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# The Comparative Teratogenic Effects Of Prenatal Exposure To Varied Doses Of Phenobarbital And Phenytoin On Fetal Growth In Utero In Albino Rats (Rattus Norvegicus)

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***ABSTRACT***
*The in-utero exposure to phenytoin or Phenobarbital during pregnancy in the management of maternal neurological disorders like epilepsy, bipolar diseases, seizures among other has been associated with a wide range of fetal congenital malformation ranging from musculoskeletal, neurological and organ system disorders. However, their comparative teratogenic effects in terms of fetal growth have not been well elucidated hence the basis of this study. Therefore, this study seeks to comparatively evaluate fetal effects when exposed to phenytoin or Phenobarbital in development of fetal skeleton in albino rats. In carrying out the study a total of 57 nulliparous female Albino Rats dams from a pure colony/breed 3rd generation was used. The 57 albino rats were categorized into 54 rat experimental groups and 3 rats control. Further, the 54 experimental were broadly categorized into two major groups of 27 rats each based on the drug administered. The first group received phenytoin while second group received phenobarbital. Each of the Experimental groups were further divided into 3 groups of 9 rats based on the trimester i.e. one, two and three respectively. To evaluate the effect of dosage level the 9 rats were further subdivided into 3 groups of low dosage, medium and high dosage each composed of 3 rats. The Comparative effects on growth parameters between phenobarbital and phenytoin on fetal weight, bi-parietal diameter (BD), head circumference and crown-rump length (CRL) were evaluated. Excel spread sheet were used for data entry and SPSS version 25 was used for analysis and tables were used to present finding.*
*The result of this current study demonstrated that the timing of drug exposure significantly influenced fetal growth and development parameters and the dosage administered for both phenobarbital and phenytoin. Particularly, exposure during the 1st and 2nd trimesters, especially at medium to high doses, had more pronounced effects on fetal growth. The study revealed that mean fetal weights, crown-rump lengths, bi-parietal diameters, and fetal head circumferences decreased with increasing dosages and longer exposure times. Moreover, phenytoin exhibited greater effects on growth parameters compared to Phenobarbital throughout all trimesters.*
*In conclusion, this research establishes that both Phenobarbital and Phenytoin, at varying doses, lead to a significant decrease in fetal growth parameters when exposed prenatally. The magnitude of this decrease was dependent on both the timing of exposure and the dosage used. Therefore, it emphasizes the critical importance of considering the dose and timing of exposure to these drugs during pregnancy. Therefore is need for further research to elucidate the potential mechanisms responsible for the observed effects of these drugs and to identify appropriate dosages for both Phenobarbital and phenytoin. Such insights will contribute to better management of maternal neurological disorders while safeguarding fetal development.*

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## I. INTRODUCTION

Studies have demonstrated that anticonvulsant medications used in management of maternal neurological conditions including, epilepsy, seizures, and bipolar diseases, have been associated with teratogenic effects during organogenesis. Due to these potential risks to the developing fetus, the U.S. Food and Drug Administration (FDA) classify these drugs as class C medicines, indicating that there is evidence of adverse effects in animal studies, but there may be situations where the benefits of using the medication in pregnant women outweigh the potential risks (Gedzelman & Meador, 2012). Phenobarbital and phenytoin are some of the most commonly used medicines in the management of maternal neurological conditions during pregnancy in the developing countries like

Kenya(Taylor et al., 2003). However, their comparative teratogenic effects when exposed prenatally on fetal growth in-utero that include, fetal weights, crown rump lengths, head circumference and bi-parietal diameters is not well elucidated(Taylor et al., 2003). Further-more whether or not the observed effects on fetal growth are dose and time dependent is also not very clear.

Existing literature has shown that, many anticonvulsant drugs have a well-established safety profiles in adults, but less is known about their teratogenic outcomes in the developing foetuses when prenatally exposed at varying doses and at different gestational periods (Al Watatr et al., 2015). Drug choice is influenced by the pharmacological factors including efficacy, toxicity, and ease of use, which should be considered with respect to patient needs (Reisinger et al., 2013).

