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ORIGINAL ARTICLE

Drug Persuaded Growing Defects of Teeth

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ABSTRACT
The purpose of this research was to determine the impact that regularly prescribed drugs have on dental tissues. Certain drugs can cause sensitivity in dental tissues if they are used by pregnant women for an extended period. This research focused on a small set of drugs, such as aspirin, estrogen, and lithium that have been shown to have adverse effects on human tissue throughout the developing stages of pregnancy. Only female rabbits participated in the study. The animals in the experiment were split into four groups, and each group had (n=7) subjects. Three of them were for the study of drug treatments and the fourth one was taken as a control. They were administered drugs in predetermined doses based on their weights up until they gave birth. These rabbits were bred specifically to be utilized in scientific studies. Variations in tooth size, mineral content, and composition of enamel (the hard, protective layer of dental tissue), and ultrastructural changes in enamel surfaces were among the variables examined by scanning electron microscopy (SEM). At the age of three months, researchers analyzed the teeth to look for signs of congenital abnormalities that may have begun in utero. Six hundred seventy-two samples were analyzed using volumetric methods prior to tooth extraction. After the teeth were removed, 336 samples were analyzed using a scanning electron microscope and energy-dispersive X-ray spectroscopy to determine the mineral composition and examine the surface structure of the enamel (SEM-EDX). The chemical analyses and volumetric measurements showed a huge range of variance among samples between the control and experimental groups. The incisors and the premolars were found to be teeth with aesthetic and functional flaws. It was observed that the incisors and molars were aesthetically and functionally compromised teeth. However, this research has the potential to link long-term drug usage with dental drugs. It may also help future researchers focus on the role of drug-related factors in disease development. In dentistry, it could be useful for cosmetic and practical purposes. The results of the study were supposed to reveal which drugs should be avoided or used with caution during pregnancy and provide new avenues for further study.
Keywords: drug persuaded, growing defects, teeth

INTRODUCTION
The maturation process is a part of human development. To put it in biological terms, this means developing from a single-celled zygote into an entire human person. The process of human development is complicated and complex, impacted by many factors that can have an effect on the body's developing tissues and lead to a wide range of congenital abnormalities. An anatomical or physiological defect that is present at birth or within the first few weeks of life is said to be congenital (The New Penguin Encyclopedia 2003). It is possible that disruptions in myeloblastic activity during matrix secretion or enamel maturation lead to poor enamel development (Jalevik et al., 2001). There are two stages in enamel development, which Bhasker (2003) classified as matrix formation and maturation. Enamel hypoplasia occurs if matrix formation is disrupted, and enamel hypocalcification occurs if maturation is impaired. Enamel hypoplasia is a cosmetic abnormality. Hypocalcification refers to a condition in which the mineral content of the enamel is deficient. Disrupted morphogenesis causes gross anatomical deformities, as the organic structures are thrown off balance at a time when they are still developing (Das 2003). In addition to being caused by fluoride ion levels in drinking water above 2 parts per million (PPM), dental fluorosis can also be caused by excessive fluoride intake during tooth growth. (Peter 2006). Nanci (2008) suggests that fever may contribute to the development of enamel abnormalities. As the condition progresses, it causes enamel production to be disrupted, resulting in misshapen bands of enamel on all newly developing teeth. A tetracycline-induced tooth disturbance can lead to the formation of a second abnormality. Antibiotic tetracyclines become absorbed in bone tissue during the mineralization process. It is possible that the dark bands in enamel are the result of this integration.

Significance of developmental defects

Certain drugs have an adverse effect on dental tissues if used for an extended period of time during pregnancy Prescription, over-the-counter, or illicit drugs, more than 90% of pregnant women use medicine of some kind (The Merck Manual 2007). Most drugs administered by pregnant women are able to cross the placenta, where they can then exert their pharmacologic and teratogenic effects on the developing embryo and fetes (Koren 2007). The prenatal field of pharmacology is just beginning to explore the potentially fatal effects of medicines. . Researchers have found that the age of the kid, the dosage, and the length of treatment all play a role in the severity of dentofacial developmental and tooth-related abnormalities that occur as a result of the therapy. Agenesis (the absence of teeth), halted tooth development (microdontia), and anomalies affecting the hard tissues of the teeth (enamel, dentin, cementum) are all examples of dental abnormalities.

Primary objective

- To investigate the effects of some regularly used drugs on the developing dental tissues of fetus during pregnancy.

Secondary objective

- To look into possible problems with the way mineralized dental tissues develop.
- To explain how certain drugs should be used during pregnancy.
- To find new directions for research.

Review of Literature

Congenital abnormality: The problem of congenital anomalies must be taken very seriously. Malformations can occur in the developing tissues of any area of the body when exposed to certain environmental factors They occur often; 5% of the population is affected by them annually. Chromosome abnormalities and other forms of inheritance are responsible for some of them. Infections like rubella and drugs taken by the mother during pregnancy are examples of environmental variables that can cause birth defects. Malformations of the heart and the lips and palate that result from them are just two examples (The New Penguin Encyclopedia 2003). Many birth defects that appear in the head and neck have their origins in the branchial apparatus's transition into fully formed adult tissues. Congenital abnormalities of the face and palate can occur as a result of a failure of fusion between prominences and processes during development, which is a very delicate process (Moore 1982a). Disrupted

morphogenesis, during which the organic structures are not yet complete, is the cause of gross anatomical deformities, as stated by Das (2003). The most dangerous period of fetal development is between the ages of 18 and 55 days. One dysmorphogenetic substance can cause many malformations in different tissues by disrupting simultaneous organization.

