Developmental Defects of Teeth Triggered By the Estrogen Given During Pregnancy

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Abstract

Objective: To explore the impact of Estrogen administered during pregnancy, on the development of teeth in intra-uterine life (IUL) and in the direction to assess the changes in the morphology of dentition of new born rabbits.

Methods: It was an experimental animal study which was conducted to evaluate the modifications in the morphological features of developing dentition in newborns. Female rabbits were selected having the weight of about 1.5 to 2.0 kg for trial purposes using the resource equation method. They were treated with Estrogen throughout the pregnancy phase. Offspring of these treated feminine bunnies were utilized for the trials. Three types of teeth i.e. central incisors, first premolars, and first molars were selected from both the jaws and extracted when the offsprings reached the age of three months to analyze the modifications developed in IUL, the samples were evaluated for volumetric assessment. The data was analysed using SPSS software version 21.

Results: The analysis of volumetric modifications between the dimensions of the control and the treatment groups unveiled that statistically significant difference between the dimensions of the teeth among both the sets was observed and analyzed. It revealed that maxillary central incisors, first premolars, and first molars showed the P values of 0.166, 0.782, 0.433 respectively while the mandibular teeth presented central incisors, first premolars, and first molars with P values of 0.142,0.001, 0.522 individually. However, Mandibular Premolars showed a noteworthy difference with a P-value of 0.001.

Conclusion: It was thus concluded that systemic administration of estrogen during pregnancy influenced the developing embryo and effected the morphology of growing teeth of the offsprings. Therefore, preventive measures might be taken regarding self-medication during pregnancy, which could help to evade the risk of teratogenic consequences on the newly erupting teeth of newborns.

Keywords: Dentition, developmental disorders, Estradiol, female rabbits.

IRB: Approved by Ethics Committee, Baqai Medical University. Ref# EC/Ph.D/BMU-01, Dated: 25th April, 2014.

Citation: Nazir S, Mirza A. Developmental Defects of Teeth Triggered By The Estrogen Given During Pregnancy New Born Rabbits [Online]. Annals of ASH & KMDC,2024:29(3): 376-383

Introduction

Tooth size is one of the features that can accomplish normal occlusion with respectable intercuspation of teeth. The dental tissues are sensitive throughout their morphogenic stages which may cause various types of teratogenic effects on dental morphology. Madalena IR *et al.,* 2023, assessed the impact of estrogen (Estradiol) insufficiency on the tooth eruption rate (TER) and gene manifestation of estrogen receptor alpha and beta (*ERá and ERâ*) in the odontogenic area of teeth with constant creation in a rat model. Estrogen deficiency decreased the TER. Estrogen shortage also increased the ERâ gene expression in the odontogenic area with constant development of dentition. Hormonal instabilities were observed to be upsetting estrogen levels and reasons for modifications in the teeth development and eruption[1]. It was investigated in a former study that estrogen standardizes the ap

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Date of Submission: 19th April, 2024
Date of Revision: 17th November, 2024
Date of Acceptance: 25th November, 2024

pearance of some genes in diverse cells, including dental cells. The role of estrogen shortage for the duration of tooth development concerning the tooth configuration morphology and its influence on the manifestation of odontogenesis-related genes was discovered. ESR1 (Estrogen Receptor 1), a Protein Coding gene entangled in enamel mineralization and their size, which is liable to the polymorphism within the gene. The study delivered proof that genetic polymorphisms in *ESR1* and *ESR2* could be related to tooth dimensions in permanent teeth[2]. Gerber JT *et al.,* 2023, associated that the inconsistency in tooth crown size (TCS) was subjective by genetic aspects and might be controlled by the modification in hormonal reaction which evaluated the relationship among differences in TCS of permanent teeth with the supplementary aspects and genetic polymorphisms in hormonal-related genes (ESR1, ESR2 and PTH). Different dentitions (incisor, canine, premolar, and molar) in the maxillary along with mandibular dental arch, that the genetic polymorphisms of hormonal-linked genes have been recycled, which revealed that genetic polymorphisms of *parathyroid hormone* (*PTH*) were related to variations in the buccolingual (BL) dimensions of tooth and crown size (TCS) of permanent human teeth. The study suggested that genetic polymorphisms of PTH were related to disparities in the BL TCS of permanent human dentition[3]. Neves JA *et al.,* 2020, worked on the measurements of teeth and recognized that the mean mesiodistal width regarding maxillary along with mandibular canines, premolars, and molars was established meaningful dissimilarities among females and males. Concerning the incisors, there were no substantial alterations were initiated concerning the sex. The maxillary left canine, the mandibular right lateral incisor, and the mandibular right canine were considered to be the supreme suitable and with good replicability. On the subject of the compliance of their boundaries of study, it was established that an occurrence of sexual dimorphism among the teeth except the incisors and the canines exhibited the best conspicuous change among sexes, trailed by the first mandibular molars and premolars[4].