In terms of their usage, Phenobarbital usually retails by among other names as Nembutal, Luminal, and others, is a barbiturate drug while Phenytoin is a hydantoin derivative with a molecular formula of C15H12N2O2 and molecular weight of 252.27. It is a common anticonvulsant medicine with similar effectiveness as Phenobarbital (Dizon et al., 2019). Both of these two medicines are currently being used as a first-line treatment in several developing countries including Kenya (Lutes, 2020). Both are used as anti-depressants acting in the central nervous system, or as sedatives in the management of maternal epilepsy among other neurological conditions. The prior uses were however designed to treat anxiety, anxiety related disorders, and seizures(Kwan & Brodie, 2004). They exert their anticonvulsive effect by inhibiting serotonin (5-HT) and γ-amino butyric acid (GABA) neurotransmitters in the brain (M. Keppel Hesselink, 2017).

Their prenatal teratogenicity is thought to be caused by the ability of their metabolites namely 4′-hydroxylated DP and 3′,4′-Dihydroxylated product (3′,4′-diHPPH) to cross the blood-placenta barrier between the mothers blood to the developing fetal tissues hence these metabolites accumulate in the fetal tissues interfering with the process of embryogenesis, organogenesis and morphogenesis .Though it's not very clear on specific effects on the fetal organs systems, based on the periods of exposure there are some studies that indicate that the two medicines could be having a relationship with the duration of exposure (Czeizel et al., 2011).

The use of both Phenobarbital and phenytoin prenatally has been associated with some detrimental effects to the fetus including major congenital malformations (Birnbaum et al., 2020). Although these anticonvulsants drugs like phenytoin during pregnancy are associated with major congenital malformations in the fetus, their use cannot be discontinued in pregnancy because of the risk of uncontrolled seizures that can be harmful to both maternal and the fetuses (Galappatthy et al., 2018). Unfortunately, histomorphological and histosteological data on pregnancy outcomes of fetal use of anticonvulsive drugs is scarce in sub-Saharan Africa and especially in Kenya. This study therefore seeks to assess effects of exposure to Phenobarbital and phenytoin on fetal parameters including feta weight, bi-parietal diameter, and head circumference and crown-rump length in albino rats.

Many studies have linked exposure to Phenytoin and Phenobarbital related drugs to negative fetal outcomes that include major congenital malformations, developmental delay, and cognitive impairment(Weston et al., 2016)(Gedzelman & Meador, 2012). In addition, the occurrence of maternal seizures during pregnancy has also been linked to poor neonatal outcomes and cognitive impairment in children (Weston et al., 2016). The balance between maintaining maternal seizure control during pregnancy and not over-exposing the developing fetus to AEDs remains a challenge for clinicians (Lb et al., 2001). The growing concerns about the effects of AEDs on the fetus usually results to reduction or discontinuation in the dose of the AEDs that may increase the risk of convulsions (Meardor et al. 2018). Due to an increase on the use of Phenobarbital and phenytoin in many clinical settings and the inadequate information on their safety when exposed in-utero, it is essential to provide evidence based study to help in providing information on their maternal and fetal safety.

## II. MATERIALS AND METHODS

**Study location**

Breeding, weighing and administration of Phenobarbital and phenytoin were carried out at the animal house based in the University of Nairobi, Chiromo campus in Nairobi County, Kenya.

**Study design**

A post-test only experimental study design was adopted.

**Study subjects**

The study subjects were pure breeds of female' albino rats of species *Rattus norvegicus* that were bred up to the 3rd generation series. The reason for selecting this bread was that, they are known to possess the following scientific traits (i) Their litter size is large with an average of 7-12fetus, (ii) they have low chances of developing spontaneous congenital malformation, (iii) It is easier to get study subjects since they have short gestational span. (iv) The cost of maintaining the animals is lower, (v) there is readily available reproductive information vi) they

are small in size and this makes it easy to handle and care during an experiment (vii) They are more tolerant in withstanding many experimental medicines (Hard, T., Barnes, H., Larsson, C., Gustafsson., Lund, 1995)).