Defects in the teeth's structure: Amelogenesis imperfecta is a syndrome caused by mutations in the genes that code for proteins found in the enamel matrix. Enamel hypoplasia, enamel hypo mineralization, and enamel hypo maturation all contribute to the classification process. Teeth can have a smooth, rough, or pitted appearance (Cawson and Odell 2002). There is a primary deficiency in matrix production in hypoplastic amelogenesis imperfecta. The enamel has a normal structure upon eruption, but is opaque, white to brownish yellow, and affected by hypo maturation amelogenesis imperfecta. Mottled fluoride effects, as opposed to the severely hypocalcified kind, are visible on the teeth (Cawson and Odell 2002).

Amelogenesis imperfecta with hypocalcification occurs when a typical amount of enamel matrix is generated but the matrix itself is not well calcified. The enamel's thickness and shape are typical, but it has a distinctly thin, opaque, or chalky look (Cawson and Odell 2002). Lamellae of enamel are tiny, leaf-like projections that go from the enamel surface to the dentin enamel junction. They are mostly organic, with a negligible mineral content (Bhasker 2003).

Developmental abnormalities in tooth size

Microdontia: This word refers to teeth that are smaller than usual. There are three types of microdontia; True generalised microdontia: Every tooth is smaller than usual. The teeth are said to be well-shaped but small (Rajendran 2006). Relative generalised microdontia: When normal teeth or teeth that are just a little bit smaller than normal are present in the jaw, it looks like the person has true microdontia. Rajendran (2006). (2006). When only one tooth is affected by microdontia: It happens to a lot of people. Most of the time, it affects the lateral incisor on the upper jaw and the third molar. Most people are born without these two teeth. One of the most common types of localised microdontia is the "peg lateral," which affects the maxillary lateral incisor (Rajendran 2006).

Macrodontia: It's the opposite of having small teeth. There are more teeth than usual. Teeth can be grouped the same way microdontia can. True generalised macrodontia is when all of a person's teeth are bigger than usual (Rajendran 2006). Relatively generalised macrodontia: This is more common and happens when small jaws have normal-sized or slightly bigger-than-normal teeth. The difference in size makes it look like macrodontia (Rajendran 2006). Single-tooth malocclusion: It doesn't happen very often, but it does happen sometimes. The tooth might look normal in every way except for how big it is (Rajendran 2006).

Numerical abnormalities: There may be one or more extra teeth, or the normal number of teeth may not form. Most extra teeth show up in the maxillary incisors, where they interfere with the normal teeth's position and growth. Most of the time, the extra teeth come in after the normal ones (Moore 1982b).

Partial anodontia: It is often in the genes to be born without one or more teeth (Moore 1982b).

Total anodontia: No teeth develop, a condition that occurs extremely rarely. Consistent associations with congenital ectodermal dysplasia have been found (Moore 1982b). Caps and teeth during birth: Rarely, only one or two of the mandibular incisors will erupt at birth (Moore 1982b). Teeth that are fused or linked are the result of a tooth bud separating or two tooth buds combining in part. This is usually seen in the mandibular incisors of the first set of teeth (Moore 1982b). Teeth that aren't white: This happens when foreign substances get into the enamel while it's developing (Moore 1982b).

Developmental defects: In terms of teratologic and toxic consequences of drugs, Giacoia and Mattison (2008) divided the fetal development process into three stages:

First, a fetotoxic substance can cause the death of an embryo during the time it is undergoing fertilisation and implantation (days 0–17).

The most sensitive time for the development of abnormalities is during organogenesis (days 18-55).

Drugs can reduce cell size and quantity or alter the structure of cerebral cortical layers throughout the third trimester (from week 56 to birth).

Children are more likely to have problems with the way the enamel develops on their primary teeth. Enamel formation is known to be affected by a number of systemic variables. Potentially linking some of these is issues with calcium use in the body (Bhat and Nelson 1989). Acceleration of mineralization in outer enamel, a form of enamel malformation, was found to be produced by a disruption in the cellular regulation of calcium transport under extremely hazardous conditions by Sato et al. (1996), who used anti-microtubular drugs. In a 1997 paper, Zhang et al. considered the possibility of a paracrine/autocrine role for growth hormone or a protein comparable to growth hormone in fetal tooth development. Both enamel opacity and enamel hypoplasia were found to be strongly associated to the presence of dental caries in a study by Zheng et al. (1998). Several growth factors and extracellular matrix molecules were studied by about and Mitsiadis (2001), who found that they were first expressed in developing teeth and were later found to be upregulated in sick dental tissues.Variable calcification during certain stages of growth can cause many structural problems in the teeth of primates. Most of the time, the breaks were areas of low mineralization in the enamel, called Striae of Retzius and Hunter Shreger bands. The differences were caused by differences in the calcifying properties of their diets, which led to differences in their overall health (Molnar and Ward 2005). Wozniak et al. (2005) said that because enamel doesn't change, any changes that happened to it while it was forming are permanently written on the tooth surface. Developmental changes in enamel often showed up as differences from the way tooth enamel usually looks, which is clear. Based on how the defects looked from a distance, they put them into four groups: hypoplasia, demarcated opacities, diffuse opacities, and discolored enamel. They looked at premolars from sites in the south-west of Poland that had been dug up by archaeologists. Defects were looked for on the buccal, lingual, and occlusal surfaces of the mouth. Paine and Snead (2005) wrote about how amylogenic self-assembly is a crucial part of making a good enamel organic matrix. Changes to the matrix led to problems in the way the structure of the enamel was put together. Moradian-Oldak and Goldberg (2005) said that tooth enamel is made in the space between cells, in an organic matrix that is rich in amylogenic proteins. The assembly of amylogenic nanospheres was a key factor in controlling how the crystals of enamel apatite grew and how they were arranged. Researchers found a link between dental caries and problems with the enamel (hypoplasia, demarcated opacity, and dental fluorosis). Hoffmann et al (2007). Caries experience in permanent dentition was only linked to hypoplasia and demarcated opacity.