Prior studies have specified that the modification in dimensions of the canine marks the flawless means designed for sexual disparities. A significant variance was seen amongst the right and left canine widths of males and females. Hence, usage of the left Mandibular canine index (MCI) to estimate the gender of individual could provide more specific results than the right canine. It revealed noteworthy dissimilarity concerning the right and left MCI between males and females by means of substantial modification among the inter-canine distance (ICD) of males and females, revealed by Sivakumar N. *et al.,* 2020. It was also recommended to be employed with inadequate facilities for investigation as it turned out to be economical, and familiar to perform, being not much time-consuming and a rationally consistent substitute to conclude the sex estimation. It might not be a affirmative test, but instead, it possibly might be castoff as an addition to further tests for gender identification[5]. A surplus report by Abaid S. *et al.,* 2021, regarding mesiodistal dimensions appeared to be significantly vary among teeth in contralateral quadrants, and in maxillary and mandibular arches. This indicated that a maximum of the teeth displayed sexual dimorphism, which appeared maximum for permanent mandibular canines. It was discovered that the Mesiodistal proportions were meaningfully contrasted concerning teeth in contralateral quadrants, in maxillary and mandibular arches. Maximum teeth displayed sexual dimorphism, showing the maximum for permanent mandibular canines[6]. Human teeth are the toughest mineralized tissue of the body having marked heat and erosion resistance. In situations of accidents where the identification of a person is problematic, teeth frequently play a vital part for proof of identity. It was reported by applying 3-dimensional technology to attain odontometrics of permanent maxillary teeth to scrutinize the sexual dimorphism, for appropriate pointers to paradigm the suitable equivalences for sex estimation. However, there are means to evaluate the three-dimensional digital technology which deals with a favorable procedure for odontometry. Merging mesiodistal and buccolingual space of specific teeth or employing the maxillary canine index was an acep-

table secondary means for sex assessment in the forensic arena. Related to other resources, it was established that the left canine index needed a better precision ratio and might aid as a supplementary technique for assessing sex[7].

Teeth and dental arch determination are significant features in dentistry and forensic medicine. Recommendations of Johari M, *et al.,* 2022, showed that cone-beam computed tomography (CBCT) is a extremely perfect device meant for measuring the dimensions of mesiodistal tooth and arch sizes. Their trial gaged those teeth and dental arch measurements of males and females on CBCT pictures of the patients showed a contrast in the mesiodistal measurement of teeth concerning males and females and reflected a noteworthy difference in the mesiodistal breadth of the maxillary and mandibular canines and first premolar, which appeared lesser in females. Similarly, the arch size at maxillary inter-first premolars, maxillary and mandibular inter-second premolars, and maxillary and mandibular inter-first molars were considerably reduced in females than males. Some variances in standards were also eminent concerning both the genders, which might be considered in dental treatments[8]. Gender dimorphism of permanent teeth was testified in former reports. Almugla YM. *et al.,* 2023, indicated the gender-specific variances in rectilinear proportions of maxillary permanent canines in the study trials, where mesiodistal (MD) size of maxillary canines was larger than 7.43 mm, and a 95% probability of male gender. The maxillary canine index might not be valuable in gender assessment owing to little precision. The trial presented a varied judgment role that delivered a greater level of exactness (80.5%), and one variable analysis using inter-canine distance (ICD). The use of 3D digital models might be a favorable substitute for plaster models for odontometry through clinically satisfactory, precision and consistency of tooth measurements[9]. Ajmal, MA. *et al.,*2023, showed together with rectilinear and volumetric dimensions of teeth which could aid in sex assessment. Dimensions of permanent canines showed more divergence, mostly in mandibular canines, representing a maximum sexual dimorphism. Odontometrics of human permanent dentition employing cone beam computed tomography (CBCT) demonstrated a positive gradation of sexual dimorphism. Both rectilinear and volumetric dimensions of teeth could help gender assessment[10].