**Description of this species of Albino rats used in the study**

In this particular species of Albino rats used in this study, both the male and the female albino rats resembles **'**Japanese hooded rats', hence identical in genetic composition from a common ancestor, (Pritchett & Corning, 2016). Female rats acquire reproductive maturity at 15 and 20 months of age (Pallav Sengupta, 2013**),** with gestation period of 21 days. Each trimester takes 7 days after conception. The first trimester takes between day one to day seven, trimester two starts at day eight to day fourteen while third trimester from day fifteen to day twenty first. Pregnancy is detectable two weeks post conception. Baby rats are deaf and blind at birth. Weaning takes place at 21st day after birth. The weight of adult female is 250 to 350 grams while that of male rats weighing 350 to 450 grams. For the mating purposes 29 male albino rats were used in the current study.

**The acquisition of the albino rats used in this study.**

The 57 albino rats that were used in this study were procured from institute of primate Research in Nairobi County.

**Sampling Method**

In determining the sample size of albino rats used in this study, a resource equation for One Way Analysis of Variance (ANOVA) was used (Arifin & Zahiruddin, 2017) . The acceptable range of degrees of freedom (DF) in analysis of variance (ANOVA) is between 10 and 20. Since a value lower than10 as per the formula requires adding more animals, that subsequently increases the power of the study. The formula is **n = DF/k + 1,** where DF = total number of subjects, k = number of groups, and n = number of subjects per group(Charan & Kantharia, 2013). **Therefore, n=20/10+1 =3**

To eliminate bias and to ensure objectivity, systematic uniform random sampling was applied to select the foetuses to use in this study. Three foetuses from each rat were chosen making a total of 171 foetuses. The rest of the foetuses were preserved in 10% formaldehyde solution for future use in case of any problem arising from the experiment.

**Grouping of Dams**

The 57 albino rat dams were first randomly assigned to three broad study categories of three controls and 54 experimental categories. These 54 rats in the experimental category were further subdivided into two broad experimental groups of 27 rats each per the drug under the study hence 27 rats for Phenobarbital and 27 rats for phenytoin experimental group. To establish whether the effects of phenytoin and Phenobarbital were dose dependant, the 27 rats in treatment category were divided further into 3 study groups of: 9 rats for the low dose of phenytoin and Phenobarbital group; 9 rats for the medium dose of phenytoin and Phenobarbital group; and 9 rats for the high dose. To further assess if the effects of phenytoin and Phenobarbital were time dependent, the 9 rats in each of the three study categories of the low, medium and high phenytoin and Phenobarbital groups were further divided into another three subgroups of three rats in every trimester (TM1, TM2&TM3).

**Selection criteria**

**Inclusion criteria**

i.) Rats that conceived after male rats were introduced
ii.) All healthy rats
iii.) All alive foetuses at point at the end of 3rd trimester.

**Exclusion criteria**

i.) Rats that had tested negative for pregnancy test.
ii.) All rats that developed sign of a disease

**Feeding process of the rat**

These dams were fed at 0900hrs on rodent pellets and water *adlibitum* procured from Unga feeds limited in Thika town. Feeds were done in spacious standard cages (Allen *et al.,* 2016).

**Handling of Rats**

In handling the animals, the process began by acclimating the animals in the new environment where the experiments were being carried out at animal house in Chiromo Campus University of Nairobi. This entailed putting them in their respective cages for 7 days before the start of the experiment to enable them acclimatise with the new environment. To ensure humane and consistent handling of the animals, the rats were handled by the investigator and his trained assistant as per the recommendations of the animal ethics committee. They were

weighed every morning between 0830 hrs and 0900hrs. All procedures performed were as per the stipulated guidelines for care of laboratory animals as per the The Norwegian National Reserach Ethics Committees, (2018).

**Rats breeding**

Sexually mature albino male rats were introduced overnight in standard cages measuring143 square inches' floor space each assigned to two female rats from 2100HRS (+/- 30 minutes) to 0900 HRS (+/- 30 minutes) the following day, after which they were taken back to their separate cages.

**Determination of pregnancy**

The determination of pregnancy was done in 2 steps as follows: -

**Step 1: was to determine whether mating took place.** Spermatozoa on the vaginal smear were observed under the microscope which was an indication that coitus had taken place.

**Step 2: determination whether fertilization had taken place and start of pregnancy**

The polyhedral epithelial cells present from vaginal wash was an indication that fertilization had taken place. This denoted day one of gestation (Arifin & Zahiruddin, 2017).