Adverse drug reactions: Like all other tissues in the body, dental tissues can be affected by certain drugs when they are in their early stages. Several examples of evidence can back up this idea. Flynt Jr.'s (1976) research on the birth defects linked to Thalidomide showed that the embryo sensitive period was between 34 and 50 days after the first day of the last period. Embryos that were exposed during this time were messed up, but those that were exposed outside of this time were not affected. Rubin suggested in 1986 that the drugs should be used during pregnancy in a careful way. No harm should come to the baby because of the drug, and no harm should come to either the mother or the baby because of a disease that is not being treated well enough. Rubin's (1998) research showed that drugs taken during pregnancy could hurt the fetus. However, of all the drugs that are used, only a few have been proven to hurt the fetus. The drugs could cause physical problems, like a cleft lip or spina bifida,

or problems with how the body works, like slowing growth. In the first 12 weeks or so, the major body parts are formed. Interfering with this process can lead to birth defects. If a drug is given after this time, it won't cause a major change in the way the body works. Drugs given to a pregnant woman can hurt the baby in many ways. Since no drug has no side effects at all, a lot of care should be taken when prescribing during pregnancy (Shehata & Nelson-Piercy 2000). It was also said that drug companies and the medical community should do everything they can to protect women and their unborn babies from both risks. Abdollahi and Radfar (2003) backed a study that said every drug can have bad effects, even when used in the way that is recommended or standard. Every organ and system in the body could be affected by a bad reaction to a drug. The mouth and structures around it may be affected. An oral infection caused by a drug can affect different parts of the mouth, such as the oral mucosa and tongue, periodontal tissues, dental structures, salivary glands, cleft lip and palate, and salivary glands. Abdollahi and Radfar (2003) said that knowing about the bad effects of drugs on the mouth can help doctors better diagnose oral diseases, give drugs, get patients to take their medicine as prescribed, and make people use drugs more wisely.

Das (2003) talked about some bad effects of drugs that are more likely to happen to babies and young children because they are not fully developed, are growing quickly, or have a disease that makes them more likely to be harmful. Tetracycline use has been linked to discolored teeth and slower bone growth, hepatotoxicity with aspirin or paracetamol, and a higher risk of Reye's syndrome after taking aspirin for a viral infection. According to a study by De Santis et al., about 1% of birth defects with known causes were caused by drug therapy (2004). It was suggested that the right way to use drugs, especially for women who are pregnant, could be a good way to stop the spread of HIV. It has also been said that figuring out if a drug caused a teratogenic effect in an animal experiment or in a person is a complicated process. Any drug that is known or thought to cause birth defects must only be used under strict medical supervision. Tredwin et al. (2005) said that many drugs can hurt teeth in some way. According to them, it was important for anyone prescribing these drugs to fully understand and know about any possible side effects and to prescribe them after carefully weighing the benefits against the risks. Liu et al. (2006) said that dental professionals are usually in charge of oral health care. Therapeutic agents have been sent to the skeleton using systems that bind to biominerals. If those systems were used in the oral cavity. They thought that it would stick to the teeth and gums and make it easier for the drug to stay in the body. Brent and Fawcett (2007) found that about 10% of human birth defects were caused by the environment and less than 1% were caused by drugs, chemicals, or radiation. But birth defects caused by drugs and other medical treatments were important because the exposures might be avoidable. Briery and Morrison (2008) said that something could go wrong or develop during pregnancy that would make the pregnancy high risk. For example, pregnant women may be exposed to something that can cause birth defects (teratogens), like radiation, certain chemicals, drugs, or infections, or they may develop a disorder. Buhimschi et al. (2009) looked into the fact that almost every pregnant woman takes some kind of medicine while she is pregnant. Even though most pregnant and nursing women take prescription or over-the-counter drugs on a regular basis, only a few drugs have been specifically tested for safety and effectiveness during pregnancy. Even though there is evidence of possible teratogenicity, many drugs that are thought to be safe are still given.

Antibiotics: Antibiotic use was more likely to cause clear spots on the permanent first molars in the children who were affected, according to Jalevik et al (2001). It was also found that, except for tetracycline, no previous study has linked any other antibiotics to problems with the development of enamel (DDE). Crowley (2008) found that when a pregnant woman took the antibiotic tetracycline, it got into the developing teeth of the fetus. This slowed down the development of the teeth and turned the enamel a yellow-brown color. It wasn't clear that something was wrong until the teeth came in.