Most of the aforementioned studies reported gender-specific variations in the size of teeth and jaws among different populations using various parameters e.g. (CBCT). Odontometrics of human permanent dentition using CBCT exhibited a certain degree of sexual dimorphism. In addition the linear and volumetric dimensions of teeth could support the sex assessment. The objective of the study aided in the sex estimation, while in the contemporary study, the influence of a selected drug was evaluated on the developing teeth when the medication was administered systemically throughout the pregnancy, the study revealed the disparities in the dimensions of a newborn's teeth. Practice of self-medication by the pregnant women could distract the growth of the embryo, so the present study was focused on the consequences of the use of Estrogen on the developing teeth of newborns.

Methodology

The present study was piloted utilizing fully-grown female rabbits, treated throughout the pregnancy with a selected medication i.e. Estrogen. The teeth of their offspring were certified to assess the effect of the drug on the morphological features of the teeth.

This *in-vivo* study was conducted using female rabbits as an animal model. Before selection, they were checked by a competent veterinary surgeon for certification of their health.

The study was conducted at Baqai Medical University, and the subjects for the study were taken from the animal house of the University.

The duration of the study was about two years, from January 2022 till the end of 2023. Female rabbits of 1.5 to 2.0 kg were included in the study. Offspring about three months of age and declared healthy were utilized. Male rabbits were not taken. Subjects less than 1.5 to 2.0 kg or over

weight and less than three months of age are excluded. Unhealthy animals with any injuries, rashes, or edema were also excluded

The sample size was calculated using the 'Resource Equation Method'. The method applies to all animal experiments. Any sample size, which keeps E (E is the degree of freedom of analysis of variance) between 10 and 20 should be considered as adequate. It can be measured by following the formula E = Total number of animals " Total number of groups[11].

The selected subjects designated for the investigational options were distributed into two sets, the study, and a control group, each one composed of (n=7) subjects.

The chosen medicine used for trial purposes was (Gynaecosid® Reg. No. 001715), one tablet containing Methyloestrenolone 5mg and Methyloestradiol 0.3 mg. The medicine was administered by oral route, and the strength of the dose was calculated, established on Clark's rule, according to the body weight of the subject, Dose = Adult dose × Weight (Kg) / 70[12].

A single tablet was liquefied in 10 ml. of distilled water to dispense the medicine, (0.176 mg/ Kg.). Thus, 0.5 ml. of the prepared medicine was administered orally, two times a week to the female rabbits of the investigational set till the delivery of their offspring. These offspring were sacrificed once they reached three months of age. Their teeth were then extracted from the upper and lower jaws for the experimental purpose. Extraction of teeth was achieved including three entities of teeth in each group which were incorporated for the analysis i.e. central incisors, first premolars, and first molars of different quadrants from the maxillary and mandibular arches.

Thus, twelve teeth from each subject were selected, so a total of 168 samples were amalgamated in the study. This accumulation of benchmarks could practically abstract sufficient evidence to portray the conclusion.

These samples were utilized to check the effect on the morphological features of the teeth by intrauterine exposure to the selected drug. Measurements of the crowns of all the selected teeth were done with the help of a Vernier calliper. Crowns of the teeth were measured taking three dimensions measured in millimetres; Cervico-incisal/ occlusal, Mesio-distal, and Labio/Bucco-lingual.

Measurements were recorded, and the volume of each dentition was calculated separately for both the treatment and control sets. The obtained results were documented in mm^3.

Data analysis was then analysed according to their volumes.

Data were analyzed on SPSS version 21. Descriptive analysis was achieved by calculating mean and standard deviation whereas inferential analysis was performed by applying an independent t-test after checking the data for normality. The significance level was kept at 0.05.

Results

The outcomes unveiled that the influence of Estrogen on morphological features of the teeth provoked in intrauterine life by the drug administered during pregnancy was evaluated according to the described procedure. The methodology used was adopted from the technique piloted according to the procedure described in one of our published articles[13].

