IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 5 Ver. 4 (May. 2018), PP 28-41
www.iosrjournals.org

Aetiology of Congenital Abnormalities in Nigeria.

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Abstract: ***Background:*** *Worldwide 94% of birth defects (i.e. 8.46 million infants) occur in the developing countries of the world to which Nigeria belongs. Tertiary centres-based studies showed that there must be variations in aetiological factors of birth defects in different regions of Nigeria.*
Objective: *The objective of the study was to ascertain the aetiology of congenital abnormalities in Nigeria and identify any regional variation in the causative factors.*
Methodology: *This was a mixed method study – systemic review and descriptive observational. 120 published works were reviewed and where any factor was blamed for birth defects, the prevailing situation was extrapolated to the present condition in Nigeria. The Nigerian national register of birth defects and national guidelines on its management were looked for. A qualitative review of the socioeconomic life, environmental pollution in Nigeria and telephone communication with consultants Obstetricians and Paediatricians on birth defects in different University Teaching Hospitals in Nigeria were carried out.*
Results: *Nigeria has no nnational register of birth defects, no guideline on their management and also no record of causative factors of birth defects. The causes of birth defects in Nigeria are largely not known. The known causes are of genetic and non-genetic origin. Survival advantage of healthy carriers of the genes for sickle cell anaemia (SCA) and glucose-6-phosphate dehydrogenase (G6PD) deficiency against the lethal effects of malaria and parental consanguineous marriage lead to an increase in the birth prevalence of those defects and other autosomal recessive conditions. Non-genetic causative factors of birth defects are neglect of environmental protection policies and therefore significant environmental pollution, advanced maternal age at delivery, low socioeconomic levels, non-affordability of proper antenatal care and prenatal diagnosis, poor maternal nutrition, maternal illness (diabetes mellitus and phenylketonuria), unregulated maternal exposure to recreational (alcohol) and therapeutic drugs (antiepileptic and warfarin) and maternal prenatal infection.*
Conclusion: *The aetiology of birth defects in Nigeria is largely unknown but the known causes are either of genetic and/or non-genetic origin and intertwine with each other - gene–gene, gene–environment and gene–nutrient interactions.*
Key words: *Aetiology, congenital abnormalities, Nigeria, birth defects*

Date of Submission: 23-04-2018 Date of acceptance: 10-05-2018

I. Introduction

Congenital anomalies also known as birth defects or congenital malformations are defined as structural or functional anomalies that occur during intrauterine life and can be identified prenatally, at birth, or sometimes may only be detected later in infancy, such as hearing defects. [1] Serious anomalies are life threatening or have the Potential to result in disability (physical, intellectual, visual or hearing impairment, or epilepsy).

The only classification of congenital anomalies that takes into account etiological factors was that of D Wellesley et al in 2005 - a robust, hierarchical method of classifying birth defects into eight categories for use at source of data registration in conjunction with, but independent of, ICD coding. [2] Generally congenital abnormalities are differentiated into the following groups based on their aetiology: [3]

- Birth defects originating in the pre-conception period (Chromosomal abnormalities, single gene disorders - autosomal dominant, autosomal recessive, X-linked disorders and multi-factorial malformations).
- Birth defects arising after conception but before birth (post-conception) - caused by teratogens and other non-genetic causes.
- Birth defects of unknown cause.

An estimated 7.9 million children are born yearly worldwide with serious birth defects of genetic or partly genetic origin.[4] Over 1 million more infants are born with serious birth defects of post-conception origin. [5] Thus, an estimated 9 million infants – representing approximately 7 percent of all births – are born annually with a serious birth defect that may kill them or result in lifelong disability. 94% of the birth defects (i.e. 8.46

million infants) occur in the developing countries of the world to which Nigeria belongs. So it is obvious that the burden of congenital abnormalities in Nigeria and other developing countries is enormous and therefore demands adequate attention from Government of those countries and from healthcare providers.

The prevalence and pattern of congenital abnormalities varies from one region of Nigeria to the other. The prevalence in South Southern Nigeria represented by the University of Port Harcourt Teaching Hospital was 20.73 cases per 1,000 live births. [6] The predominant abnormalities in that same study were those of the central nervous system at 27.0%, gastrointestinal system 11.95%, cardiovascular system 10.69%, anterior abdominal wall 8.18%, skeleton 6.29%, and chromosomal abnormalities at 5.6%. In the North Eastern Nigeria, the prevalence was 5.51% while the predominant abnormalities were those of the gastrointestinal system at 34.5%, unclassified abnormalities at 33%, and those of the central nervous system at 13.6% of the total birth defects. [7] In the South Western Nigeria, the prevalence was 15.84 per 1000 live births while the predominant abnormalities were those of the cardiovascular and gastrointestinal systems, followed by the abnormalities of the musculoskeletal, cardiopulmonary, and genitourinary systems. [8] In the South East, abnormalities of the gastrointestinal system predominated at 36.7% followed by those of the skeletal and then the cardiovascular systems and the prevalence was 4.15 out of 1000 live births. [9] Therefore, it is clear that there were some similarities in the pattern of the abnormalities in the South West, South East, and North Eastern Nigeria in contrast to the Niger Delta, where the pattern was distinct. There must therefore be variations in aetiological factors of birth defects in different regions of Nigeria.

Aim: The purpose of this study was therefore to ascertain the aetiology of congenital abnormalities in Nigeria and identify any regional variation in the causative factors.

II. Material And Methods

Setting: This was a multicentre study that was coordinated at the University of Port Harcourt Teaching Hospital in Rivers State. Rivers State is located in the South-South region of Nigeria called the core Niger Delta.