Fluoride: Dental fluorosis can develop if the fluoride ion concentration in a person's drinking water is higher than 2 parts per million (Parts per million), (Peter 2006). Montherrat-Carret et al. (1995) compared the total fluoride content of tooth germs and mandibular bone from fluoridated and non-fluoridated areas using chemical analysis and X-ray microanalysis to study the benefits of administering fluoride to pregnant women. It appeared that as fluoride levels in drinking water increased, fluoride levels in tooth germs and mandibular bone also increased. The overall quantities of phosphate and calcium in the mandibles and femurs of both populations were similar. Dental fluorosis is increasing, as reported by Kirkham et al. (2001). They examined and measured the surface properties of enamel crystals extracted from the incisors of fluorotic and control rats at various ages. Their data demonstrated that as control tissue expanded, crystal surfaces became smoother. Crystals grown from fluorotic tissue were much rougher and more amorphous than control crystals at every stage of development.

In 1979, researchers Berry and Nickols looked investigated the link between aspirin and birth abnormalities in rats exposed to high dosages of the drug. Drugs for potential teratogenic effects are tested in multi-species animal research, as was discussed. A dose-related effect on mouse tooth size was observed in an animal testing system at significantly lower concentrations. Gingival hyperplasia and hypertrophy, discoloration of the oral mucosa and teeth, oral ulceration and stomatitis, cervical lymphadenopathy, cleft lip and palate, blood dyscrasias, and bleeding from aspirin are just a few of the side effects of drugs that can affect the orofacial region that were discussed by Sapone et al. (1992).

. Parfitt (1999) said that when aspirin is taken during pregnancy, its possible side effects easily cross the placenta and have been shown to cause birth defects in animals. There have been reports of bleeding problems in babies whose mothers took aspirin while pregnant, as well as bleeding problems in mothers who took salicylates. Patients who are thought to have a high risk of abruption placentae or perinatal death because of their pregnancy. Cappon et al. (2003) looked at the nonsteroidal anti-inflammatory drug (NSAID) and found that rabbit fetuses exposed to the drug in utero had a small number of heart and spine problems. Acetylsalicylic acid has been studied a lot in rats, and it has always increased the number of heart defects and midline closure problems that happen rarely. Also showed that acetylsalicylic acid did not cause birth defects in rabbits, unlike rats, even when given in high doses on a single day during certain stages of development. Aspirin can do a lot of damage to both hard and soft tooth tissues (Pravda 2004).

Effect of drugs on the size of teeth during development: Microdontia and macrodontia, which are birth defects of the teeth, can happen in newly grown teeth. No one knows what caused this condition. Smith and Nanci's (1989) research showed that the linear distance from the end of the socket to the same molar reference line increased as body weight went up, while the linear distance from the ramus to a reference line reflected from the first and second molars decreased by a large amount as body weight went up. Risnes et al. (2005) found that the dental enamel of Tabby phenotype cats had problems with how they grew and developed. There were differences in the number, size, and shape of the teeth. Tabby mice had more variation in every size that was measured. In wild-type mice, the upper incisors were wider, while the lower incisors were wider.

MATERIAL AND METHODS

Adult female rabbits were used in this study. They were given three different kinds of drugs: aspirin, oestrogen, and lithium. For the study, the teeth of the children who had been given the drugs were used to try to figure out what happened when the drugs were given to the babies while they were still in the womb. Nonhuman primates were used more and more as a non-rodent animal model

in preclinical toxicology and safety testing because they are similar to humans and can be used as a good comparison. The validity of the nonhuman primate models applies to many parts of toxicological testing. This is especially true for the evaluation of reproductive toxicology and developmental toxicology, as described by Buse et al (2003). Oshiro et al. (2007) say that human teeth are usually used for in vitro studies. Bovine teeth, on the other hand, are used because they are easy to get in large numbers, are in good shape, and have less variation in their makeup than human teeth. People say that the mineral distribution in carious lesions in bovine teeth is similar to that in human teeth, and that the structural changes in both types of teeth are the same. Animal models are the best way to figure out how bad things happen to a fetus, according to Giacoia and Mattison (2008).

RESULTS OF ANALYSIS

Effect of drugs on the size of the developing teeth: The teeth were measured (except for the third molars in the maxilla and mandible), and their volumes were calculated for both the treated and the control groups. There were (n=7) people in each group. Then, the volume (mm3) of 672 samples taken in three directions (cervico-incisal/occlusal, mesio-distal, and labio/bucco-lingual) was measured and analyzed.

Table 1a:

Group	N (n=7)	T-1(n=7)	P-Value	Remarks
Mean ± sd	28.14 ± 11.90	25.14 ± 10.49	0.62	Insig.

Table 1b:

Group	N (n=7)	T-2(n=7)	P-Value	Remarks
Mean ± sd	28.14 ± 11.90	20.68 ± 6.15	0.16	Insig.

Table 1c:

Group	N (n=7)	T-3(n=7)	P-Value	Remarks
Mean ± sd	28.14 ± 11.90	24.0 ± 8.61	0.47	Insig.

Z— Control group, T-1—Treatment with Aspirin, T-2—Treatment with Estrogen, T-3 Treatment with Lithium

Table 2a:

Group	N (n=7)	T-1(n=7)	P-Value	Remarks
Mean ± sd	2.14 ± 0.37	3.14 ± 0.37	0.00	Sig.

Table 2b:

Group	N (n=7)	T-2(n=7)	P-Value	Remarks
Mean ± sd	2.14 ± 0.37	2.00 ± 0.00	0.33	Insig.

Table 2c:

Group	N (n=7)	T-3(n=7)	P-Value	Remarks
Mean ± sd	2.14 ± 0.37	2.50 ± 0.50	0.15	Sig.

