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REVIEW ARTICLE

Congenital Abnormalities: Consequence of Maternal Zika Virus Infection: A Narrative Review

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Abstract: ***Background*:** Zika virus (ZIKV) is a deadly flavivirus that has spread from Africa to Asia and European countries. The virus is associated with other viruses in the same genus or family, transmitted by the same mosquito species with known history of fatality. A sudden increase in the rate of infection from ZIKV has made it a global health concern, which necessitates close symptom monitoring, enhancing treatment options, and vaccine production.

***Objectives*:** This paper reviewed current reports on birth defects associated with ZIKV, mode of transmission, body fluids containing the virus, diagnosis, possible preventive measures or treatments, and vaccine development.

***Methods*:** Google scholar was used as the major search engine for research and review articles, up to July, 2016. Search terms such as "ZIKV", "ZIKV infection", "ZIKV serotypes", "treatment of ZIKV infection", "co-infection with zika virus", "flavivirus", "microcephaly and zika", "birth defects and Zika", as well as "ZIKV vaccine" were used.

***Results*:** ZIKV has been detected in several body fluids such as saliva, semen, blood, and amniotic fluid. This reveals the possibility of sexual and mother to child transmission. The ability of the virus to cross the placental barrier and the blood brain barrier (BBB) has been associated with birth defects such as microcephaly, ocular defects, and Guillian Barre syndrome (GBS). Preventive measures can reduce the spread and risk of the infection. Available treatments only target symptoms while vaccines are still under development.

***Conclusion*:** Birth defects are associated with ZIKV infection in pregnant women; hence the need for development of standard treatments, employment of strict preventive measures and development of effective vaccines.

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INTRODUCTION

ZIKV is a deadly virus that belongs to flaviviridae and flavivirus family and genus respectively transmitted by female *Aedes* mosquito. The occurrence of ZIKV has been dated to the 1940s in Uganda [1]. This virus was first isolated in 1952 from the serum of monkeys that developed fever from a research conducted on yellow fever; it was described as 'Zika' from the name of the forest, where the study was carried out [1]. It was first isolated from the human serum in Nigeria in 1954; from patients that presented with jaundice suspected to be as a result of yellow fever infection [2]. The isolation of this virus and similarly such as dengue and yellow fever in different age groups and gender were also reported from a study conducted in southern part of Nigeria between 1964 and 1975 [3, 4]. Infections from these viruses were found to be more during the rainy season and less during the dry season in Nigeria. Several incidences of neutralizing antibodies in serum of patients with suspected symptoms of this virus have also been reported in Asian countries such as India, China, and Indonesia between 1950s and 1980s [5-8]. Incidence of isolation of this virus was also reported in other west, central, and east African countries such as Gabon, Sierra Leone, Central African Republic, and Egypt [9]. In America, the first incidence of ZIKV isolation was reported from Yap Island in the Federated State of Micronesia from the serum of patients, who presented with symptoms such as arthralgia, rash, and conjunctivitis in 2007 [10]. Recently, infection from this virus have spread to different parts of America especially, the Central and Southern regions, as well as Europe. Reports on ZIKV have been few; in tens and hundreds, but recently from 2014 to 2016 reported cases have increased to thousands affecting mostly women and children [11, 12]. This sudden increase has made infection from ZIKV a global health concern, which necessitates close symptom monitoring, enhancing treatment options, and vaccine production. The objective of this review was to determine the relationship between mother to child transfer of ZIKV infection and birth defects, preventive measures, treatments and vaccine development.

METHODS

Google scholar was used as the major search engine for research and review articles, to July, 2016. Search terms such as "ZIKV", "ZIKV infection", "ZIKV serotypes", "treatment of ZIKV infection", "co-infection with zika virus", "flavivirus", "microcephaly and zika", "birth defects and Zika", as well as "ZIKV vaccine" were used as shown in Fig. (**1**). Articles used were mainly from affected areas such as Africa, Asia, Brazil, and the United States.

MODES OF TRANSMISSION

Transmission of ZIKV infection can be *via* bite from a female *Aedes* mosquito, blood, sexual relationship, and in rare cases mother to child transfer.