**The human dose equivalent**

In determining the highest, medium and the lowest dose to be administered the adult dose was determined first. The Phenobarbital dose in human ranges between 30mg-400mg per day while Phenytoin range is between 300-1200mg in divided dosages (Azar & Abou-Khalil, 2008). Both drugs were obtained from through Kobian ltd company, an Indian supply firm.

**Phenobarbital and phenytoin doses determination**

To determine the dosages of Phenobarbital and Phenytoin to be used, a guide for conversion of animal from human dosages was used. It states that Human Equivalent Dose mg / kg = Animal dose mg / kg multiplied by a constant ratio (Km) 6 Nair & Jacob, 2016)

**Phenobarbital and phenytoin dosages calculation**

The highest therapeutic dose of Phenobarbital dose in humans is 400mg, medium dose is 185mg and minimum dose is 30mg. The average weight of an adult human is 60kg (Nair & Jacob, 2016). On the other hand, the highest dose for phenytoin in human being is 1200mg; medium dose is 600mg while the lowest dose is 300mg.

**Calculation of Phenobarbital dosages**

**a) High Phenobarbital dose group**

Highest Phenobarbital dose 400mg
Human weight avarage-60kg
400mg = 60kg
X=1kg
XH=1x400/60 =6.67mg/kg
Thus, 6.67mg/kg x 6.2 =12.4mg/kg

**b) Medium Phenobarbital dosage determination**

Medium Phenobarbital dose-185mg
Average human weight-60kg
185mg =60kg
X=1x185/60 =1mg/kg
AED = HED X Km factor
Therefore, 3.08mg/kg x 6.2 =19.10mg/kg

**c) Determination of low dose Phenobarbital group**

Phenobarbital low dos-30mg
Human weight-60kg
30mg = 60kg
X=1kg
X=1x30/60 =0.5mg/kg
Thus, 0.5mg/kg x 6.2 =3.1mg/kg

**Calculation of phenytoin dosages**

**a) Phenytoin group high dose determination**

Phenytoin high dose-1200mg
Human Average weight -60kg
1200mg-60 kg
X=1x1200/60 =20mg/kg
Thus, 20mg/kg x 6.2 =124mg/kg

**b). phenytoin group medium dose determination**

Medium dose phenytoi-600mg
Average weight of a man-60kg
600 = 60kg
X=1k
X=1x600/60 =10mg/kg
Thus, 10/kg x 6.2 =62mg/kg

**c. Phenytoin group low dose determination**

Phenytoin lowest dose -300mg
Human average weight -60kg
300mg =60kg
X=1kg
X=1x300/60 =5mg/kg
Thus, 5mg/kg x 6.2 =31mg/kg

**Phenobarbital and Phenytoin administration**

The researcher on daily bases at 0900hrs administered both Phenobarbital and phenytoin.

**Sacrificing of the pregnant albino rats**

The Female dams were humanely sacrificed through inhalation of concentrated carbon dioxide between 0900HRS and 1100HRS at 20 day of gestation to avoid devouring dead fetuses or the congenitally deformed foetus.

**Harvesting of fetuses**

Twenty minutes after anesthetizing the rats with concentrated carbon dioxide, a longitudinal incision along the anterior abdominal wall of the dams was done along the linear Alba and the uterus exposed. All foetuses and their placentas were removed, weight taken and the fetal morphology examined and recorded. The fetuses then were inserted in 10% formalin to continue with fixation.

**The findings on the comparative fetal pregnancy outcomes following prenatal exposure to low, medium and high Phenobarbital and phenytoin dosages on the fetal weight, the crown-rump length, the bi-parietal diameter and the head circumference, at TM1, TM2 &TM3 against control.**