N—Control group, T-1—Treatment with Aspirin T-2—Treatment with Estrogen T-3—Treatment with Lithium

Table 3a:

Group	N (n=7)	T-1(n=7)	P-Value	Remarks
Mean ± sd	16.21 ± 5.03	18.21 ± 7.46	0.56	Insig.

Table 3b:

Group	N (n=7)	T-2(n=7)	P-Value	Remarks
Mean ± sd	16.21 ± 5.03	17.36 ± 8.98	0.77	Insig.

Table 3c:

Group	N (n=7)	T-3(n=7)	P-Value	Remarks
Mean ± sd	16.21 ± 5.03	15.52 ± 8.82	0.85	Insig.

N—Control group, T-1—Treatment with Aspirin, T-2—Treatment with Estrogen, T-3—Treatment with Lithium

Aspirin treated group: Maxillary Central Incisor have (Mean ± SD) 25.14 ± 10.49 as compared to the control, which is 28.14 ± 11.90 with the P-value 0.62 _ 0.05. (Table: 1.1.1.a. Fig: 1.1.1.a. & Fig: 1.1.1.b.) Maxillary Lateral Incisor showing (Mean ± SD) 3.14 ± 0.37, the control is 2.14 ± 0.37 with the P- value 0.00 _ 0.05.

(Table: 1.1.2.a. Fig: 1.1.2.a. & Fig: 1.1.2.b.) Maxillary first Premolar have (Mean ± SD) 18.21 ± 7.46, the control is 16.21 ± 5.03 with the P-value 0.56 _ 0.05.

(Table. 1.1.3.a. Fig: 1.1.3.a. & Fig: 1.1.3.b.) Maxillary second Premolar have (Mean ± SD) 18.64 ± 3.00, the control is 19.78 ± 6.63 with the P-value 0.68 _ 0.05.

(Table: 1.1.4.a. Fig: 1.1.4.a. & Fig: 1.1.4.b.) Maxillary third Premolar have (Mean ± SD) 20.21 ± 3.78, the control is 15.36 ± 5.36 with the P-value 0.07 _ 0.05.

(Table: 1.1.5.a. Fig: 1.1.5.a. & Fig: 1.1.5.b.) Maxillary first Molar have (Mean ± SD) 17.64 ± 4.67, the control is 15.00 ± 5.12 with the P-value 0.33 _ 0.05.

(Table: 1.1.6.a. Fig: 1.1.6.a. & Fig: 1.1.6.b.) Maxillary second Molar showing (Mean ± SD) 15.71 ± 5.93, the control group is 8.57 ± 4.01 with a P- value 0.02 _ 0.05.

(Table: 1.1.7.a. Fig: 1.1.7.a. & Fig: 1.1.7.b.) Mandibular Incisor have (Mean ± SD) 33.14 ± 5.11, the control is 38.14 ± 7.75 having a P-value 0.18 _ 0.05.

(Table: 1.1.8.a. Fig: 1.1.8.a & Fig: 1.1.8.b.)

Mandibular first Premolar have (Mean ± SD) 25.32 ± 7.99, the control is 26.36 ± 9.15 with the P-value 0.82 _ 0.05.

(Table: 1.1.9.a. Fig: 1.1.9.a. & Fig: 1.1.9.b.). Mandibular second Premolar have (Mean ± SD) 13.86 ± 3.18, the control is 10.66 ± 4.19 with the P-value 0.13 _ 0.05.

(Table: 1.1.10.a. Fig: 1.1.10.a. & Fig: 1.1.10.b.) Mandibular first Molar have (Mean ± SD) 12.57 ± 2.50, the control is 10.12 ± 2.59, with the P-value 0.09 _ 0.05.

(Table: 1.1.11.a. Fig: 1.1.11.a & Fig: 1.1.11.b.) Mandibular second Molar showing (Mean ± SD) 10.86 ± 1.79, the control is 7.77 ± 3.27, with the P- value 0.04 _ 0.05.

(Table: 1.1.12.a. Fig: 1.1.12.b. & Fig: 1.1.12.b.)

Statistically maxillary lateral incisors revealed significant difference in the volumes the aspirin treated groups, which seemed to be larger as compared with the control ones, having the P-value, 0.00 _ 0.05.

(Table: 1.1.2.a. Fig: 1.1.2.a. & Fig: 1.1.2.b.) Maxillary and mandibular second molars were also showing significant difference which appeared comparatively larger than the control group

with the P-values 0.02 _ 0.05 and 0.04 _ 0.05 respectively.

(Table: 1.1.7.a. Fig: 1.1.7.a. & Fig: 1.1.7.b.) and (Table: 1.1.12.a.

Fig: 1.1.12.a. & Fig: 1.1.12.b.).

Estrogen treated group: Maxillary Central Incisor have (Mean ± SD) 20.68 ± 6.15, the control is 28.14 ± 11.90 with the P-value 0.16 _ 0.05.

(Table: 1.1.1.b. Fig: 1.1.1.a. & Fig: 1.1.1.b.) Maxillary Lateral Incisor have (Mean ± SD) 2.00 ± 0.00, the control is 2.14 ± 0.37, with the P-value 0.33 _ 0.05.

(Table: 1.1.2.b. Fig: 1.1.2.a. & Fig: 1.1.2.b.) Maxillary first Premolar have (Mean ± SD) 17.36 ± 8.98, the control is 16.21 ± 5.03 with the P-value 0.77 _ 0.05.