Study Design: It was a mixed method study – descriptive observational and systemic review.

Actual methods: We reviewed published studies on causes of fetal abnormalities in different regions of Nigeria and also in different parts of the world with specific attention to countries that have the same economical and environmental terrains like Nigeria. We carried out literature search using Pub med (MEDLINE), Biomed central, and Google and Cochrane database. Keyword search statements used were 'Prevalence of fetal abnormalities', 'Fetal abnormalities in Nigeria', 'Aetiology of birth defects in Nigeria' and also different regions of the country, 'Causes of congenital abnormalities in Nigeria', Congenital abnormalities in developing countries', 'Chromosomal abnormalities in Sub-Sahara Africa and Nigeria, Genetic birth defects in Nigeria, 'Genetic causes of fetal abnormalities', 'Environmental pollution and congenital abnormalities', 'Water pollution and congenital abnormalities,' etc.

The inclusion criteria for the literature search were as follows: the literature must be published after 1990 with a view of knowing more about recent developments unless the content of older studies is indispensable to the present study, the studies must be associated with similar terrain like Nigeria and if not it should be addressing those factors that affect Nigeria, the study must be on aetiology and /or prevalence of birth defects and lastly pathogenesis of birth defects is a bonus. The literatures that met the outlined criteria were synthesized by two researchers, relevant information was retrieved from them and agreement on inclusive data was reached by dialogue. Where environmental pollution and any other factor were blamed for birth defects, the prevailing situation was extrapolated to the present state in Nigeria, especially environmental degradation in the Niger Delta area of the country.

Summary of the literature review:

Number of articles identified through search = 307
Number of articles dropped for duplication = 50
Number of articles left = 257
Number of articles screened = 257
Number of articles dropped = 137
Number of articles that met the inclusion criteria = 120

Furthermore we looked for Nigerian National registers on birth defects, guidelines and strategies on the management of congenital abnormalities. We also conducted a qualitative review of the socioeconomic and educational aspects of life and environmental pollution in different regions of the country with a view of having an insight into possible causative factors of birth defects. This was carried out by reviewing Nigerian statistics on the socioeconomic development of the regions and interactive discussion with the locals. Telephone communication was also conducted with consultants Obstetricians and Paediatricians in different University

Teaching Hospitals located in all the geopolitical regions that make up Nigeria; discussion was on the prevalence and causes of fetal abnormalities in their respective tertiary centres and region.

III. Result And Discussion

Nigerian national Birth defects register: There was no Nigerian nation al register of birth defects. There was also no record of causative factors of birth defects, neither was there any literature or publication that specifically dealt with the subject 'aetiology of birth defects in Nigeria.'

Nigerian national guideline on the management of birth defects: There was no national guideline on the management of congenital abnormalities in Nigeria. There were however pockets of tertiary centre-based studies in all the geopolitical regions of the country on the prevalence and patterns of regional birth defects.

Causes of birth defects: Although approximately 50% of all congenital anomalies cannot be linked to a specific cause there are some known genetic, environmental and other causes or risk factors. [1] Known aetiological factors of birth defects were extrapolated and assigned to different regions of the country on the basis of enabling local social, economic, cultural and environmental conditions.

1. Genetic factors

Several factors contribute to variations in the prevalence of birth defects between and within countries and across regions. [5, 10, 11] In many middle- and low-income countries with Nigeria inclusive, the prevalence of certain genetic conditions is high. Compared with non-carriers, healthy carriers of recessive genes for haemoglobin disorders (sickle cell anaemia and Thalassemia) and glucose-6-phosphate dehydrogenase (G6PD) deficiency have a well-documented survival advantage against the lethal effects of malaria. As a result, carriers are more likely to reach reproductive age. Over time, this has led to an increase in the population prevalence of these genes in tropical regions. Consequently, the birth prevalence of thalassemia, sickle cell disease, and G6PD deficiency is high in malaria-endemic regions of the world such as sub-Sahara Africa, the Eastern Mediterranean and North Africa, Southeast Asia and the Western Pacific. [12, 13] It is particularly so in Nigeria but thalassemia is not characteristic.

Haemoglobinopathies unlike cystic fibrosis found in Caucasians are the most common lethal inherited disorders in humans. Currently, worldwide, an estimated 307,900 children are born annually with severe haemoglobin disorders. Of this number, 60 to 70 percent are in sub-Saharan Africa, where an estimated 224,200 infants are born annually with sickle cell disorder, with the highest percentage in Nigeria; the majority die before age 5. [14] More than 5 million infants are born annually with G6PD deficiency, an X-linked recessive disorder of varying severity, mainly in tropical sub-Saharan Africa with Nigeria inclusive, the Eastern Mediterranean and North Africa, South and East Asia, and the Pacific.

Parental consanguineous marriage, a social custom, involving the marriage of cousins or uncles and nieces, is accepted by at least 20 percent of the world's population. This practice is common in some parts of Nigeria and it leads to an increase in the birth prevalence of autosomal recessive defects, almost doubling the risk of neonatal and childhood death from those defects. [13, 15-18] Other single gene disorders found in Nigeria are oculocutaneous albinism and also the rare ones with prevalence of 1 in 10,000. e.g. haemophilia. Oculocutaneous albinism is highly prevalent in sub-Sahara Africa, ranging from 1 in 3,900 to 1 in 5,000 people. Affected individuals are prone to skin cancer, the susceptibility for which increases with age and proximity to the equator. It is a cause of early death in Tanzania and Nigeria. Only 10 percent of those affected survive beyond 30 years of age. [19, 20]