Mosquito

Human transmission of ZIKV occurs *via* female *Aedes* mosquitoes such as *Aedes aegypti* and *Aedes albopictus*; these same mosquito species are responsible for transmitting other viruses such as dengue and chikungunya [12]. ZIKV like plasmodium parasite reside in areas with stagnant waters, damp areas, and dirty environment; its life cycle from egg to adult stage is usually 12 to 14 days and the adult virus can live for a few weeks to one month depending on the environmental condition. Studies have revealed that the incubation period for this virus may be from 6-10 days; because symptoms do not become apparent until 10 days after history of exposure [8,13]. Several studies have been conducted and reported on the transmission of this deadly virus *via* an infected mosquito bite, or human to human transfer from the blood of infected individuals to un-infected mosquito, which then infect humans through a bite [13-15].

Blood

Blood transmission of this virus has also been reported as a significant source of transmission, especially in cases of blood transfusion; this may be limited because blood is usually screened in most cases before transfusion [16]. A study carried out in French Polynesia an area that has experienced large outbreaks of ZIKV, produced a technically possible method of detecting the virus even in individuals with no symptoms by employing specific nucleic acid method of testing blood obtained from donors by polymerizing chain reaction (PCR) [17]. The virus showed positive results in donors' bloods that were asymptomatic using this

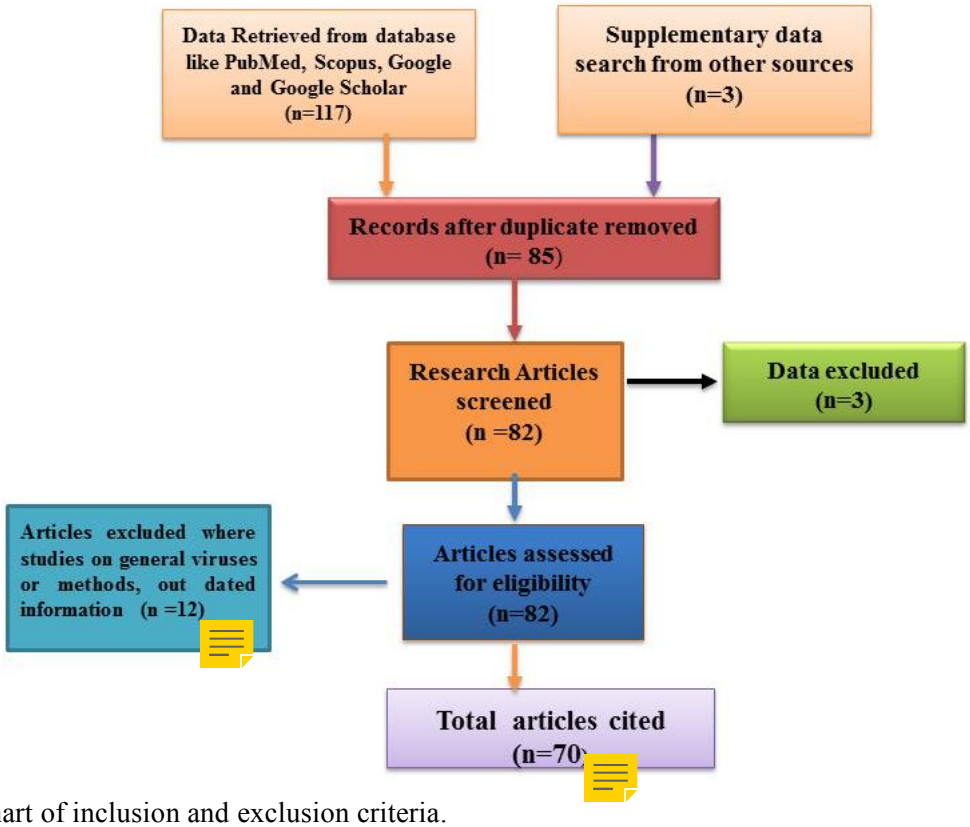

Fig. (1). Flow chart of inclusion and exclusion criteria.

method. The possibility of transmission *via* blood has increased the rate at which this viral infection can spread wide over a short period of time. Center for disease control (CDC) reported two cases of ZIKV infection through blood transfusion from a blood center and the health department in Sao Paulo, Campinas; in which the former was confirmed through genetic testing.

Sexual Relationship

There is also a possibility of sexual transmission of this virus. In a recent study conducted in an area (French Polynesia) with the virus outbreak, ZIKV was isolated from a patient's semen (Table **1**), which presented with hematospermia and had previous symptoms of infection from the virus [18]. Another study conducted on two Americans, who worked in Senegal before returning back to the United States presented with symptoms such as swollen ankles, rash, arthralgia, and hematospermia were observed from 6 days after their return [13]. Similar symptoms were also observed in the wife of one of the patients; which may be as a result of sexual contact since the patient had not travelled to any endemic area, and no case of ZIKV infection had been reported in that area as at the time of the study. Dallas County Health and Human Services (DCHHS), in 2016 also reported a case of the viral infection of an individual who had a sexual relationship with a partner that recently returned from the ZIKV endemic area.