(Table: 1.1.3.b. Fig: 1.1.3.a. & Fig: 1.1.3.b.) Maxillary second Premolar showing (Mean ± SD) 12.82 ± 4.87, the control is 19.78 ± 6.63, with the P- value 0.04 _ 0.05.

(Table: 1.1.4.b. Fig: 1.1.4.a. & Fig: 1.1.4.b.) Maxillary third Premolar have (Mean ± SD) 12.12 ± 5.53, the control is 15.36 ± 5.36 with the P-value 0.28 _ 0.05.

(Table: 1.1.5.b. Fig: 1.1.5.a. & Fig: 1.1.5.b.) Maxillary first Molar have (Mean ± SD) 12.75 ± 4.37, the control is 15.00 ± 5.12 with the P-value 0.39 _ 0.05.

(Table: 1.1.6.b. Fig: 1.1.6.a. & Fig: 1.1.6.b.) Maxillary second Molar have (Mean ± SD) 8.68 ± 4.91, the control is 8.57 ± 4.01 with the P-value 0.96 _ 0.05.

(Table: 1.1.7.b. Fig: 1.1.7.a. & Fig: 1.1.7.b.) Mandibular Incisor have (Mean ± SD) 33.04 ± 3.69, the control is 38.14 ± 7.75 with the P-value 0.14 _ 0.05.

(Table: 1.1.8.b. Fig: 1.1.8.a. & Fig: 1.1.8.b.)

Mandibular first Premolar have (Mean ± SD) 24.18 ± 4.38, the control is 26.36 ± 9.15 with the P-value 0.58 _ 0.05.

(Table: 1.1.9.b. Fig: 1.1.9.a. & Fig: 1.1.9.b.) Mandibular second Premolar have (Mean ± SD) 11.14 ± 3.92, the control is 10.66 ± 4.19 with the P-value 0.82 _ 0.05.

(Table: 1.1.10.b. Fig: 1.1.10.a. & Fig: 1.1.10.b.) Mandibular first Molar have (Mean ± SD) 8.66 ± 4.63, the control is 0.12 ± 2.59 with the P-value 0.48 _ 0.05.

(Table: 1.1.11.b. Fig: 1.1.11.a. & Fig: 1.1.11.b.) Mandibular second Molar have (Mean ± SD) 6.54 ± 5.38, the control is 7.77 ± 3.27 with the P-value 0.61 _ 0.05.

(Table: 1.1.12.b. Fig: 1.1.12.a. & Fig: 1.1.12.b.)

Volumes of maxillary second premolars have a significant difference and appeared smaller than all the other treated groups with the P-value 0.04 < 0.05. (Table: 1.1.4.b. Fig: 1.1.4.a. & Fig: 1.1.4.b.)

All the other maxillary and mandibular teeth have insignificant difference in the volumes of estrogen treated group compared to the control group.

Lithium treated group: Maxillary Central Incisor have (Mean ± SD) 24.0 ± 8.61, the control is 28.14 ± 11.90, with the P-value 0.47 _ 0.05.

(Table: 1.1.1.c. Fig: 1.1.1.a. & Fig: 1.1.1.b.) Maxillary Lateral Incisor have (Mean ± SD) 2.50 ± 0.50, the control is 2.14 ± 0.37 with the P-value 0.15 _ 0.05.

(Table: 1.1.2.c. Fig: 1.1.2.a. & Fig: 1.1.2.b.) Maxillary first Premolar have (Mean ± SD) 15.52 ± 8.82, the control is 16.21 ± 5.03 with the P-value 0.85 _ 0.05.

(Table: 1.1.3.c. Fig: 1.1.3.a. & Fig: 1.1.3.b.)

Maxillary second Premolar have (Mean ± SD) 15.53 ± 6.34, the control is 19.78 ± 6.63, with the P-value 0.24 _ 0.05.

(Table: 1.1.4.c. Fig: 1.1.4.a. & Fig: 1.1.4.b.) Maxillary third Premolar have (Mean ± SD) 11.36 ± 5.53, the control is 15.36 ± 5.36 with the P-value 0.19 _ 0.05.

(Table: 1.1.5.c. Fig: 1.1.5.a. & Fig: 1.1.5.b.)

Maxillary first Molar have (Mean ± SD) 10.92 ± 3.56, the control is 15.00 ± 5.12, with the P-value 0.11 _ 0.05.

(Table: 1.1.6.c. Fig: 1.1.6.a. & Fig: 1.1.6.b.) Maxillary second Molar have (Mean ± SD) 7.57 ± 3.81, the control is 8.57 ± 4.01, with the P-value 0.64 _ 0.05.

(Table: 1.1.7.c. Fig: 1.1.7.a. & Fig: 1.1.7.b.)

Mandibular Incisor have (Mean ± SD) 34.52 ± 8.01, the control is 38.14 ± 7.75 with the P-value 0.40 _ 0.05.

(Table: 1.1.8.c. Fig: 1.1.8.a. & Fig: 1.1.8.b.) Mandibular first Premolar have (Mean ± SD) 27.71±14.73, the control is 26.36 ± 9.15, with the P-value 0.83 _ 0.05.

(Table: 1.1.9.c. Fig: 1.1.9.a. & Fig: 1.1.9.b.)

Mandibular second Premolar have (Mean ± SD) 12.00 ± 3.17, the control is 10.66 ± 4.19 with the P-value 0.51 _ 0.05.

(Table: 1.1.10.c. Fig: 1.1.10.a. & Fig: 1.1.10.b.) Mandibular first Molar have (Mean ± SD) 10.66 ± 3.95, the control is 10.12 ± 2.59, with the P-value 0.77 _ 0.05.