2. **Chromosomal Disorders**

The prevalence of these disorders, particularly Down syndrome, should be high in Nigeria because of the following reasons: advanced maternal age at delivery in all the regions of the country, majority of child-bearing women are of low-income bracket and therefore poverty prevails in that age group. Unfortunately there is no facility for social security as obtainable in the developed world. Women cannot therefore afford maternity care and services which are free in many developed countries. Prenatal diagnosis for chromosomal anomaly is not available and therefore diagnosis of the anomaly which would have necessitated termination of pregnancy is not made in the first nor second trimester of pregnancy. A study that was carried out in our unit at the University of Port Harcourt Teaching Hospital showed that the prevalence of Down syndrome and Edward syndrome was 1.17 per 1000 live births at term with the percentage in the unbooked patients (poor) twice as much as that in the booked maternities. [6] This implies that if diagnosis were to be made in the first trimester by carrying out prenatal screening, the figures would have been higher than what was obtained in the study. By comparison, the birth prevalence of Down syndrome is as low as 1.2 per 1,000 live births in high-income countries. [13]

3. **Other aetiological or predisposing factors to birth defects**

Pregnancies in middle- and low-income countries, compared with those in high-income countries, are more likely to be at risk from potential teratogens for several reasons which are also applicable to Nigeria. They include the following: low socioeconomic and educational levels, demographic factors, poverty, poor maternal nutrition, maternal illness and metabolic status, poorly regulated maternal exposure to recreational and therapeutic drugs, maternal prenatal infection, and lack of environmental protection policies and therefore significant environmental pollution.

3a. Socioeconomic and demographic factors

Low-income may be an indirect determinant of congenital anomalies, with a higher frequency among resource-constrained families and countries. It is estimated that about 94% of severe congenital anomalies occur in low- and middle-income countries; that relates to a possible lack of access to sufficient nutritious foods by pregnant women, an increased exposure to agents or factors such as infection and alcohol, or poorer access to healthcare and prenatal screening. Maternal age is also a risk factor for abnormal intrauterine fetal development. Advanced maternal age increases the risk of chromosomal abnormalities, including Down syndrome**.**

A research work that was carried out in our tertiary centre at the University of Port Harcourt teaching hospital showed that there was significant difference between the prevalence of congenital abnormalities in the babies of booked patients and that in the babies of the unbooked maternities. [9] This is probably due to poverty and illiteracy among the unbooked patients. Since there is no universal free maternal care in Nigeria, the unbooked patients tend to undergo antenatal care with traditional birth attendants, faith healers, health centres and some with general medical practitioners. [21, 22] All these categories of obstetric practitioners have no formal training in obstetrics and therefore can neither conduct pre-pregnancy care nor offer effective maternal or neonatal care. [23] These factors could be responsible for the higher prevalence of birth defects in the unbooked patients.

3b. Maternal nutritional status

Periconceptional FA supplementation has beneficial effects in terms of reduction of 50–70% in the occurrence of NTD, [24] and substantial reduction in the incidence of several other non-neural anomalies. Neural tube defects NTD are particularly prevalent in China, Mexico, [25] Central America, [26] and Chile, [27] probably because of a combination of nutritional deficiencies, especially in folic acid and exposure to environmental pollutants. If that is the case, then Sub-Saharan Africa including Nigeria should have more cases of the defects and many other abnormalities than those countries because of abject poverty and nutritional inadequacies in sub-Sahara Africa.

Another maternal nutritional ingredient of vital importance is vitamin A; its excessive intake may affect the normal development of an embryo or fetus. Furthermore UNICEF considers iodine deficiency the most important cause of preventable brain damage and intellectual disability, with most cases happening before birth. Iodine deficiency causes spontaneous miscarriage, perinatal death, cretinism and childhood intellectual, motor and auditory disabilities (Iodine Deficiency Disorder). Iodine deficiency should be evident in Nigeria where there is no central water supply and therefore water is not checked for its iodine content; individual family uses water from boreholes that is not certified for human consumption. Furthermore, iodine content of table salt is not properly monitored or regulated.

3c. Maternal illness

Maternal illness such as maternal insulin-dependent diabetes mellitus is another cause of birth defects. IDDM affects 0.5 percent of pregnancies in industrialized countries but its prevalence is more in middle- and low-income countries where diabetic control is poor. [28] A study carried out in our unit at the University of Port Harcourt Teaching Hospital showed that the prevalence of overt diabetes (IDDM and Non-IDDM) in the first trimester was 2.4% while that of gestational diabetes was 21.2% when maternities were screened in the first trimester, using fasting blood glucose. [29] The risk of congenital malformations is slightly increased in infants of mothers with GDM compared to the general population because of the undiagnosed type 2 diabetes among women with GDM. [30]

The pathogenesis of congenital malformations which are 4-10 times higher in incidence in pregnant women with diabetes than in non-diabetic is very complex and possibly has a multifactorial origin. [31-33] It may be associated with poor metabolic control during the period of organogenesis probably due to the negative impact of a hyperglycaemic milieu on the growing fetus. [33] The precise mechanism by which it occurs has not been completely elucidated. It is supposed that hyperglycaemia could cause damage to the developing yolk sac, an increased production and liberation of free oxygen radicals, deficiency of myoinositol and arachidonic acid and disruption in intracellular signalling by inositol-derived effectors and prostaglandin precursors such as

arachidonic acid. [33-36] Major congenital malformations among offspring of women with diabetes are found in the following systems: cardiovascular, central nervous system, gastrointestinal, musculoskeletal (talipes, arthrogryposis), urinary tract, caudal regression syndrome, cleft lips and palate anomalies. [37, 38]

3d, Maternal exposure to recreational and therapeutic drug

Examples of these drugs are alcohol, tobacco, antiepileptic drugs and warfarin. Children born to mothers on antiepileptic drugs, particularly phenytoin and sodium valproate, are at risk of developing anticonvulsant embryopathy, major malformations, growth retardation, intellectual disability, and hypoplasia of the midface and fingers. This risk is greater for infants in middle- and low-income countries where the mothers' anticonvulsant therapy is less likely to be well controlled, multiple drugs therapies are used, and cheaper, more teratogenic drugs (such as phenytoin) are more likely to be used. [1, 5, 39] Most of the drugs are bought over the counter. This situation is typical of Nigeria.

