Review Article

Emerging role of paediatric dentists in the management of children with teratogen-induced congenital disorders in India

Short running title: Paediatric dentists in teratogen-induced congenital disorders in India.

ABSTRACT

In present world, globalization and economic liberalization is at its peak and India has been a part of it since last decade. While many see the benefits of globalization, it has its ill-effects too. India has also witnessed a change in the trend of drinking and smoking where women have participated in large numbers and at will. The review focuses on the role of paediatric dentists in prenatal counseling of pregnant mothers on consumption of alcohol or tobacco and diagnosis and management of affected infants. Maternal abuse of substances poses threat to foetal growth and development, creating a burden on medical and social care. Embryopathies arising due to the teratogenic effects of alcohol and tobacco present a specific pattern of physical anomalies and reduced birth size among the neonates along with characteristic facial features and central nervous system disorders that cause cognitive and behavioural problems. The fact that there lies no specific cure and early intervention and limiting secondary disabilities being among the treatment options makes the condition worse. At present, large scale awareness programmes have been undertaken by the Indian Government, eg. Alcohol Atlas of India, banning of broadcasting tobacco advertisement, smoking in public places, etc. as dealing with substance-related disorders. Pedodontists should not limit themselves in just spreading awareness amongst women of child bearing age but should also be updated with latest diagnostic tools and treatment strategies so as to provide the required symptomatic and rehabilitative treatment.

Keywords

Teratogen, embryopathy, congenital malformations, teratogenic malformations, pediatrics.

INTRODUCTION

The epidemiological evolution in India has led to the identification of birth defects as a leading cause of infant mortality in the recent years.[1] Contrary to the previous era where communicable diseases, low birth weight, premature labor and sepsis were focused on to diminish infant and childhood mortality rates, the spotlight is now on congenital birth defects, their varying etiology, prevention strategies and management.[1,2]

March of Dimes (2006) defined birth defects as 'the presence of a structural or functional abnormality that is present at birth and has medical, social or cosmetic consequences. It includes structural malformation(s), inborn errors of metabolism, single gene disorders, developmental disabilities, intrauterine growth retardation (IUGR) and prematurity.'[3] The global report estimated that India has the largest number of infants born with birth defects in the world.[2] The National Health Portal of India reports an annual prevalence of 6-7% which approximates to 1.7 million birth defects a year.[4] A recent systematic review that took account of 802,658 births concluded the pooled prevalence of the same to be 184.48 per 10,000 births.[5] The etiology of such anomalies may be genetic, environmental or an interplay of both. Risk factors like advanced maternal age, compromised nutritional status of the mother, infections during gestation, uncontrolled maternal diabetes and exposure to teratogenic drugs may contribute to malformations in the fetus.[6]

A teratogen has been defined as an exposure in pregnancy that has a harmful fetal effect.[7] The resultant defect is due to an interaction between the genes of the embryo and the

teratogen itself. The effect produced, depends on the stage of formation of the fetus[8] (Table 1).

Table 1: Relationship between stage of fetal development and teratogen susceptibility

Phases of prenatal development	Susceptibility to teratogen	Related cause
Fertilization – 2 weeks (ovular / germinal period)	Relatively low; safe time for embryo regarding teratogenic exposure	It is the 'all or none' period, where an insulting agent can either cause death of the zygote or intact survival. The safety of the undifferentiated zygote is attributed to the presence of totipotent cells that have the capacity to repair and regenerate the lost cells. However, malformation may occur if the teratogenic agent persists in the body beyond this period.
3 weeks – 8 weeks (embryonic period)	Maximum sensitivity to teratogenicity. Gross structural defects may occur in this period.	It is the period of organogenesis; damage to the highly differentiating tissues is irreparable. Major malformational defects may arise depending on the amount and time of exposure.
9 weeks – 40 weeks (foetal period)	Sensitive to teratogenic exposure. Growth is affected.	It is the post – differentiation period, when growth and functional maturation of the already formed organs occur. A teratogenic exposure in this period can thus cause retardation of foetal growth and affect the functioning of an organ. The term foetal toxicity is commonly used to describe such an effect.