The data was collected to estimate volumes of the selected teeth and recorded according to the above-stated three dimensions which revealed that none of the teeth were statistically significantly different in their dimensions when the three types of teeth in both the sets i.e. control and treatment groups were compared. The maxillary and mandibular central incisors appeared noticeably reduced in their dimensions among the treatment group as compared to the teeth in the consistent group. However, Mandibular Premolars showed a noteworthy variance with a P-value of 0.001. (Table 1) and (Figures 1,2).

Table 1. Dimensions of Teeth

Teeth Samples	Control Group Mean±Std. Deviation	Treatment Group Mean±Std. Deviation	P-Value
Max. CI	28.14 ± 11.90	20.67 ± 6.15	0.166
Max. 1st Pm	16.21 ± 5.03	17.22 ± 8.73	0.782
Max. 1st M	15 ± 5.12	12.75 ± 4.37	0.433
Mand. CI	38.14 ± 7.75	30.25 ± 9.36	0.142
Mand. 1st Pm	26.35 ± 9.15	24.89 ± 4.91	0.001
Mand. 1st M	10.12 ± 2.59	8.6 ± 64.63	0.522

Max = Maxillary, Mand = Mandibular, CI = Central Incisor, Pm= Premolar, M = Molar

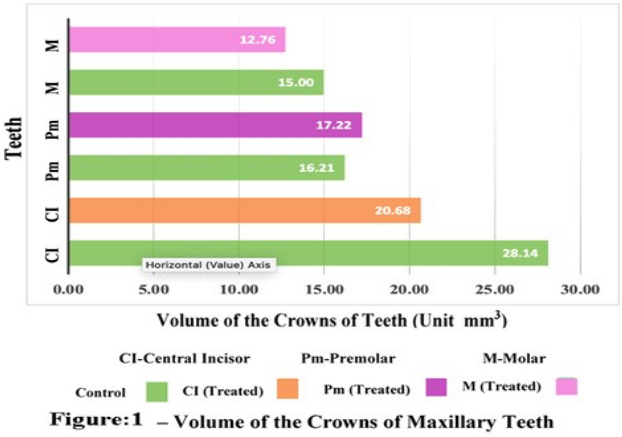

Figure:1 – Volume of the Crowns of Maxillary Teeth

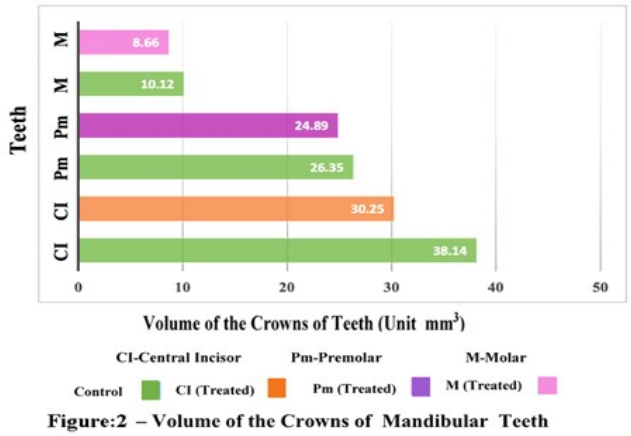

Figure:2 – Volume of the Crowns of Mandibular Teeth

Discussion

Some drugs can transport, endocrine, and as a result, abnormal placental functions could occur and affect the development of fetal organs. It was also reported that Estrogen insufficiency disturbs gene expression in the odontogenic area and tooth configuration morphology[14].

According to Cinelli F, *et al*., 2024, the range of tooth sizes could be used as references, they might vary in both sexes. Males showed larger measurements and limited central–lateral and canine–lateral associations. Current reports proposed an amended Golden Percentage with central–lateral–canine percentages of 22.5–15–12.5%. Such standards were reported to be considerably a supplementary demonstration of the Golden Percentage[15]. A minor unit of sexual dimorphism occurred in all human teeth. Second molars and canines revealed the maximum sexual dimorphism. Furthermore, lesser racial differences were obtained in mesiodistal crowns among the groups living in diverse geographic areas reported by da Silva PR *et al*., 2019[16]. Mediating the literature survey of various trials, the measurement of teeth appeared to be the most modest and steadfast method to investigate sexual dimorphism.