Maternal exposure to antiepileptic drugs: (AED): Approximately 1% of all pregnancies are in woman with epilepsy and although, majority of children born to epileptic mothers are normal, they are at increased risk for malformations. The incidence of major malformations in offspring of mothers with epilepsy treated with AEDs is higher than that in offspring of mothers with untreated epilepsy and in the general population. [40, 41] In addition, mean plasma AED concentrations are higher in mothers with malformed infants than mothers with healthy children. Polytherapy and daily high dose of the drugs increase the risk of birth defects further in children [42]

The associated malformations include spina bifida, cleft palate, limb reduction defects, cardiac abnormalities, hypospadias, and gastrointestinal atresia. Selected AED are thought to be associated with specific malformations. [43] Traditional antiepileptic drugs e.g. phenobarbital, phenytoin, carbamezapine (CBZ), valproate are associated with increased risk of congenital abnormalities. [42, 44, 45] Fetal hydantoin syndrome is a rare disorder that is caused by exposure of a fetus to the anticonvulsant drug phenytoin (PHT). The symptoms of this disorder may include abnormalities of the fingers and toes, and/or mild developmental delays, cleft lip and palate, microcephaly and other brain malformations. [44, 45] Barbiturates like phenobarbital (PHE) have also been associated with congenital heart defects, facial clefts, craniofacial abnormalities and growth deficiency. Valproate (VPA) has a clear link with spina bifida and other neural tube defects, as well as hypospadias. [46] Other congenital malformations associated with the exposed fetus include heart defects, oral clefts, genital abnormalities, and limb defects. [47]

Buehler believed that there is a similarity between the clinical presentation of exposure to CBZ and fetal hydantoin syndrome and concluded that they follow the same teratogenic mechanism. [48] Morrow and collaborates yielded contradictory results. In a prospective study on 3607 cases, they found that exposure to CBZ monotherapy was associated with the lowest risk of major congenital malformation (MCM). Individual AED results for MCMs included 2.2% for CBZ (1.4%–3.4%), 6.2% for VPA (4.6%–8.0%), 3.7% for PHT (1.3%–10.2%), and 3.5% for no AED exposure (1.8%–6.8%). [42] Currently, many new AEDs including lamotrigine, gabapentin, oxcarbamazepine topiramate, pregabalin and levetiracetam have been introduced into clinical practice. They are known for their better toleration. However, a new survey on 1317 Australian women with epilepsy has reported that the incidence of malformations associated with lamotrigine monotherapy was 12/231 (5.2%), with topiramate 1/31 (3.2%) and with levetiracetam 0/22 (0%). [49]

The exact mechanism by which the AEDs mediate abnormalities in the fetus is uncertain. However, there are several hypotheses to explain them. Some of the drugs may be teratogenic because of alteration in vitamin K metabolism, folic acid deficiency, bioactivation of PHT to a reactive toxic intermediate (epoxide) by cytochrome P450, co-oxidation of PHT to free radical intermediates, apoptosis and hypoxia-reoxygenation damage. [50-52] and genetic susceptibility. [53] Folic acid (FA) appears to play a major role in the metabolism of the developing fetus because it is essential for DNA methylation, protein methylation, DNA synthesis, and maintenance of the overall integrity of DNA. [54] Also, there are some evidence that demonstrate FA deficiencies can cause alterations in the levels of proteins and genes. [55]

Fetal alcohol syndrome: Although many factors may modify the risk, the primary and only cause of fetal alcohol syndrome or fetal alcohol syndrome disorder is maternal alcohol consumption. The quantity and pattern of maternal drinking and, therefore, the dose and duration of exposure to alcohol are the critical factors in conferring risk. Current evidence supports the conclusion that women who drink heavily during pregnancy may produce children with features of fetal alcohol syndrome. Low-to-moderate levels of maternal alcohol consumption have not been well studied in human pregnancy, but evidence has not suggested a threshold dose below which no effects on cognitive performance or behavior are seen. In the absence of adequate data, no level of alcohol consumption in pregnancy is known to be safe, and the US Surgeon General advises women who are pregnant or who may be pregnant to abstain from alcohol consumption throughout the gestation.