Drugs, radiation, heavy metals, environmental teratogens, intrauterine infections and maternal habits like alcohol abuse, tobacco consumption are some of the recognized human

teratogens.[7] Women willing to conceive, but with chronic medical conditions are often exposed to various drugs and their subsequent hazards, when used beyond threshold level. A study conducted on 200 pregnant women in Surat, India, reported that 8.5% of the sample was on self medication.[9] The teratogenic effects of drugs first surfaced in 1967 with the thalidomide tragedy, post which the FDA implemented labeling requirements in 1979 with the aim of providing evidence-based information about use of medication in pregnancy.[10]

The focus of Indian culture involving the use of psychoactive substances and alcohol abuse has been male gender sensitive in the past. But with globalization and economic liberation, females have been active participants in substance use and abuse. In a rapid assessment study of 4648 substance users in the community, 371 women substance users (7.9%) were identified.[11] A study focusing exclusively women with substance abuse, concentrated on 110 Non Governmental Organizations, surveyed more than 6000 women of which 86% of the sample belonged to urban population and mean age at onset of substance use was 30.5 years.[12] A national reproductive health survey in women s of 15-49 years showed an overall rising trend of female smoking with significant ($p < 0.001$) rise (1.4–2.9%) during the period 2005–2009. States with lower female literacy rates, such as Jammu and Kashmir, Uttar Pradesh, Arunachal Pradesh, Manipur, and Nagaland were shown to have higher prevalence of current female smoking.[13] The current smokeless tobacco use was less than 1% in most countries, but was found to be highly prevalent in Indian females (15%).[14] A high prevalence of smokeless tobacco use among pregnant women was observed with as many as 64% from an urban slum.[15] In a survey of 500 pregnant women, 33% reported tobacco use, mainly as tooth powder.[11] In multiple surveys prior to 2001, 20% of all women reported consuming some alcohol during pregnancy. Between 2002 and 2003, 9.3% of pregnant women reported use of some alcohol, with 4% reporting binge drinking. In 2005, 12% to 15% of pregnant women reported use of some alcohol, with 3% to 4% reporting binge drinking during

pregnancy.[16] Previously, alcohol use was confined to tribal women, women of lower socio-economic status, commercial sex workers and to a limited upper crust of the rich and not favored by women from the middle or upper socioeconomic classes. In another recent study alcohol use has been reported in 2.2% of Indian women of child-bearing age.[17] Rapid Assessment Study of drug use across 9 urban centres (Amritsar, Jamshedpur, Shillong, Dimapur, Hyderabad, Bangalore, Thiruvanthapuram, Goa and Ahmedabad), of 2831 drug users identified for a detailed interview, 251 (8.9%) were women. The study revealed different trends – younger, more educated women drug users, with unsafe injecting and unsafe sexual practices.[18] In 2013, global HIV prevalence among women who inject drugs was 13%, compared to 9% among men who inject drugs.[19]

One may argue the amount of intake of any teratogenic agent that might trigger the foetal malformation. Mills et al. suggests, pregnant women be told that anything less than one drink a day is "safe" as a safe level for malformations has not been established.[20] Smoking in the periconceptional period and early pregnancy results in teratogenic malformations in the foetus.[21] Illicit drugs themselves, or in conjunction with other drugs, act as a powerful teratogens during pregnancy. Drugs like thalidomide, aminopterin, tetracycline, retinoids, etc. have definite time frames during which an exposure will lead to a birth defect.

Congenital birth defects are huge public health concern. Patients with no lethal anomaly usually survive till later periods of life. However, there is no absolute cure and the patients live with the disability, with only supportive treatment. In most of the countries, medical teams are set up to provide comprehensive care to syndromic patients. Pediatric dentist, an important member of this team, works with the patient from the period of infancy through childhood to adolescence. Adult individuals with special health care needs are often managed by pediatric dentists. A recent study amongst Belgian dentists elaborated that they do not feel ‘comfortable’ treating patients with Down’s syndrome and in most cases refer the patients to

special care hospitals.[22] As pediatric dentist one should be well versed with the spectrum of birth anomalies arising due to particular teratogenic agents and their management strategies. The present article throws light on the teratogenic syndromes most commonly encountered in India and emphasizes on the diversified role of pedodontists in the management of such patients.

COMMON TERATOGENIC SYNDROMES

Foetal alcohol syndrome (FAS): Primarily characterized by central nervous system dysfunction, intrauterine growth retardation and characteristic facial appearance, FAS has been reported to have an incidence of 1 – 2 per 1000 live births.[23] The documentation of extensive maternal abuse of alcohol, lead to the placement of warning labels on liquor, beer and wine bottles as per the instructions of The United States Food and Drug Administration in 1977.[24] AE has been reported in every race and in many countries.[25] It is also very important to note that the teratogenic effects of alcohol can arise during any time in pregnancy.[26] Consumption of more than 1.6 ounces of absolute alcohol (AA) per day was found to be associated with stillbirths, low birth weights and other abnormalities in large survey of 9,236 women in France.[27] Similar results have been reported in other studies in women who were heavy drinkers (more than 1.5 ounces of AA per day and at least five drinks on occasion).[28,29] However, no significant difference has been found in infants born to mothers who have been moderate drinkers or rare ones.[28] A study shows clinically significant mental impairment in fetuses born to mothers drinking at least 0.5 ounces AA per day during pregnancy.[30]

