balanced allocation sequence numbering 1 to 86. These numbers corresponded to either Group A (control) or Group B (intervention). Participants in Group A did not receive combined oral contraceptive pills (OCPs) prior to ovarian

stimulation, whereas those in Group B were pre-treated with OCPs for cycle programming before stimulation commenced.

Allocation Concealment

To maintain allocation concealment, the sequentially numbered assignments (1–86) were placed in small opaque envelopes, each stapled and stored in a secure container. This process prevented prior knowledge of group allocation.

Implementation

Eligible participants randomly selected an envelope, and the enclosed number was referenced on the randomization chart to determine assignment to Group A or B. The randomization process was conducted by the principal investigator or a trained research assistant who did not participate in oocyte retrieval or embryology procedures, ensuring separation between allocation and outcome assessment.

Data Collection

A structured proforma was used to capture socio-demographic details, reproductive and gynecologic history, BMI, and other relevant clinical information. Data collection was performed by trained research assistants and cross-checked for completeness and accuracy.

Data Management

Information from the paper proformas was entered into IBM SPSS Version 23. Double-entry verification was performed to reduce transcription errors, and all electronic datasets were stored on a password-protected computer accessible only to the research team.

Data Monitoring

Trial oversight followed the standard operating procedures of the study center, ensuring adherence to the protocol, accurate data recording, and participant safety. Compliance with study procedures was regularly verified by the principal investigator throughout the study period.

DATA ANALYSIS

All analysis were performed according to the intention-to-treat (ITT) principle. Participant characteristics were summarized using descriptive statistics: continuous variables were expressed as means with standard deviations, while categorical variables were reported as frequencies or percentages. Comparisons between the two groups were made using the student's t-test for continuous data and Pearson's chi-square test for categorical data. Results were displayed in tables and figures as appropriate. A p-value < 0.05 was considered indicative of statistical significance.