The principal features of children with fetal alcohol syndrome or fetal alcohol syndrome disorder (FASD) are as follows: facial abnormalities (smooth philtrum, thin, smooth vermilion border of the upper lip, Short palpebral fissures i.e. <10th percentile for age, midface hypoplasia, microphthalmia, strabismus and ptosis), central nervous system (CNS) and neurobehavioral abnormalities include the following (microcephaly, intellectual impairment i.e. mild-to-moderate mental retardation, cognitive impairment, developmental delay, delayed or deficient myelination, agenesis or hypoplasia of the corpus callosum). Other anomalies are skeletal (radioulnar synostosis, flexion contractures, camptodactyly, aberrant palmar creases, especially hockey-stick palmar crease, Clinodactyly, Klippel-Feil anomaly, Hemivertebrae, Scoliosis, Dislocated joints) and major congenital anomalies including Cleft palate, heart defects, renal anomalies and many others. [56-59]

Drinking in all 3 trimesters poses a risk. Women older than 30 years and/or those with a long history of alcohol consumption, poor maternal nutritional status and having one child with fetal alcohol syndrome further increase the risk of producing subsequent children with fetal alcohol syndrome. Genetic susceptibility to fetal alcohol syndrome has been suggested in some studies, with alcohol dehydrogenase (ADH) polymorphisms as a risk factor. ADH alleles, which result in rapid metabolism of alcohol to acetaldehyde, were shown to be protective against FAS. However, the mechanism by which this protective effect occurs is unknown. Some suggest that rapid metabolism of alcohol to acetaldehyde lowers peak blood alcohol levels and therefore lowers fetal exposure. As an alternative, rapid metabolism may increase levels of acetaldehyde with associated noxious effects on the mother and therefore reduce levels of alcohol consumption, which lowers fetal exposure

3e. Maternal Infections

The maternal prenatal infections of interest are TORCH infection, Syphilis, Varicella-Zoster Virus and added to this group of recent is the zika virus. TORCH infection is a group of viral, bacterial, and protozoan infections that gain access to the fetal bloodstream through the placenta via the chorionic villi. Hematogenous transmission may occur at any stage during gestation or occasionally at the time of delivery via maternal-to-fetal transfusion. The TORCH infections that cause fetal abnormalities are toxoplasma, rubella cytomegalivirus and syphilis.

Testing for these infections is usually carried out for the following reasons: maternal exposure to an infectious pathogen, finding sonographic markers of fetal infection during a routine ultrasound scan or, more rarely, symptomatic maternal infection. In most cases the infections do not present with maternal symptoms except in syphilis and chickenpox. There is evidence of susceptibility of Nigerian obstetric patient to TORCH infections. IgG and IGM have been detected in the serum of antenatal population in different tertiary centres in Nigeria. [60-66] Some of the abnormalities caused by the TORCH infections are as shown in the table below

Toxoplasmosis	**Rubella**	**Cytomegalovirus**
Features Include: Ventriculomegaly, Hydrocephalus, Microcephaly, Intracerebral Calcification, Cataract Formation And Ascites. Hepatosplenomegaly.	Some Features Of Congenital Rubella Syndrome: [67] CVS Defects (Pulmo. Artery Hypoplasia, Coarctation Of The Aorta), Microphthalmos, Microcephaly, Polycystic Kidney, Hepatosplenomegaly	Features: Microcephaly, Ventriculomegaly, Intracerebral Calcification, Periventricular Cyst Formation, Leukomalacia, Hepatic Calcifications. Oculo Defects, Hepatosplenomegaly,

Congenital syphilis continues to represent a significant burden in developing countries, in spite of efficient preventive methods. [68, 69] In Sub-Saharan Africa, anywhere from 6–16% of pregnant women have active syphilis. [70] These infections cause congenital abnormalities of different fetal organs. Unfortunately, they are prevalent in Nigeria but their diagnosis and management are almost non-existent except syphilis. Rubella is important because of its high teratogenicity and the possibility of its eradication by immunization. [71] More recently, the effect of in utero exposure to Zika virus on the developing fetus has been reported. In 2015, Brazil detected cases of Zika virus and a spatio-temporally associated increase in microcephaly. By 2016, Brazil reported that of 4180 suspected cases of microcephaly, 270 were confirmed, 462 were discarded and 3448 are still under investigation. [1]

3f. Environmental factors

Maternal exposure to certain pesticides may increase the risk of having a fetus or neonate affected by congenital anomalies. Physical agents such as radiation and environmental pollutants can also cause birth defects. In Nigeria there are laws on the control of radiations and environmental protection from different sources but they are not implemented. Therefore congenital abnormalities from radiations and environmental pollutants are rife in the country. This is particularly so in the Niger Delta which has been exposed for the past 55 years to environment devastation by the products of petroleum exploration, extraction, refining, transport,

pipe lines vandalisation and gas flaring among many other unfriendly environmental factors. There is unfortunately no statistics on possible environmental causes of fetal anomalies in Nigeria.

Environmental pollution can cause congenital anomalies through preconception mutagenic action (maternal or paternal) or postconceptional teratogenic action (maternal). [3] Preconception mutagenic effects may include chromosomal anomalies and syndromes as a result of new mutations. Postconceptional action depends on the precise timing of exposure to the teratogens. Organogenesis starts from conception till about the 10^{th} week of pregnancy; it is during this 'sensitive period' that exposure to a teratogenic agent may lead to an anomaly. Thus, a particular chemical may cause a congenital anomaly after exposure in, say, the sixth week of development, but exposure during the previous or succeeding week may have no effect. Where a child has more than one anomaly, this may be because exposure has covered a number of sensitive periods for different congenital anomalies, or because exposure at one developmental stage has a number of different effects on organogenesis.

Much attention was paid to environmental pollution as a causative factor of birth defects because of the presence of several sources of pollution in Nigeria, ranging from the Sahara desert in the North, usage of old cars with poor exhaust function and also generators for light all over the country, burning of fossil fuel in the south to the unregulated processes of oil and gas production and chemical industries in the core Niger Delta area in the southern part of the country. Noticeably Ogoniland which is one of the main clans in Rivers State in the core Niger delta was in 2011 declared a zone of environmental disaster by the United Nations. [72] So environmental pollution in the present project was considered under different subheadings namely air pollution and congenital abnormalities, drinking water contamination and congenital abnormalities, exposure to naturally occurring radioactive materials (NORM), chlorinated and aromatic solvents (trichloroethylene, benzene) in drinking water and waste disposal (landfill sites and incinerators) and contaminated land.