General findings: Microcephaly is usually associated with FAS. Mental retardation, cerebellar dysplasias and neurologic impairment are amongst the commonly found CNS defects. Hyperactivity is often reported. Studies demonstrate IQ of children born to alcoholic

mothers to be as low as 16 or on an average below 80.[31] Cardiac anomalies include atrial and ventricular septal defects as well as congenital heart defects like patent ductus arteriosus; Skeletal anomalies include retarded bone age, copper-beaten skull, an increase in radio-ulnar and cervical vertebral fusions, hip dislocation, hypoplastic distal phalanges, and stippled epiphyses of the lower extremities; Hypoplasia of the optic nerve head and increased tortuosity of retinal vessels are extremely common; Most infants with FAS are growth deficient at birth for both length and weight.[20,25,,31,32,33]

Craniofacial findings: A comparatively flat mid-face, deficient mandible at birth, short palpebral fissures, hypoplastic upper lip, thin upper vermillion, hypoplastic philtrum, anteverted nostrils, posterior rotation of ear helix and increased intercanthal distance comprise of the characteristic facial features in FAS.[23,26,34] The characteristic facies have been reported to disappear with age.[35] This has been attributed to the growth of the retrussive mandible as compared to the midface in some patients with age resulting in an apparent prognathism in adolescence. Growth of the nasal bridge and morphological changes in the ala nasi has also been recorded in medical literature.[25,31]

Diagnosis: Infants with FAS present with a distinctive facial dysmorphology that is easily identifiable. A thorough maternal history inclusive of maternal age, pattern of drinking and other associated habits are to be taken into account to reach a precise diagnosis. Evidence of growth retardation and CNS neurodevelopmental anomalies are also included in the key diagnostic criteriae.[36]

Differential diagnosis: The superficial features of FAS have at times been confused with patients of Down's syndrome, de Lange syndrome and Noonan syndrome.[26,31]

Cocaine embryopathy: Cocaine, an alkaloid extracted from Erythroxylum coca plant, endogenous to South America, Mexico, Indonesia and West Indies, started gaining immense popularity as a recreational drug because of its euphoric effects in early 1900s. A hike in the

use of cocaine in the Indian subcontinent was noted in the 21st century, which still continues, and is currently a matter of national concern. Cocaine itself, or in conjunction with other drugs, can act as a powerful teratogen during pregnancy. The drug causes accumulation of neurotransmitters, norepinephrine and dopamine by blocking their re-uptake by nerve cells of CNS. Increased levels of norepinephrine, in turn causes the accumulation of cocaine at the nerve terminals resulting in constriction of maternal blood vessels and increased blood pressure at the placenta – uterus junction. This leads to reduced blood flow and deficient oxygen supply to the fetus as well as maternal conditions like tachycardia and ventricular arrhythmias leading to rupture of the amnion. Also, cocaine can readily cross the placenta owing to its low molecular weight, hydrophilic and lipophilic nature. Thus, the fetus starts swallowing the amniotic fluid infused with cocaine. Detrimental effects on the developing fetus accentuates not only because of the mentioned causes, but also due to the slower rate of metabolization of cocaine by the fetus. [37,38]

General and craniofacial findings: a study by fries et al. documents features that are present exclusively in cocaine embryopathy as neurologic irritability 71%, depressed nasal bridge 64%, periorbital oedema 57 %, large fontanelles 42 %, short mandible, low set ears, cleft palate, and anteverted nares all 21%, cleft lip 14 %, and cardiac abnormalities and short palpebral fissures 14% each.[39]

Clinical features often overlap as pregnant mothers consuming cocaine may also take other drugs and alcohol like depressed nasal bridge 83%, long philtrum 78%, periorbital oedema 72%, neurologic irritability 67%, thin upper lip 44%, small jaw 33%, flat supraorbital ridges 28%, ears low set and posteriorly rotated 28%, short palpebral fissures 22 %, hypotonic mouth and protuberant tongue 11%, narrow penis and umbilical hernia 11 %.