The fetal growth parameters that were evaluated to assess the fetal growth and development *in-utero* included the fetal weights whose normal ranges are 5.5 to 6.7 grams(Chahoud & Paumgartten, 2005), the crown-rump length whose normal ranges are 3.1 to 4.6cm(Ypsilantis et al., 2009), the head circumference whose normal ranges 2.8 to 3.8 cm(Poojari et al., 2022) and the bi-parietal diameter whose normal ranges 2.9mm to 18.1mm(Kirberger et al., 2019) deviation of this normal fetal ranges either below or above are an indicator of a toxic in-utero environment that would subsequently predispose the fetus to developmental challenges and probable causation of congenital anomalies. In this current study, it was observed that the means of the four parameters evaluated were all statistically significant from the controls in that they were found to be remarkably reduced compared with the control: mean fetal weight (6.3667±.11056), mean head circumference (3.7142±.13991), bi-parietal diameter( 1.5597±.05488) and crown- rump length (4.3613±.10284); for the treatment groups combined (a) mean fetal weights ($F(18,38)=16.840$, $P<0.001$), (b)mean crown-rump length ($F(18,38)=19.139$, $P<0.001$), (c)mean fetal head circumference ($F(18, 38)=8.936$, $P<0.001$), and (d) mean bi-parietal diameter ($F(18, 38)=18.407$, $P<0.001$). as per table 3.1

On doing pair wise comparison on how the two medicines compared in influencing the four parameters, it was noted that the two medicines at low dosages in trimester 3, there was no statistical significance from the control in all the four parameters. At trimester one and trimester two they showed slight reduction in all growth parameters. Those subjected to medium and high dosages in trimester one and two showed reduction in mean fetal

weight, mean crown-rump length, mean head circumference and mean bi-parietal diameters. Phenytoin treatment groups at trimester one, trimester two and trimester three had increased fetal parameters as compared to phenobarbital at equal dosages. Upon Evaluating how the two medicines influenced the head circumference, the fetal weight, the bi-parietal diameter and the head circumference, it was established that the reduction in means of the fetal weight, the crown-rump length, the bi-parietal diameter and the head circumference, were dependent on the dosages and time of exposure. All groups denoted that there was a statistically significant difference ($P<0.001$) in different trimesters with the highest fetal weight, crown-rump length, bi-parietal diameter and head circumference observed in trimester three ($TM_3$), followed by trimester two ($TM_2$) and lastly by trimester one ($TM_1$). Similarly, it was observed that, the fetuses from the rats in Phenobarbital and phenytoin treatment groups that received high doses were associated with low mean fetal weight, low mean crown-rump length, low mean bi-parietal diameter and low mean head circumference, followed by medium dosage groups and lastly by low dosage groups. It was however noted that those exposed to Phenobarbital treatment groups showed that there was statistically significantly lower means of the fetal weight , the crown-rump length ,the bi-parietal diameter and the head circumference ($p<0.05$) as compared to the phenytoin treatment group (table 3.1)

**Table 3.1: The findings on the comparative fetal pregnancy outcomes following prenatal exposure to low, medium and high Phenobarbital and phenytoin dosages on the fetal weight, the crown-rump length, the bi-parietal diameter and the head circumference, at TM1, TM2 &TM3 against control**