3fi. Air pollution and congenital abnormalities.

An association has been established between congenital heart defects (CHD), including ventricular septal defects (VSD) and carbon monoxide exposure. [73] Another study showed an increased risk of CHDs [VSD and tetralogy of fallot (TOF)] with increasing Ozone exposure and also a positive association between carbon monoxide (CO) exposures during the third month of pregnancy and VSD. [74] A meta-analyses of 10 studies showed that nitrogen dioxide (NO2) and sulphur dioxide (SO2) exposures were related to increases in the risk of coarctation of the aorta and TOF while particulate matter ≤ 10 μm exposure was related to an increased risk of atrial septal defects. [75] In another study, NO_2 concentrations were significantly associated with coarctation of the aorta (OR = 1.20 per 10 ppb, 95% CI, (1.02, 1.41). [76] unfortunately, in Nigeria including the Niger Delta region ambient air quality assessment is not done except in some isolated environmental impact assessment by companies in their immediate area of operation. Worse still, there is no national or regional statistics on the prevailing concentrations of named air pollutants and their ill effects including birth defects and consequently no national strategy on dealing with the problem. [77]

There are therefore many questions that deserve urgent answers. Does air in Nigeria, especially the Niger Delta region satisfy the WHO or the Nigerian standards for good quality air? Is the air detrimental to human health? Is it safe to continue to live there? We have no answers to these questions. Countries such as South Africa, Jamaica, Cuba and many others that fall within the bracket of developing countries as Nigeria conduct air quality check daily. Why is it not done in Nigeria or specifically in the Niger Delta, given its famous ascription by the United Nations UNEP in 2011 as a region of environmental disaster. [78] In contrast to what is obtainable in Nigeria and in many developing countries, ambient air quality is checked many times a day in the developed world of Europe, North America and part of Asia.

3fii. Drinking water contamination and congenital abnormalities

Inorganic contaminants in drinking water that have been studied in relation to congenital malformation risk include heavy metals (lead, cadmium, arsenic, barium, chromium, mercury, selenium and silver), nitrates, nitrites, fluoride and other elements. Two studies reported conflicting results in relation to neural tube defects and lead in water supply [79] and an Italian study reported a positive association between lead pollution emitted by ceramic factories and the prevalence of cardiovascular anomalies, oral clefts and musculoskeletal anomalies. [80]

When oil is pumped out of the ground, a mixture of oil, gas and water emerges. The wastewater (known as "produced water" or "formation water") carries such heavy metals as arsenic, cadmium, cyanide, lead, and mercury, maintenance wastes (including industrial solvents and acids), volatile aromatic hydrocarbon and the related effluvia of the oil-extraction process. [81] This is exactly the situation in the Niger Delta area of Nigeria where there is constant pollution of water bodies. These substances can adversely affect humans and they have the potential to cause embryopathy. Generally the produced water can be treated using a range of mitigation techniques including filtration, biological processes, and reverse osmosis before being reintroduced into the environment. But these methods entail a great deal of expense and seem to be employed selectively.

Following treatment and in some cases without any treatment much of this wastewater is discharged into rivers and the sea, e.g. Warri River in the Niger Delta. [82] Sometimes, the waste water is disposed into oil-waste pits.

Mercury contamination of fish has become an increasing route of human exposure to this neurotoxin, believed to cause birth defects, heart problems, severe neurological disorders ("Minamata disease") and death with very high levels. Mercury is found in fish- groupers, amberjack, yellow fin tuna, reds snapper, swordfish and others. These fish may have mercury levels that make them unsafe for human consumption because of possible ill effects on mother, baby and others. It is known that damage to the fetal brain including microcephaly can result from high exposures to mercury. [83] Some studies have been supportive of a potential effect of high nitrate levels on central nervous system defects, [84] cardiac defects [85] and anencephaly. [86] This should also be applicable to the Niger Delta area of Nigeria where there should be high levels of nitrares in ground water because of oil production activities, especially gas flaring, acid rain, indiscriminate disposal of waste and poor sanitation? A study in North Cornwall, United Kingdom examined outcomes of pregnancy after an incident where aluminium sulphate was added to the local water supply accidentally. [87] There was an increased incidence of talipes among the exposed pregnancies. Acid rain produced in the Niger Delta area of Nigeria leaches lead, copper and aluminium into drinking water, therefore, there is high chance that ground water and bore hole water that people drink in the Niger Delta area of Nigeria may have high concentrations of aluminium and consequently give rise to a high incidence of talipes.

3fiii. Exposure to naturally occurring radioactive materials (NORM).

Norm are commonly found in underground geologic deposits and are frequently brought to the surface during crude oil recovery and also leached to the environment (water) as a result of acid rain e.g. radium. Crude oil recovery and acid rain occur in the Niger Delta area of Nigeria and is very likely that the inhabitants there will be exposed to NORM. Unfortunately new studies reveal that even low-level NORM radiation may have mutagenic impacts. [88]

3fiv. Chlorinated and aromatic solvents (trichloroethylene, benzene) in drinking water and occupational exposure to environmental teratogens.