Abnormalities of the genitourinary tract have been significantly more common in cocaine exposed babies; apart from long term behaviour depression, CNS abnormalities like agenesis

of the corpus callosum and septum pellucidum, septo-optic dysplasia, schizencephaly, and neuronal heterotopias have also been reported; growth retardation, low birth weights and limb reduction defects are frequent.[40,41,42]

Diagnosis: A careful assessment of the presenting features of the affected infant and a thorough history obtained from the mother will provide major clues for diagnosis. Maternal blood / urine analysis and segmental hair analysis during early pregnancy can also indicate the use of toxic recreational drugs.[43]

Differential diagnosis: Alcohol embryopathy, retinoid embryopathy and syndromes with limb reductions are to be considered.

Diabetic embryopathy: Diabetic mellitus (DM), a metabolic disorder, characterized by high levels of circulating glucose in the body and absence / reduced production of insulin or dysfunction of insulin signaling, was designated as a teratogenic maternal condition nearly two centuries past the recognition of the disease, i.e. in early 1900s.[44] With the advent of insulin in 1920s and advances in perinatal care and neonatal management, the mortality rates had a sharp drop from 40 – 70% to nearly 12%.[45] The present birth defect rate associated with MDM is approximately 10% and is increasing with modernisation.[45] 7.5% of Indian females belonging to lower – middle income group were diagnosed with DM in 2016. However, a huge number has gone undiagnosed.[46] Pregestational diabetes has shown to have major adverse effects on the fetus than gestational diabetes.[44] Hyperglycaemia, hypoxia, ketone and amino acid abnormalities, as well as glycosylation of proteins and precipitation of free radicals, occurring during embryogenesis, at the end of blastogenesis and organogenesis, between 3rd and 7th weeks of gestation, have been widely reported as the teratogenic factors affecting molecular signaling pathways leading to malformations.[47,48] In fact, a lot of malformations are blastogenic in origin indicating that DM acts early in gestation.[44]

General findings: Congenital cardiovascular defects including atrial and ventricular septal defects, transposition of great vessels, pulmonary valve defects, Tetralogy of Fallot are commonly found. Holoprosencephaly is amongst the most common CNS abnormalities, others being encephaloceles, microcephaly and spina bifida. Anorectal atresia, renal agenesis, malrotation of bowel, femoral hypoplasia and club foot is also frequently reported.[44,45,49] The most commonly found feature is caudal regression characterized by varying degrees of vertebral anomalies from partial sacral agenesis to complete absence of the lumbosacral spine.[50]

Craniofacial findings: Significant micrognathia, thin upper lip, smooth long philtrum, upslanting palpebral fissures are some of the commonly reported features. Clefting of lip and palate is also frequently observed; other features include macrostomia, hemifacial microsomia, anotia / microtia, hearing defects, bifid tongue, choanal atresia, short nose, facial skin tags, frontonasal dysplasia and defects of the eye. [44,45,47,51] It is important to note that the craniofacial features are non-blastogenic malformations.

Diagnosis: A three – generation family history for a diabetic mother is must. Preconceptual Hb1Ac > 9% puts the fetus at high risk. Prenatal screening for chromosomal and structural defects, ultrasound examination of fetus starting from first month to check for fetal growth later and at 18 – 20 weeks for assessment of cardiac morphology should be done along with fetal echocardiography. Clefting of lip can be diagnosed by coronal scan images and that of palate by the axial scan of maxilla. Caudal regression syndrome can be diagnosed in the second trimester by sonography.[26]

Differential diagnosis: Femoral hypoplasia-unusual facies syndrome.

Folic acid antagonist embryopathy: Aminopterin gained popularity in 1950s as a folic acid antagonist but soon its use was discontinued due to its deleterious effects, including human teratogenicity.[26] Methotrexate, a methyl derivative of aminopterin, is widely used at present

to treat malignancies, inflammatory and rheumatic conditions, autoimmune disorders and dermatological entities.[52] It has also found its use in medical termination of pregnancy in the first trimester.[53] However, the use of Methotrexate later in pregnancy can cause malformational disorders in the newborn. The medical literature records approximately 60 such cases of aminopterin and Methotrexate embryopathy.[26] The folic acid antagonists act by inhibiting dihydrofolate reductase, thereby blocking the synthesis of thymidine and inhibiting DNA synthesis. The teratogenicity of Aminopterin and Methotrexate can be explained on the basis of its interference with rapidly dividing mitotic cells, leading to inhibition of cell growth.[53] The teratogenic exposure during 6 to 8 weeks of gestational period has been considered as critical.[52]

General findings: Short extremities, club foot, hypoplasia of phalanges and nails, syndactyly of fingers, partial ossification of bones, dextrocardia, spina bifida, hydrocephaly, varying degrees of mental retardation are the commonly associated malformations seen in folate antagonist embryopathies. [52,54,55]