| Drugs | *Dosage level* | Exposure time | Fetal Weights | Crown-Rump Length | Bi-parietal diameter | Head circumference |
|---|---|---|---|---|---|---|
| | *None* | Control | 6.3667±.11056 | 4.3613±.10284 | 1.5597±.05488 | 3.7142±.13991 |
| Phenobarbital | *Low* | Trimester 1 | 6.1927±.14396* | 3.0753±0.39253 | 1.3163±.06959* | 3.5937±10571* |
| | | Trimester 2 | 6.1907±.20184 * | 3.2990±0.15418* | 1.4063±.04881* | 3.6197±.47083* |
| | | Trimester 3 | 6.3240±.10173 | 4.3547±0.3828 | 1.5633±.01234 | 3.7057±.05387 |
| | *Medium* | Trimester 1 | 5.2227±.17379* | 3.4147±.18501* | 1.0370±.10559* | 3.1843±.09903* |
| | | Trimester 2 | 5.3920±.51894* | 3.4540±.41746* | 1.1197±.08849* | 3.2973±.09630* |
| | | Trimester 3 | 5.8103±.20641* | 3.5587±.13815* | 1.2657±.31973* | 3.3210±.51594* |
| | High | Trimester 1 | 4.3350±.33056 * | 2.9113±.09416* | .7163±.06369* | 2.6220±.08461* |
| | | Trimester 2 | 5.0140±.08202 * | 3.1677±.01361* | .7853±.01501* | 3.0973±.06258* |
| | | Trimester 3 | 5.7790±.15795 * | 3.5387±.10023* | .8377±.31467* | 3.6910±.19194* |
| Phenytoin | Low | Trimester 1 | 6.2077±.16905 *b | 3.6797±.09232* b | 1.3457±.02101* b | 3.2047±.16013* |
| | | Trimester 2 | 6.2287±.19405 *b | 3.9027±.07104* b | 1.4367±.007578* b | 3.4160±.13750*b |
| | | Trimester 3 | 6.3587±.15338 | 4.3978±.12355 | 1.5493±.01795b | 3.6913±04974b |
| | Medium | Trimester 1 | 5.6943±.23435 *b | 3.1093±.05260* b | .9673±.05352*b | 3.5687±.14610*b |
| | | Trimester 2 | 6.0263±.16028 *b | 3.1982±.08721* b | 1.0513±.03331* b | 3.4677±.09287*b |
| | | Trimester 3 | 6.0003±.34858 *b | 3.3373±.09063* b | 1.1670±.05645*b | 3.4033±.08386*b |
| | High | Trimester 1 | 4.5900±.33166 *b | 3.0014±.00573* b | .6583±05204*b | 2.9610±.18578*b |
| | | Trimester 2 | 5.5543±.50529 *b | 3.0983±.08836* b | .7957±.02281*b | 3.2483±.05179*b |
| | | Trimester 3 | 5.9867±.03137 *b | 3.1613±.10284* b | .9167±.06010*b | 3.8960±.046788* b |
| | **ANOVA statistic** | **F (18,38)** | **16.840** | **19.139** | 18.407 | 8.936 |
| | **Significance level** | **P VALUE** | **<0.001** | **<0.001** | <0.001 | <0.001 |

***Key:*** *Means±SD that bears (*) means that they are statistically significant difference with the control at ($p<0.05$),*

*While Means±SD of phenytoin that bears ($^b$) means that they are statistically significant different with Phenobarbital at the same dosage level ($P<0.05$*

## III. DISCUSSION:

This study has established that there was a mean reduction in fetal weight, crown-rump length, bi-parietal diameter and head circumference in Phenobarbital and phenytoin treatment groups as compared to the control

group. Additionally, the mean reduction in crown rump length, fetal weight, bi-parietal diameter and head circumference were observed to be time and dose dependant. Statistically significant lower means (P=0.001) were associated with low and medium dosage groups as compared to high dosage groups. Further, statistically significantly higher means of fetal body weights, crown rump length, bi-parietal diameter and head circumference were observed in trimester three ($TM_3$), followed by trimester two ($TM_2$) and lastly by trimester one ($TM_1$).

The current study results agrees with previous results of Matalon et al., 2002) on teratogenic morphological effects on the development of the fetal skeleton which showed that carbamazepine which is in the same class with the drugs of this study causes detrimental effects on fetal parameter. On dose comparisons, it was observed that high dosage groups on both Phenobarbital and phenytoin treatment groups were associated with low fetal weights, head circumference, crown rump length and bi-parietal diameter, followed by medium dosage groups and lastly by high dosage groups. This agrees with the finding of another study that showed that exposure to lamotrigine which has the same mode of action with the drugs in this study on albino rats given at different dosages and gestation period have effects on fetal parameters(Anatomy, 2020). It was however noted that those exposed to phenobarbital had slightly lower fetal weight, crown -rump Length, head Circumference and bi-parietal diameter compared to the phenytoin in all groups' i.e. low, medium and high doses and time of exposure.

## IV. CONCLUSION AND RECOMMENDATIONS

The findings of this study established that both Phenobarbital and Phenytoin at varied doses, leads to remarkable decrease in fetal parameters for growth when exposed prenatally. The mean decrease in these fetal parameters was observed to be time and dose dependant. However, it was established that the mean reduction was more in Phenobarbital treatment groups as compared to the phenytoin treatment group. This evidence indicates that Phenobarbital has more detrimental effects as compared to phenytoin.

The study therefore recommends for further follow up studies and clinical trials to be carried out in species close to human.

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