Chlorinated and aromatic solvents enter drinking water from leaking underground storage tanks, landfill, and other waste disposal facilities. A typical example was in Woburn, Massachusetts where toxic chemicals (industrial solvents, mainly trichloroethylene) from a waste disposal site were detected in municipal drinking water wells. Residents of Woburn reported a cluster of childhood leukaemia and pregnancy outcome survey found associations with congenital abnormalities of the eye, ear, central nervous system, oral cleft and chromosomal anomalies (mostly Down syndrome). [89] The same situation should be expected to be worse in the Niger Delta area of Nigeria where chlorinated and aromatic solvents should be abundant in drinking water due to accidental or deliberate oil spillage, inappropriate discharge of waste waters, building of underground petroleum reservoir near sources of drinking water, innumerable landfills and waste pits which are built by multinational oil companies. The problem is made worse by non-enforcement of laws guiding disposal of industrial waste in Nigeria.

Chlorination by-products which are halogenated solvents, predominantly trihalomethanes THM (chloroform, bromodichloromethane, dibromochloromethane and bromoform) have been associated with specific anomalies, including NTD, oral clefts, cardiac anomalies and urinary tract defects but it is not yet clear which of them represent causal associations. [84, 89, 90] Occupation (e.g. nursing, processing food and beverages, farming, textile dye and leather industries, spraying pesticides) and possible occupational exposure to noxious agents such as organic solvents, anesthetic agents, sterilants, viruses, pesticides, paints, X-radiation, have been reported to be associated with a high risk for NTD. [91, 92] Maternal exposure to contaminated drinking water with carbon tetrachloride, trichloroethylene, and benzene has been reported to confer an increased risk of NTD and major cardiac defects.

3fv. Waste disposal (landfill sites and incinerators) and contaminated land

The contribution of waste disposal to birth defects was illustrated with some specific examples. Large quantities of toxic materials (residues from pesticide production) were dumped at a landfill in Love Canal in New York during the 1930s and 40s, followed by the building of houses and a school on and around the landfill in the 1950s. By 1977 the site was leaking and chemicals were detected in neighbourhood creeks, sewers, soil, and indoor air of houses. [58] Chemicals detected at Love Canal were primarily organic solvents, chlorinated hydrocarbons and acids, including benzene, vinyl chloride, PCBs, dioxin, toluene, trichloroethylene and tetrachloroethylene. There was increase in the occurrence of different birth defects in the area surrounding the Love canal. [93]

Geschwind et al found a 12% increase in congenital malformations (nervous system, musculoskeletal system, and skin, hair and nails) for people living within 1 mile of 590 hazardous waste sites in New York State.

[94] Some associations between specific malformation types and types of waste were evaluated, and found to be significant.

A European multisite study reported a 33% increase in risk of all non-chromosomal birth defects (Neural tube defects, specific heart defects) for residents living within 3 km of 21 hazardous waste landfill sites in 10 European regions. [95] Further works showed an increase in chromosomal anomalies. [96]

Therefore if toxic waste can cause embryototoxicity, it means Nigeria should have more associated abnormalities than in the developed countries as already reviewed. This is because in Nigeria, waste generated from within the country and from abroad are dumped in different places unchecked. In all cases of dumps, locals do not know the content and the implication of the waste to them and their environment. This is particularly so in the Niger Delta. Maternal ambient exposures to airborne chemicals in close proximity to their source (e.g. polyvinyl chloride) [97] and chemicals from toxic wastes (landfill sites) located within 3 km of residence [98] have been associated with NTD in offspring. Some studies have reported negative results for maternal exposures from landfill sites located at distance of over 3 km. [99] Landfill sites contain a range of chemicals which might further contaminate surface and ground water, plants and cattle grown in the vicinity and the air.

3g. Multifactorial birth defects

Examples of these defects are congenital heart disease (CHD), Neural tube defects (NTD) and cleft lips and palate (CLP). These birth defects are caused by genetic and non-genetic factors.

3gi. CHD

CHD occur in 4 to 8 per 1,000 live births, and about 90 percent of affected cases have a multifactorial aetiology. [100, 101] The most common CHD in Nigeria was ventricular septal defect (VSD) (40.6 - 46.6%) followed by patent ductus arteriosus (12.1 - 18.4%), atrial septal defect (8.7 – 11.3%), atrioventricular septal defect (8.2%), and tetralogy of Fallot (7.8 - 11.8%). [102, 103] A study that looked at the prevalence of CHD in the Niger Delta area of Nigeria showed its prevalence among children who were referred to 2 centres in Port Harcourt, a city in the core Niger Delta to be 14.4 per 1000 children. 277 (83.4%) of the patients had acyanotic CHD and 55 (16.6%) had cyanotic CHD. Ventricular septal defect and tetralogy of Fallot were the commonest acyanotic and cyanotic heart defects, respectively. [104]

The implication of the above findings with respect to the etiological factors of CHD in Nigeria is that they are likely to be similar and uniform across the whole country with some variations in the Northern part where higher proportions of atrial septal defects were noted. CHD may be genetic and/or non-genetic in origin, including environmental pollution which is characteristic in the whole country. It is also important to note that the Niger Delta harbours children with the highest prevalence of CHD in Nigeria and probably Africa. [104] This may be attributable to the increased oil spillage and gas flaring from petroleum exploitation in the region.