Craniofacial findings: Craniosynostosis and large open fontanelles constitute an abnormal shape of the calvaria. Severe micrognathia and clefting of lip and palate are found along with hypertelorism, short palpebral fissures, hypoplasia of supraorbital ridges, low set ears, beaked nose, short smooth philtrum and at times a high arched palate. Widow's peak at the frontal hairline is a common finding. [52,54,55]

Diagnosis: It is usually based on maternal history and clinical examination. However, sonography during second and third trimesters remains the basis for antenatal diagnosis to detect intrauterine growth retardation and other malformations.

Differential diagnosis: Pierre Robin syndrome, Oromandibular limb-hypogenesis.[26]

Hydantoin embryopathy: Hydantoin or glycolylurea, is an oxidised derivative of imidazolidine, derivatives of which form a class of anticonvulsants, eg. phenytoin.

Approximately 10% of infants born to epileptic mothers treated with phenytoin during pregnancy suffer from Fetal Hydantoin syndrome.[56] The incidence of congenital defects is two to three times greater in children born to epileptic mothers receiving anti-epileptic drugs than in the children of non-epileptic mothers.[57] The exact etiopathogenesis is yet not known but there have been several hypotheses. One hypothesis states that women with mutations in the methylenetetrahydrofolate reductase (MTHFR) gene are at an increased risk of having an offspring with hydantoin embryopathy. It is believed that the protein product of this gene plays a role in the metabolism of phenytoin or one of its metabolites. A second hypothesis states that the intermediate metabolites of phenytoin are free radicals that bind to DNA, proteins and lipids and thereby affect the neurodevelopment of the fetus. [58]

General findings: Pre-natal and post-natal growth and development retardation representing as low birth weight, decreased length and head circumference and mental deficiency are identified. Distal phalangeal hypoplasia, nail hypoplasia, finger-like thumb, abnormality of genitalia like bifid scrotum, inguinal hernias, absence of an umbilical artery, congenital heart defects and renal malformations are some of the most commonly seen anomalies. These patients are also prone to embryonal neoplasms such as neuroblastoma, ependymoblastoma, ganglioneuroblastoma, melanotic neuroectodermal tumor of infancy, Hodgkin's lymphoma and cystic hygroma.[59]

Craniofacial findings: Large fontanelles, craniosynostosis, telecanthus, horizontal nystagmus, depressed nasal bridge with anteverted nostrils, high arched palate are often found. Of particular importance are the clefts of lip and palate that predispose the patients to nutritional deficiencies. [60,61,62]

Diagnosis: There is no diagnostic test in gestation period to identify and confirm Hydantoin syndrome in the fetus. Diagnosis is made purely on clinical knowledge of the symptoms and a history of phenytoin intake in the pregnant mother. However, abnormalities in the

developing face and orofacial clefting may easily be identified by ultrasonography or transvaginal ultrasound and 3D ultrasound.

Differential diagnosis: Fetal alcohol syndrome, embryopathies due to other anticonvulsant drugs.[26]

Retinoid embryopathy: Retinoids are a class of compounds chemically related to Vitamin A. The teratogenic potential of oral retinoids got well established by mid 1980s after Isotretinoin (13-cis-retinoic acid), was introduced into clinical practice in the early 1980s, as Accutane to treat acne, due to its stimulating action on bone growth and epithelial differentiation.[63,64,65] It has been estimated that approximately 1 in every 500 of the childbearing population would be exposed to isotretinoin. The risk of fetal malformations in liveborn infants exposed to isotretinoin in utero has been estimated to be 20–35%.[64] The mechanism by which retinoids exert their teratogenic effects is debated till date. A direct cytopathic effect with morphologic alterations in cell and reduced number of neural crest cells, either due to cell death or decreased proliferation has been proposed alongside another hypothesis that interference with migration of neural crest cells and their localization may account for the observed malformations.[66,67] The biphasic effect of retinoic acid has also been discussed as an etiologic factor, with general cytotoxic effects following earliest exposure and specific malformations produced with later exposures, possibly as a result of delayed appearance of cellular retinoic-acid binding proteins.[68]

General findings: Hypoplasia or aplasia of thymus, hydrocephalus, and congenital heart defects like Tetralogy of Fallot, trunkus arteriosus communis, ventricular septal defects are found along with transposition of great vessels and various cranial nerve deficits.[26,69,70]

Craniofacial findings: Microcephaly with unruly hair pattern, frontal upsweep, narrow sloping forehead, facial asymmetry, increased intercanthal distance, preauricular skin tags,

preauricular pits, posterior auricular pits, lowest ears, absence of helix, flat nasal bridge, micrognathia and cleft of the uvula are most commonly seen. The triangular shaped head and ear abnormalities are the characteristic craniofacial features of the syndrome. [26,69,70]

Diagnosis: A proper maternal history on the use of retinoids, i.e. the route, period of intake or topical application and dosage, is to be noted. The external appearance of the newborn along with the history will lay the path for diagnosis.