(Table: 1.1.11.c. Fig: 1.1.11.a. & Fig: 1.1.11.b.) Mandibular second Molar have (Mean ± SD) 9.00 ± 4.01, the control is 7.77 ± 3.27 with the P-value 0.54 _ 0.05.

DISCUSSION

The developmental defects of teeth, expected to be caused by the selected drugs for the study (aspirin, estrogen and lithium), were thoroughly searched and studied in the published literature. There was a dearth of studies showing the effects of commonly used medicines on the dental tissues. It was useful to review the prior art and categorize it, using the parameters for the analysis in this work. It is through such scrutiny that the gaps in the knowledge become apparent.

CONCLUSION

Public and dentists have become aware of the impact of facial aesthetics, which is related to the dentition and facial tissues. The dentofacial abnormality may cause psychological disturbances in children. It is therefore important to understand the etiological factors responsible for the developmental defects of dental tissues. Few drugs identified in the previous literature are definitely teratogenic in human dentition. We have selected some commonly used drugs in this study to investigate and gain a better understanding of their gross morphological consequences on the dental tissues and the treatment needs of this condition. It was hypothesised that by treating the rabbits with these selected drugs, the changes in dental structure will occur. There are various congenital dental defects attributed by this study that can be classified quantitatively and qualitatively. Quantitative information is provided by analysis of the mineral contents of teeth. Visual examination for dimensional measurements and gross morphological appearances by the scanning electron microscope (SEM) regarding the ultrastructure of the enamel provides qualitative understanding. The dentitions of the treated and non-treated controls, were examined.

By carefully measuring the dimensions, it was not possible to identify, except in few areas, any gross morphological effects of drugs on the dental development. It was found that dental asymmetries in size are more apparent in the posterior teeth as compared to the anterior ones. In addition, no significant differences were detected within the experimental group, regarding the chemical composition of teeth with some exceptions e.g. aspirin indicated the effect on mandibular teeth and estrogen and lithium have a least effect on all the premolars and tending to exhibit the effects on incisors and molars. So it can be concluded that the incisors and molars are esthetically and functionally compromised teeth. The nature of the insult is unlikely to be determinable. These results are generally not in accordance with the predicted outcome. A variety of factors might also have implications for the development of teeth i.e. general health, malnutrition and febrile diseases. It is important to establish that this study does not necessarily

Prove that the in utero exposure to these drugs does not cause any unwanted variations in the teeth of the offspring. A key finding of this work is that the methods utilized in this study require a sample set that is several times larger to achieve statistical significance. There is a need for well-designed studies for further investigation regarding the relationship between drug related response to the defects of teeth and its clinical appearance and treatment needs of this condition. However, malformations caused by drugs are important because these exposures may be preventable. Therefore, an efficacious preventive action for these defects is possible, the drugs involved are well known in the medical field and should be used by doctor's prescription, especially during pregnancy avoiding in every way the possibility of selfmedication, which could ultimately result in teratogenic effect on the dentition of the new borns. Furthermore to achieve the esthetic and functional goals, the problem oriented logical treatment plan is especially useful.

REFERENCES

1. Abdollahi M, and Radfar M. A review of drug-induced oral reactions. J Contemp Dent Pract. 2003; 4(1): 10-31.
2. Abdollahi M, Rahimi R, and Radfar M. Current opinion on drug-induced oral reactions: a comprehensive review. J Contemp Dent Pract. 2008; 9(3): 1-15.
3. Berry CL, and Nickols CD. The effects of Aspirin on the Development of the Mouse Third Molar. Arch. Toxicol. 1979; 42: 185-190.
4. Bhat M, and Nelson KB. Developmental enamel defects in primary teeth in children with cerebral palsy, Mental Retardation, or Hearing Defects. Adv. Dent. Res. 1989; 3(2): 132-142.
5. Bhasker SN. Enamel. In: Orban's Oral histology and embryology. (Bhasker SN (ed). 2003; 11th edition. 49-105.
6. Briery CM, and Morrison J. Risk factors that develop during pregnancy. Pregnancy at High-Risk. Women's Health Issues. The Merck Manuals. 2008;
7. Brent RL, and Fawcett LB. Developmental toxicology, drugs, and fetal teratogenesis. In: Clinical Obstetrics: The Fetus and Mother. Reece EA, and Hobbins JC (eds.) 2007; 3rd edition,. 15: 217-235. Blackwell Publishing Inc., Malden MA.