3gii. NTD

Neural tube defects occur in over 300,000 newborns annually. [5] Unfortunately we do not have the statistics for these abnormalities in sub-Sahara Africa including Nigeria. Non-syndromic or isolated NTDs result when the neural tube closure fails during embryogenesis. Fundamental questions of molecular and cellular mechanisms of neural tube closure in human embryos remain largely unanswered. [104, 106] The initial step in neural tube development (neurulation) is a characteristic thickening of the ectoderm from the level of the primitive node of Hensen caudally to the prochordal plate rostrally at the beginning of the 3rd week of embryonic life. This slipper-shaped structure is called the neural plate. In humans, neural plate development into the neural tube occurs via a two-step process - primary neurulation (day 21 to 28 of embryogenesis) helps in the formation of the brain and most part of the spinal cord and secondary neurulation (day 35 to 42 of embryogenesis) leads to the formation of the neural tube caudal to the mid-sacral region. [107] Failure of primary neurulation results in open neural tube defects generally seen in anencephaly, myelomeningocele also known as open spina bifida and craniorachischisis. Any deformity in spinal cord structure that are covered by skin are called closed neural tube defects. It ranges from asymptomatic spina bifida occulta to severe spinal cord tethering and is traceable when secondary neurulation are disrupted. [108]

Various clinical presentations of NTD are as follows: Anencephaly – The neural tube fails to get close and presents with absence of large part of the brain, skull, and scalp. Encephaloceles - Cranial contents protrude beyond the normal confines of the skull through a calvarium defect. Myelomeningocele - Failure of spinal neural tube closure, especially in the lumbosacral region. It involves underlying layers that includes the spinal cord, nerve roots, vertebral bodies, meninges and skin. Craniorachischisis - Neural tube closure is completely absent in this disease, which affects both the brain and the spine. Initiating event of neurulation in the early embryo fails, resulting in craniorachischisis. [109] It is generally agreed that most NTD cases are of multifactorial origin, having a significant genetic component to their aetiology that interacts with a number of environmental

risk factors. [1, 110] It involves gene–gene, gene–environment and gene–nutrient interactions. [3] A host of physical agents (e.g. X-irradiation, hyperthermia, stress), chemical agents (e.g. organic mercury, lead), air and water pollutants and occupational exposure to environmental teratogens are associated with the development of NTD as shown under 'environmental factors' above. Other risk factors are folate deficiency, [24] antiepileptics, hypervitaminosis A and substance abuse (e.g. alcohol). [1111] Prenatal Infections, maternal metabolic conditions: (e.g. phenylketonuria, diabetes mellitus, endemic cretinism) [111-113] and hyperthermia' [114] Maternal exposure to all been associated with increased prevalence of NTD.

3giii. Cleft lip and /or palate (CLP)

In most cases, the cause of cleft lip and cleft palate is unknown. There appears to be a greater chance of clefting in a newborn if a sibling, parent, or relative has had the problem. Another potential cause may be related to a medication a mother may have taken during her pregnancy. Some drugs may cause cleft lip and cleft palate. Among them: anti-seizure/anticonvulsant drugs, acne drugs containing Accutane, and methotrexate, a drug commonly used for treating cancer, arthritis, and psoriasis.

Not taking supplements of folic acid during the first 12 weeks of pregnancy, [115, 116, 117] Smoking, [118, 119] and alcohol use [120] The results were supported by are other risk factors for developing CLP.

Recommendations

There is urgent need for creation of Nigerian national register of birth defects and formulation of national policies on their management as obtainable in the developed countries of Europe and North America. Intended marriage couples should seek genetic counselling with a view of ascertaining there genotype and thereby preventing autosomal recessive defects. There is also a call for laws that will prevent unregulated usage of recreational and therapeutic drugs. NAFDAC should ensure that salt has enough iodine and cereals are well fortified with folic acid. Given the enormous impact of environmental pollution on the prevalence of birth defects, it is highly recommended that daily air quality check should be carried out in Nigeria or at least in the cities and in the Niger Delta in particular.

Furthermore, the Federal Government should ensure that companies including multinationals observe the environmental laws of the land. Effective maternity care in Nigeria should be made free, dedicated Fetal Medicine units should be built and fully equipped in each of the federal Teaching Hospitals in the country. Creation of super centres where fetal surgery can be done is also highly recommended, one in the far North, one in the Middle-Belt, another in the Western and one in the Eastern part of Nigeria. Finally, it is highly recommended that a multicentre prospective study on the same subject involving all the geopolitical regions of Nigeria be carried out. Attention should be paid to the risk factors for birth defects in each region including physical and laboratory-based human biomonitoring.

V. Conclusion

Nigeria has no national register of birth defects, no guideline on their management and also no record of causative factors of the defects. There is therefore no nationally planned strategy on how to prevent the defects irrespective of their significant contribution to perinatal and child morbidity and mortality. Pregnancies in developing countries with Nigeria inclusive tend to be exposed to potential teratogens to a higher degree than in industrialized nations and therefore there should be more congenital abnormalities in the developing countries than in the developed world.

The causes of birth defects in Nigeria are largely not known. The known causes are of genetic and non-genetic origin which, intertwine with each other - gene–gene, gene–environment and gene–nutrient interactions. There are palpable regional variations in the presence of the causative factors. Autosomal recessive disorders (sickle cell disease, glucos6 phosphate deficiency, oculocutaneous albinosis, etc) are prominent in Nigeria because of the survival advantage of healthy carriers of the genes for sickle cell anaemia (SCA) and glucose-6-phosphate dehydrogenase (G6PD) deficiency against the lethal effects of malaria and parental consanguineous marriage

Non-genetic causative factors of birth defects are neglect of environmental protection policies and therefore significant environmental pollution, advanced maternal age at delivery, poverty, non-affordability of proper antenatal care and prenatal diagnosis, poor maternal nutrition, maternal illness (diabetes mellitus and phenylketonuria), unregulated maternal exposure to recreational (alcohol and cigarettes) and therapeutic drugs (antiepileptic and warfarin) and maternal prenatal infection.

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M, Abbey "Aetiology of Congenital Abnormalities in Nigeria. "IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 5, 2018, pp 28-41.