Differential diagnosis: Other neurocristopathies.

Thalidomide embryopathy: Thalidomide, a sedative-hypnotic was also used as an anti-emetic drug by pregnant mothers for morning sickness, until its teratogenesis was reported.[71]Approximately 1-9/1000000 liveborns are affected with thalidomide embryopathy.[72] Thalidomide is considered to be one of the most infamous drugs in history. The sensitive period during pregnancy for thalidomide effects in humans is approximately day's 20–34 post fertilization.[73] Fetal malformations were a direct result of exposure to the drug in the mentioned period and were not dependent on drug dosage. Of the several hypotheses proposed for the mechanism of teratogenesis, the most recent ones include: oxidative stress/damage, DNA intercalation, inhibition of angiogenesis, and cereblon (CRBN) binding.[74,75] Thalidomide may also decrease the expression of cell-cell adhesion receptors causing inappropriate cell-to-cell interaction involved in morphogenesis.[76]

General findings: Limb anomalies are the most striking findings. They may include amelia, phocomelia, defects of radius and thumb triphalangism or hypoplasia of thumb, aplasia of tibia, aplasia or hypoplasia of femur and polydactylism. Congenital dislocation of hip, congenital heart diseases, laryngeal and tracheal abnormalities and abnormal lobulations of the lungs, congenital absence of gall bladder and kidney defects like horseshoe kidney, hydronephrosis, and double ureter, have been found along with inguinal hernias, delayed testicular descent, double vagina and anal atresia.[26,71,77,78]

Craniofacial findings: Facial palsies are commonly found. Facial anomalies include the forehead, nose and upper lip (stork bite): anotia, microtia, ear tags, external ophthalmoplegia, anophthalmos, microphthalmos, coloboma, choanal atresia and cleft lip and palate have been recorded. Jaw winking reflex and crocodile tear syndrome are also encountered in these patients.[26]

Intraoral findings: Agenesis as well as hypoplasia of teeth is the only abnormalities related to the syndrome. Agenesis of maxillary lateral incisors has been recorded in both primary and permanent dentition. In one study, abnormalities in shape of teeth have been reported.[79]

Diagnosis: Gestational history and the striking clinical features lay the path for diagnosis. Antenatal diagnosis of facial clefting and limb defects can be made by ultrasonography at or even prior to 17 weeks of gestation.[80]

Differential diagnosis: Robert's syndrome, Holt-Oram syndrome, Thrombocytopenia-absent radius syndrome.[81]

Tetracycline embryopathy: Tetracycline (TCN) is widely used as a broad spectrum antibiotic agent. The toxic effects of TCN on developing foetus got well documented by the early 1960s.[26] These manifest as dental discoloration, enamel hypoplasia, and a 40% depression of bone growth.[82] The prevalence of tetracycline staining has been reported to be 3-4%.[83] Tetracyclines ingested by the pregnant mother from 4th month of gestation and thereafter, cross the placental barrier and get incorporated into the developing teeth and bones as they have an affinity for calcifying tissues. Calcium from teeth and bones react with the drug to form tetracycline-calcium orthophosphate complex. More rapid the rate of mineralization, more the tetracycline deposited. Drug dosage, duration of treatment, stage of tooth mineralization, and activity of the mineralization process are the factors deciding the amount of drug deposition. Right after tooth eruption, the tetracycline stained teeth exhibit fluorescent yellow pigmentation. The discoloration gradually changes over a period of

months to years to a nonfluorescent brown color. Excessive deposition of TCN during mineralization can affect the mineral content making the tooth hypoplastic. [82,84,85]

General findings: Minocycline, a TCN derivative, causes pigmentation of a variety of tissues including skin, thyroid, nails, sclera, teeth, conjunctiva, tongue and bone. Occurrence of 'black bones' is a significant side effect.[82]

Intraoral findings: TCN affected teeth show yellow to brown-grey appearance. The effects are vivid right after tooth eruption but diminish with time. Enamel hypoplasia is often associated.