RESULTS

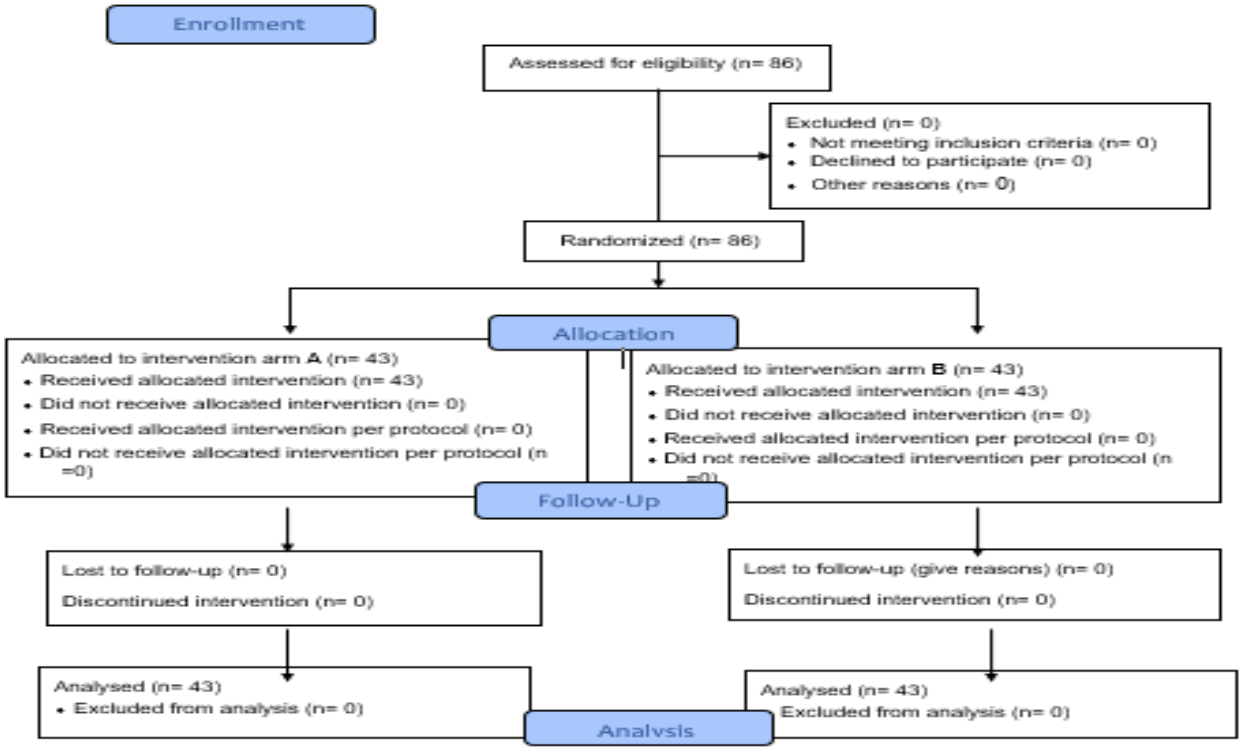

Figure 1: Study Flow Diagram

Table 1: Socio-demographic characteristics of study population

21- 25	1(50%)	1(50%)	
26 -30	**10(41.7%)**	**14(58.3%)**	
31 -35	**20(64.5%)**	**11(35.5%)**	**0.247**
36 -40	**12(41.4%)**	**17(58.6%)**	
Ethnicity			
Hausa	**5(31.3%)**	**11(68.8%)**	
Yoruba	**9(52.9%)**	**8(47.1%)**	**0.418**
Igbo	**16(53.3%)**	**14(46.7%)**	
Others	**13(56.5%)**	**10(43.5%)**	
Occupation			
Employed	**31(64.6%)**	**17(35.4%)**	**0.006**
Unemployed	**9(35.3%)**	**23(64.7%)**	
Student	**3(50.0%)**	**3(50.0%)**	
Marital Status			
Married	**38(63.3%)**	**22(36.7%)**	
Single	**2(10.5%)**	**17(89.5%)**	**0.001**
Divorced	**3(42.9%)**	**4(57.1%)**	
Widow	**0(0%)**	**0(0%)**	
Religion			
Christianity	**35(55.6%)**	**28(44.4%)**	
Islam	**7(33.3%)**	**14(66.7%)**	**0.211**
Others	**1(50%)**	**1(50%)**	

The OCP and natural cycle groups were similar in mean age (33.05 ± 3.65 vs. 33.05 ± 3.96 years), ethnicity, and religion ($p > 0.05$). Significant differences were observed in occupation and marital status, with more employed and married participants in the OCP group ($p = 0.006$ and $p = 0.001$, respectively). Age group distribution did not differ significantly between groups ($p = 0.247$).

Table 2: Comparing cleavage and blastocyst-formation rates between the two groups.

Parameters	***Study group***	***N***	***t***	***Mean***	***SD***	***P-value***
Cleavage rate						
	OCPs Group	43	0.796	70.74	21.97	*0.438*
	Natural cycle			67.16	19.69	
Blastocyst-formation rates						
	Took OCPs	43	1.482	52.37	22.54	*0.122*
	Natural cycle	43		45.18	18.26	

There was no statistically significant difference in both cleavage and blastocyst rate between OCPs participants and participants with natural cycle $p>0.05$.

Table 3: Correlation between fertilization rate, blastocyst formation rate and cleavage rate

		Blastocyst rate in %	fertilization rate in %	cleavage rate in %
Blastocyst rate in %	Pearson Correlation	1	.659**	.515**
	Sig. (2-tailed)		.000	.000
	N	86	86	86
fertilization rate in %	Pearson Correlation	.659**	1	.758**
	Sig. (2-tailed)	.000		.000
	N	86	86	86
cleavage rate in %	Pearson Correlation	.515**	.758**	1
	Sig. (2-tailed)	.000	.000	
	N	86	86	86

**. Correlation is significant at the 0.01 level (2-tailed).

There was a positive correlation between fertilization rate and cleavage rate, r (84) = 75.8%, p=0.001; fertilization rate and blastocyst rate, r (84) = 65.9%, p=0.001 and cleavage rate and blastocyst rate, r (84) = 51.5%, p=0.001.

DISCUSSION

This trial examined early embryonic developmental outcomes in women undergoing IVF using either natural cycles or OCP-programmed cycles. The study focused on cleavage and blastocyst formation as primary outcomes and evaluated correlations between fertilization, cleavage, and blastocyst rates as secondary outcomes.

The results showed no statistically significant differences between the two groups for cleavage (70.7% vs. 67.2%, p=0.438) or blastocyst formation rates (52.4% vs. 45.2%, p=0.122). These findings indicate that OCP pretreatment for cycle programming does not negatively affect early embryogenesis. The similarity between the groups suggests that OCPs primarily influence the timing of follicular recruitment without compromising oocyte quality or intrinsic embryonic developmental potential. These observations are in line with previous reports indicating that OCPs serve mainly as a scheduling tool rather than having embryotoxic effects.[16-18] For instance, Kim et al. [17] observed similar cleavage and blastocyst rates between OCP-pretreated and natural IVF cycles, while Griesinger et al. [18] reported no detrimental effect of OCP pretreatment on fertilization or early embryo development, although some studies note slightly increased gonadotropin requirements in OCP cycles due to temporary pituitary suppression.