8. Buhimschi, Catalin S, Weiner, and Carl P. Medications in pregnancy and lactation: Part 1. Teratology. Obstetrics & Gynecology. January 2009 ;113 (1): 166-188.
9. Buse E, Habermann G, Osterburg I, Korte R and Weinbauer GF. Reproductive/developmental toxicity and immunotoxicity assessment in the nonhuman primate model. Toxicology. 2003; 185 (3): 221-227.
10. Cawson RA, and Odell EW. Disorders of development of the teeth and related tissues. In: Cawson's Essentials of Oral Pathology and Oral medicine. (Cawson RA, Odell EW and Porter S. (eds) 2002; 7th edition. 18-35.
11. Cappon G D, Gupta U, Cook J C, Tassinari M S and Hurtt M E. Comparison of the developmental toxicity of aspirin in rabbits when administered throughout organogenesis or during sensitive windows of development. Birth defects research. reproductive toxicology. 2003; 68(1): 38-46.
12. Das PK. Geriatric, Paediatric and Perinatal Pharmacology. In: Pharmacology. (Das PK, (ed). 2003; 2nd edition. 501-523.
13. Flynt Jr. JW. Techniques for assessing teratogenic effects: epidemiology. Environmental Health Perspectives. 1976; 18: 117-123.
14. Giacoia, G, and Mattison, D. Glob. libr. women's med. 2008; ISSN: 1756-2228.
15. Hoffmann RH, de Sousa Mda L, and Cypriano S. Prevalence of enamel defects and the relationship to dental caries in deciduous and permanent dentition in Indaiatuba, São Paulo, Brazil. Cad Saude Publica. 2007; 23(2): 435-44.
16. Jalevik B, Noren JG, Klingberg G, and Barregård L. Etiologic factors influencing the prevalence of demarcated opacities in permanent first molars in a group of Swedish children. Eur J Oral Sci. 2001; 109(4): 230-4.
17. Kirkham J, Brookes SJ, Zhang J, Wood SR, Shore RC, Smith DA, Wallwork ML, and Robinson C. Effect of Experimental Fluorosis on the Surface Topography of Developing Enamel Crystals. Caries Res. 2001; 35(1): 50-56.
18. Moradian-Oldak J, and Goldberg M. Amelogenin supra-molecular assembly in vitro compared with the architecture of the forming enamel matrix. Cells Tissues Organs. 2005; 181 (3-4): 202-18.
19. Montherrat-Carret L, Perrat-Mabilon B, Barbey E, Bouloc R, Boivin G, Michelet A, and Magloire H. Chemical and X-ray analysis of fluoride, phosphorus, and calcium in human fetal blood and hard tissues. Arch Oral Biol. 1996; 41(12): 1169-78.
20. Nanci A. Enamel: Composition, Formation, and Structure. In: Ten Cate's Oral Histology. Development, Structure and function. (Nanci A (ed). 2008; 7th edition., 141-190. Mosby Elsevier.
21. Oshiro M, Yamaguchi K, Takamizawa T, Inage H, Watanabe T, Irokawa A, Ando S, and Miyazaki M. Effect of CPP-ACP paste on tooth mineralization: an FE-SEM study. Journal of Oral Sciences. 2007; 49(2): 115-120.
22. Peter S. Fluorides in Preventive Dentistry. In: Essentials of Preventive and Community Dentistry. (Peter S (ed). 2006; 3rd edition, 270-358.
23. Koren G. Special aspects of Perinatal & Pediatric Pharmacology. In: Basic and clinical Pharmacology. (Katzung BG, (ed) 2007; 10th edition. 971-982. The McGraw-Hill companies USA.
24. Moore KL. The Integumentary system. In: The Developing Human. Clinically oriented embryology. (Moore KL. (ed). 1982b; 3rd edition. 432-446.
25. Molnar S, and Ward SC. Mineral metabolism and microstructural defects in primate teeth. American Journal of Physical Anthropology. 2005; 43(1): 3-17.
26. Ogura H, and Ohya K. Physiology and Pharmacology of hard tissues-effect of chemicals on the formation and the resorption mechanism of tooth and bone. Nippon Yakurigaku Zasshi. 1995; 105(5): 305-18.
27. Parfitt K. Analgesics Anti-inflammatory Drugs and Antpyretics. In: Martindale. The complete drug reference. (Parfitt K. (ed). 1999; 32 nd edition. 1-91.
28. Roberts II LJ, and Morrow JD. Analgesic-Antipyretic and Antiinflammatory agents and drugs employed in the treatment of gout. In: Goodman & Gilman's. The Pharmacological Basis of Therapeutics. (Hardman JG, Limbird LE, Gilman AG (eds). 2001; 10th edition. 687731. McGraw-Hill companies USA.
29. Rajendran R. Developmental disturbances of oral and paraoral structures. In: Shafer's Text book of Oral Pathology. (Rajendran R, and Sivapathasundharam B.(eds). 5th edition. 2006; 3-112.
30. Rubin PC. Prescribing in pregnancy. Medical practice. British Medical Journal. 1986; 293:
31. Risnes S, Peterkova R, and Lesot H. Distribution and structure of dental enamel in incisors of Tabby mice. Arch Oral Biol. 2005; 50(2): 181-4.
32. Sapone A, Basaglia R, and Biagi GL. Drug-induced changes in teeth and mouth. Clin Ter. 1992; 140 (6): 575-83.
33. Smith CE, and Nanci A. A method for sampling the stages of Amelogenesis on mandibular rat incisors using the molars as a reference for dissection. The Anatomical Record. 1989; 225: 257-266
34. Shehata HA and Nelson-Piercy C. Drugs to avoid in pregnancy. Current Obstetrics & Gynaecology. 2000; 10: 44-52.
35. Tredwin CJ, Scully C, and Bagan-Sebastian JV. Drug-induced disorders of teeth. J Dent Res. 2005; 84(7): 596-602.
36. Wozniak K, Lagocka R, Lipski M, Tomasik M, Buczkowska- Radlinska J, and Chlubek D. Changes in developmental defects of dental enamel within the space of centuries. Durham Anthropology Journal. 2005; 12 (2-3):
37. Zheng S, Deng H, and Gao X. Studies on developmental enamel defects in the primary dentition of children with histories of low birth weight and prematurity and their susceptibility to dental caries. Zhonghua Kou Qiang Yi Xue Za Zhi. 1998; 33(5): 270-2.