Diagnosis: It is important to distinguish TCN stains from other intrinsic and extrinsic stains of teeth. A thorough knowledge of the same is required in addition to the maternal history. The location of tooth discoloration coincides with the developmental stage of that portion of the tooth at the time of tetracycline ingestion. A diffuse pattern of discoloration has been observed for permanent teeth when compared to the primary dentition. The affected teeth will fluoresce bright yellow under UV light in a dark room.

Differential diagnosis: Staining due to extrinsic factors like chromogenic bacteria, tobacco products, dental materials, medicaments, food and beverages, and iron. Staining due to intrinsic factors like Dentinogenesis imperfecta, Amelogenesis imperfecta, Dental fluorosis, Sulphur drugs, Hyperbilirubinaemia, Erythropoetic porphyria, Ochronosis etc.

Rubella embryopathy: Rubella is an acute mild viral infection commonly occurring in children and young adults. Maternal rubella infection often leads to spectra of congenital anomalies in the offspring. However, the chances of malformations in the fetus are inversely related to the duration of pregnancy. According to WHO Reports, before the introduction of vaccine, up to 4 babies in every 1000 live births were born with congenital rubella embryopathy.[86] A dramatic drop in the number was noted thereafter, with an estimated

incidence of less than 2 per 100,000 live births.[87] Relationship between maternal rubella interaction and chances of foetal malformation are nearly 100% at <11 weeks, nearly 35% at 13 – 16 weeks and rare at > 16 weeks.[26]

In infected mothers, the virus readily crosses the placental barrier after the first week of incubation and remains in the fetal blood for the remaining gestation period. It is believed that the virus shortens the cell life cycle and increases premature cell death by apoptosis in specific cell populations leading to variety of abnormalities. However, the severity of anomalies also depends on the sensitivity of the embryo to teratogenic effects, the transfer of maternal antibodies to the fetus and the increase in fetal immunological responses as the gestation progresses. [88]

General findings: A classic triad of cataract, perception deafness and congenital heart disease characterizes the syndrome. CHD include patent ductus arteriosis, aortic stenosis, atrial septal defect, and ventricular defect. Intrauterine growth retardation manifest as low birth weight. Thrombocytopenic purpura, atherosclerosis, hypertension, mental retardation, peripheral pulmonary stenosis, diabetes mellitus and sensorineural hearing loss are most commonly encountered. [26,89,90,91,92]

Craniofacial findings: Various eye anomalies (cataract, microphthalmia, iris hypoplasia, strabismus, glaucoma, nystagmus, retinopathy, mesodermal dysgenesis) along with microcephaly and hydrocephaly are observed in newborns with rubella embryopathy. Micrognathia and orofacial clefting have been observed in a few cases.[26,89,90,92]

Intraoral findings: Varying degrees of enamel hypoplasia, ranging from minor pitting to complete loss of enamel, usually affects both primary and permanent dentition in a symmetric fashion. Complete enamel aplasia has also been reported. Delayed eruption patterns are seen in these patients.[26]

Diagnosis: Prenatal diagnosis of rubella is possible either by detection of specific IgM in fetal blood or by using dot-blot hybridization detection of rubella nucleic acid in chorionic biopsies. This, if is desired, should be performed between the 12^{th} – 17^{th} weeks of gestation and limited to cases with rubella like symptoms only. Rubella vaccination of prepubertal girls and seronegative women of childbearing age is mandatory. In newborns with the syndrome, clinical presentation with maternal history and detection of specific IgM in the blood is confirmatory.[93]

Differential diagnosis: Various teratogenic embryopathies

Nitrous oxide: The Epidemiologists of American Society Of Anesthesiologists in their review found an increase of 30% in the rate of spontaneous abortion and an increase of 20% in the rate of congenital defects among women directly exposed to waste anaesthetic gases.[94] Anesthetic gases lead to chromosomal aberration, and abnormal cell formation. Nitrous oxide in particular causes oxidation of vitamin B12, and impairs the synthesis of methionine, folate and thiamine.[95]

N_2O -induced sympathomimetic effect is pivotal in teratogenic effects or fetal malformations as it leads to reduced maternal blood flow and direct stimulation of a1 adrenoceptors in the embryo (causes situs inversus i.e impairment of left±right body axis development).