The lack of significant differences also aligns with established physiological principles regarding oocyte competence. Oocyte quality is determined by intrinsic factors such as maternal age and ovarian reserve, as well as extrinsic factors including culture environment and laboratory handling.[19] While OCPs transiently suppress endogenous gonadotropins, subsequent controlled ovarian stimulation appears sufficient to support follicular growth and oocyte maturation, resulting in comparable embryo development to natural cycles. Clinically, OCP pretreatment remains valuable for preventing functional ovarian cysts and for flexible IVF scheduling without adversely affecting embryo quality. [16]

The study demonstrated positive correlations among fertilization, cleavage, and blastocyst formation rates. Fertilization rate showed a strong correlation with cleavage rate ($r = 0.758$, $p < 0.001$) and a moderate correlation with blastocyst formation ($r = 0.659$, $p < 0.001$), while cleavage rate also correlated moderately with blastocyst formation ($r = 0.515$, $p < 0.001$). These findings highlight fertilization success as a key determinant of early embryogenesis, as successful fertilization is necessary for zygotic genome activation and the initiation of mitotic cleavage, which in turn influences progression to the blastocyst stage. [19,20] The moderate association between cleavage and blastocyst formation suggests that while early cleavage is predictive of embryo quality, additional factors such as mitochondrial function, spindle integrity, epigenetic modifications, and culture conditions also modulate blastocyst development. [21,22]

These results indicate that OCP pretreatment does not impair cytoplasmic or nuclear maturation required for fertilization and early cleavage. By suppressing the hypothalamic–pituitary axis, OCPs prevent premature follicular development; however, exogenous gonadotropins effectively support follicle growth

and oocyte maturation once stimulation begins. The observed equivalence in cleavage and blastocyst rates between groups supports this mechanism. Furthermore, the strong correlation between fertilization and cleavage underscores the role of sperm quality and insemination technique (IVF versus ICSI) in determining subsequent embryo viability.

From a clinical perspective, these findings support the use of OCPs for cycle programming, particularly in settings requiring scheduling flexibility, such as avoiding weekend retrievals or optimizing laboratory workflow. The strong associations among fertilization, cleavage, and blastocyst rates also provide valuable prognostic information for clinicians and embryologists, as higher fertilization rates are likely to yield embryos with better developmental potential. However, early embryological outcomes alone do not always predict implantation or live birth, given the critical contribution of endometrial receptivity and uterine factors. [23,24]

STRENGTHS AND LIMITATIONS

Strengths of this study include its randomized design, standardized stimulation protocols, and detailed embryological assessment. Limitations include the single-center setting, relatively small sample size, and the absence of long-term reproductive outcomes such as implantation, clinical pregnancy, and live birth, which would provide a more comprehensive understanding of OCP impact. Future studies could examine the effect of OCP pretreatment on cumulative live birth rates, particularly in women with diminished ovarian reserve or advanced maternal age, and investigate potential interactions with different culture media and laboratory systems.

CONCLUSION

OCP-programmed and natural IVF cycles produce comparable cleavage and blastocyst formation rates, supporting the safe use of OCPs for cycle scheduling without compromising early embryo quality. These findings have important implications for both laboratory practice and clinical counseling in IVF, guiding embryo selection and optimizing treatment protocols.

RECOMMENDATIONS

Cycle programming with combined oral contraceptive pills may be incorporated into IVF protocols without negatively influencing fertilization, cleavage, or blastocyst development. The choice of natural versus programmed cycles should be guided by patient-specific factors and service logistics rather than concerns about early embryo quality. The observed associations between fertilization success and subsequent embryo development emphasize the need for careful optimization of insemination techniques and embryology laboratory conditions. In settings with limited resources, OCP-based scheduling provides a practical approach to improving service organization while maintaining acceptable embryological outcomes. Further large-scale and multicenter studies are needed to evaluate downstream reproductive outcomes such as implantation, pregnancy, and live birth rates.

AUTHOR CONTRIBUTIONS

Idea/Concept: Atemie Gordon, Augustine Osayande, John Ekweani; Design: Augustine Osayande, Atemie Gordon, Okafor C. Nwachukwu, John Ekweani, Collins E. Iyelobu, Michael J. Ofem; Control/Supervision: Collins E. Iyelobu, Michael J. Ofem, Amiete E. Fetepigi; Data Collection and/or Processing: Collins E. Iyelobu, Michael J. Ofem, Amiete E. Fetepigi, Okafor C. Nwachukwu; Analysis and/or Interpretation: Atemie Gordon , Amiete E. Fetepigi, Okafor C. Nwachukwu, ; Literature Review: Atemie Gordon, Augustine Osayande Amiete E. Fetepigi, Okafor C. Nwachukwu; Writing the Article: Atemie Gordon, Augustine Osayande; Critical Review: Augustine Osayande, Atemie Gordon, John Ekweani, Collins E. Iyelobu, Michael J. Ofem, Amiete E. Fetepigi, Okafor C. Nwachukwu

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

ETHICAL APPROVAL

Ethical approval was obtained from the ethical committee of the Federal Medical Centre, Abuja.

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