Contrary to the prior studies the results of the present trials revealed the influence on the size/volumes of the newborn's teeth during their developmental stages by the administration of a selected drug during pregnancy, therefore these results are not in proportion to the reported trials. The outcomes of Küchler EC, et al., 2021 advocated that estrogen insufficiency in the course of the prepubertal phase is related to modifications in the maxillary and mandibular bone dimension and condylar development[17]. However, Lima-Pansini LF.*et al*., 20 19, demonstrated the influence on the bone where administration of estrogen might have a shielding action on the bone resorption, which may possibly not relate to the alveolar bone which is intended to be resorbed for the duration of the eruptive progression[18]. The role of bone resorption is correlated with the eruption of teeth and the orthodontic treatment concerning the tooth drive where bone resorption is required on the pressure side and deposition on the tension side for the alignment of teeth, so estrogen could affect both the conditions and effect the clinical procedures. The association between Estrogen insufficiency and mandible/maxilla dimensions was evaluated and suggested by Omori MA., et al., 2019, that both, raised and reduced stages of Est-

rogen, devise an influence on the maxilla and mandible measurements[19].

Hydroxyapatite is the inorganic component of all the mineral tissues of the body. It could thus be considered that if the maxilla and mandible showed the effect on the dimensions as reported by Omori MA., et al., 2019; therefore, it might influence the dimensions of teeth also because Hydroxyapatite is the inorganic component of dental tissues as well.

Daoud R. *et al*., 2021; discussed that the massing in the miscellaneous dentition stage may possibly be linked by abridged jaws dimensions, furthermore, an upsurge in mesiodistal dimensions of the incisors and lower permanent first molars, also the disparities of buccolingual sizes and crown magnitudes of incisors and lower permanent first molars could affect the alignment[20]. It was also recommended that malformations in tooth development were observed during clinical checkups which need to be referred for genetic analysis and management of esthetic cases[21].

Prior studies were conducted to evaluate the consequence of Estrogen on teeth and alveolar bone in a different parameter which was not in line with the contemporary trials. However, the research done to evaluate the influence on the maxilla and mandibular dimensions showed the variation in the size of the jaws, as reported by Omori MA et al., 2019, hence considering such results could be taken into account that it would possibly influence the size of the teeth as well. Comparing the changes induced by estrogen in the maxilla and mandibular dimensions and correlating the consequence of medication on the size of teeth presented in the present study indicated a direct association with each other which could be considered while planning an orthodontic treatment. The published reports also provided information regarding the influence of estrogen on the alveolar bone which is also important to understand because resorption and deposition of alveolar bone affect the rate of orthodontic tooth drive. The present study on the other hand was conducted to assess the effect on the morphological features of the teeth developing in IUL when the selected medication was administered during pregnancy. Furthermore, the aforementioned trials described the procedure of taking the measurement of growing teeth of rabbits which was conducted by making a BUR mark on the facial surface of the teeth, and the measurement was taken up to the gingival margin. Contrary to that, in the current study, volumes of the teeth were estimated by taking the measurement from three aspects i.e. Cervico-Incisal/Occlusal, Mesio-Distal, and Labio/Buccal-lingual, which enabled us to assess the change in overall volumes of the teeth.

Most of the prior studies reported gender-specific variations in the size of teeth among different populations assessed through diverse assessment tools, particularly from a Forensic point of view. The variation in the dimensions of the teeth in response to fetal exposure to these drugs has not been reported and published.

There were some limitations faced during the experimental period in which a designated medication was administered to the female rabbits during the course of the pregnancy phase, which was a long duration. The rabbits could not bearably disperse in hot and tropical weather, therefore the survival rate of the animal was not good in the warm climates of a country like Pakistan.

It is recommended for future studies that the developing embryo being very sensitive to any peripheral augmentations, therefore the influence of medications commonly prescribed during pregnancy need to be studied and understood for the health of mother and the newborn.

Conclusion

It is concluded that systemic administration of estrogen during pregnancy influenced the developing embryo and effected the morphology of growing teeth of the offsprings. Therefore, preventive measures might be taken regarding self-medication during pregnancy, which could help to evade the risk of teratogenic consequences on the newly erupting teeth of newborns.

Conflict Of Interest: None

Disclaimer: None

Source of Funding: None

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