In addition methionine synthase inhibition leads to reduced DNA synthesis causing embryonic/fetal death. The teratogenic potential of N_2O in humans has not been well established contrary to the animal studies. [96]

Pesticides or herbicides: Pesticide exposure during pregnancy has been linked to birth defects, foetal mortality, neural tube defects, paediatric malignancies, intrauterine growth retardation and preterm delivery.[97]

Experimental data reveals that pesticide chemicals may increase the likelihood of holoprosencephaly (HPE) by disrupting the HPE-associated Sonic Hedgehog (Shh) signalling pathway.[98]

PREVENTION AND MANAGEMENT STRATEGIES:

An increasing awareness has been observed on the part of the Government as well as health care workers in India in the last decade. The establishment of Birth Defect Registry of India (BDRI) in 2013 was one of the initial steps to estimate the extent of the problem.[99] An excellent outcome of this was the online registration of all 325 000 annual births in Delhi.[100] Another programme launched in 2013 as a part of Rashtriya Bal Swasthya Karyakram (RBSK) involved screening and appropriate referral of nine specific birth defects that included neural tube defects, Down syndrome, orofacial clefts, talipes, developmental dysplasia of the hip, congenital cataract, congenital deafness, congenital heart diseases and retinopathy.[101] This programme targets to improve the quality of life of nearly 270 million children through early detection. In 2014 the Mother Child Tracking System was introduced by the Ministry of Health in India to track children with birth defects in government-run-institutes.[102] The successful implementations of these programmes enabled the designing of preventive health strategies. Several NGOs came together in a recent workshop ‘Drugs are a Women’s Issue’ in providing lifestyle guidance, preventive measures and rehabilitation to women.[103] Programmes like Alcohol Atlas of India (2008), Cigarette and Other Tobacco Products Act (2003), Framework Convention of Tobacco Control (2005) and National Tobacco Control Programme have been launched to deliver health awareness on larger scales across the country.[104] Dentists should promote these programmes in their workplace. A paediatric dentist works not only with the child but his parents / caregivers as well and in a very close-knit and empathic atmosphere. Counselling regarding substance abuse, use of non-

prescriptioned drugs, Government acts and the rising concern on various birth defects should be delivered especially to young mothers. The availability of genetic screening in major cities of India is an advantage. A total of 54 genetic counselling centres, 40 genetic laboratories, and 20 prenatal diagnostic centres listed on the national web site (http://geneticsindia.org/).[100] Antenatal 3D ultrasonography can be especially useful in identifying anomalous limbs, facial clefting and other structural defects at or even prior to 17 weeks of gestation.[80] Some common instructions to pregnant women or ones of child bearing age would include:[26]

- Pre-conception counseling at least before 6 months of conception and pregnancy planning are important aspects of the preventive strategy along with control of blood-sugar level in the pregnant mother.
- Women of childbearing age who are on thalidomide would be required to use two forms of birth control and take monthly pregnancy tests. Pregnancy complicated by thalidomide exposure requires counseling for fetal malformations.
- Pregnant mothers should be counseled against the use of TCN, especially from 4^{th} month of gestation until full term as the first tooth formation begins at 4^{th} or 5^{th} month in utero and continues till 8years of life except for the third molars. They should also be advised against the use of other TCN derivatives.
- High doses of folic acid have shown to limit the neural tube defects. Folic acid supplementation (5 mg/day) and sonographic monitoring is recommended throughout pregnancy for women exposed to aminopterin or MTX during pregnancy. However, as the neural tube closes at day 30 of development and women usually report thereafter, this has not found its proper use. Proper gestational counseling is mandatory in this regard.

Early intervention and supportive therapies are the only management strategies in children born with congenital defects. The emotional trauma of the parents is to be taken into account. Psychological counseling and support groups are to be considered. The parents are to be counseled on the importance of home care, oral care, and regular medical and dental check up, availability of speech therapy, special care schools for children with cognitive impairments or visual or hearing impairments.

CONCLUSION

Oral health care becomes an essential component of treatment strategy as dental pain or oral ulcers would lead to a nutritionally compromised patient. Parents should be instructed on brushing the child's teeth, use of electronic tooth brush, prescriptioned mouth rinses, topical fluoride therapy and pit-fissure sealants in disabled children. An overall preventive program should be mapped out to the parents in the child's first dental visit along with anticipatory guidance on infant feeding, eruption timing, dental trauma, oral habits and fluoride therapy. In children born with oral clefts, a team of dental surgeons work in harmony to attain closure of the cleft, growth of the facial bones and a normal occlusion. The pediatric dentist counsels on feeding the child using an obturator or in some cases a nasoalveolar molding appliance is delivered before the primary lip closure.

It is important that dentists realize their roles in the management of children born with birth defects. Working effectively with the medical and public health team requires the dental surgeon to have comprehensive knowledge on syndromology, teratogens and current Government Acts.

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