Saliva

Another possibility of ZIKV transmission, but very rare is through saliva (Table **1**). This method was usually employed in situations where blood availability is limited; such as in infants and children. Both saliva and blood samples were obtained from patients in French Polynesia who presented with symptoms of ZIKV infection; results obtained revealed that the virus was detected in saliva samples more than blood samples [19].

Mother to Child

Several studies have been conducted and revealed the possibility of mother to child transmission of viral infections; such as Human Immunodeficiency Virus (HIV) and different types of hepatitis virus; which can be during pregnancy or breast feeding [20, 21]. Reports and studies have indicated the possibility of transmitting ZIKV

Table 1. Fluids containing ZIKV.

Body Fluids	Areas/Countries	References
Blood/Serum	French Polynesia, New Caledonia	[17-18, 29]
Saliva	French Polynesia	[19]
Urine	New Caledonia	[18, 29]
Semen	United States, French Polynesia	[13, 18, 30]
Amniotic fluid	Brazil	[31, 32]
Breast milk	New Caledonia	[33]

from mother to neonate during pregnancy. A reverse-transcriptase-polymerized chain reaction (RT-PCR) test conducted on serum obtained from two mothers infected with ZIKV and their neonates four days after delivery revealed the presence of the virus, which has been transmitted during pregnancy or at the point of delivery [22]. Transmission of this virus to infants has been shown to cause severe birth defects such as microcephaly or complicate the condition of existing diseases such as Guillain Barre Syndrome (GBS) [23]. Over six hundred cases of congenital abnormalities, mainly microcephaly reported by Brazilian authorities have been suspected to be associated with the recent outbreak of ZIKV infection in the area [24]. During this period of the outbreak, two pregnant women with ZIKV symptoms were diagnosed with fetal microcephaly after an ultrasound; an amniotic fluid test and real time PCR were also conducted, which revealed positive results for the virus; this confirmed the possibility of transmitting the virus to the fetus while in the uterus [25]. This virus has been shown to affect the fetus at all stages of pregnancy, irrespective of trimester, but report shows more cases in the first trimester [26]. Another study has associated the occurrence of ZIKV infection with microcephaly and ocular defects in neonates born from infected mothers after the breakout incidence in Brazil, 2015 [27]. Another study in Salvador, Brazil was also carried out on a larger number of patients with microcephaly to determine ocular findings suspected to be associated with intrauterine infection with ZIKV; the results revealed ocular abnormalities such as bilateral macular and perimacular lesions in infants of mothers with signs and symptoms of ZIKV infection during pregnancy [26]. ZIKV has also been shown to increase the fatality of sickle cell disease (SCD) [28].

Possible Mechanism of Brain Defects from ZIKV Infection

Recent findings reported that ZIKV crossed the placental barrier (Fig. **2**) and thus was found in the amniotic fluid of infected pregnant mothers [25, 32]. Intracranial injection of young mice and litters revealed necrosis and inflammation of neurons within the hippocampus, and the enlargement of glial cells [34]. Viruses such as dengue and chikungunya have been associated with brain defects [35, 36]. A recent study revealed that ZIKV can cause neurological disorders by possibly reducing the growth rate of human neural progenitor cells and increasing cell death [37]. Ultrasonography of the womb of an infected mother revealed intrauterine growth retardation and microcephaly [38]. An autopsy was performed at termination of pregnancy, which revealed micrencephaly, with agyria, hydrocephalus, multifocal dystrophic calcifications in the cortex and subcortical white matter with mild focal inflammation. ZIKV has also been found in brain and placental tissues of neonates born from infected mothers using RT-PCR methods [39].

Birth Defects Associated with ZIKV

The wide spread of ZIKV is a public concern because of possibility of mother to child transmission and risk of birth defects. Many defects have been associated with the virus (Table **2**). ZIKV has also been associated with miscarriages and neonatal deaths [39]. Reports have shown that ZIKV can affect the fetus at all stages of pregnancy and cause birth defects shown in Fig. (**2**) [40]. The majority of reported cases of birth defects associated with ZIKV infection has been microcephaly [41]. A research conducted on infants with ZIKV infection

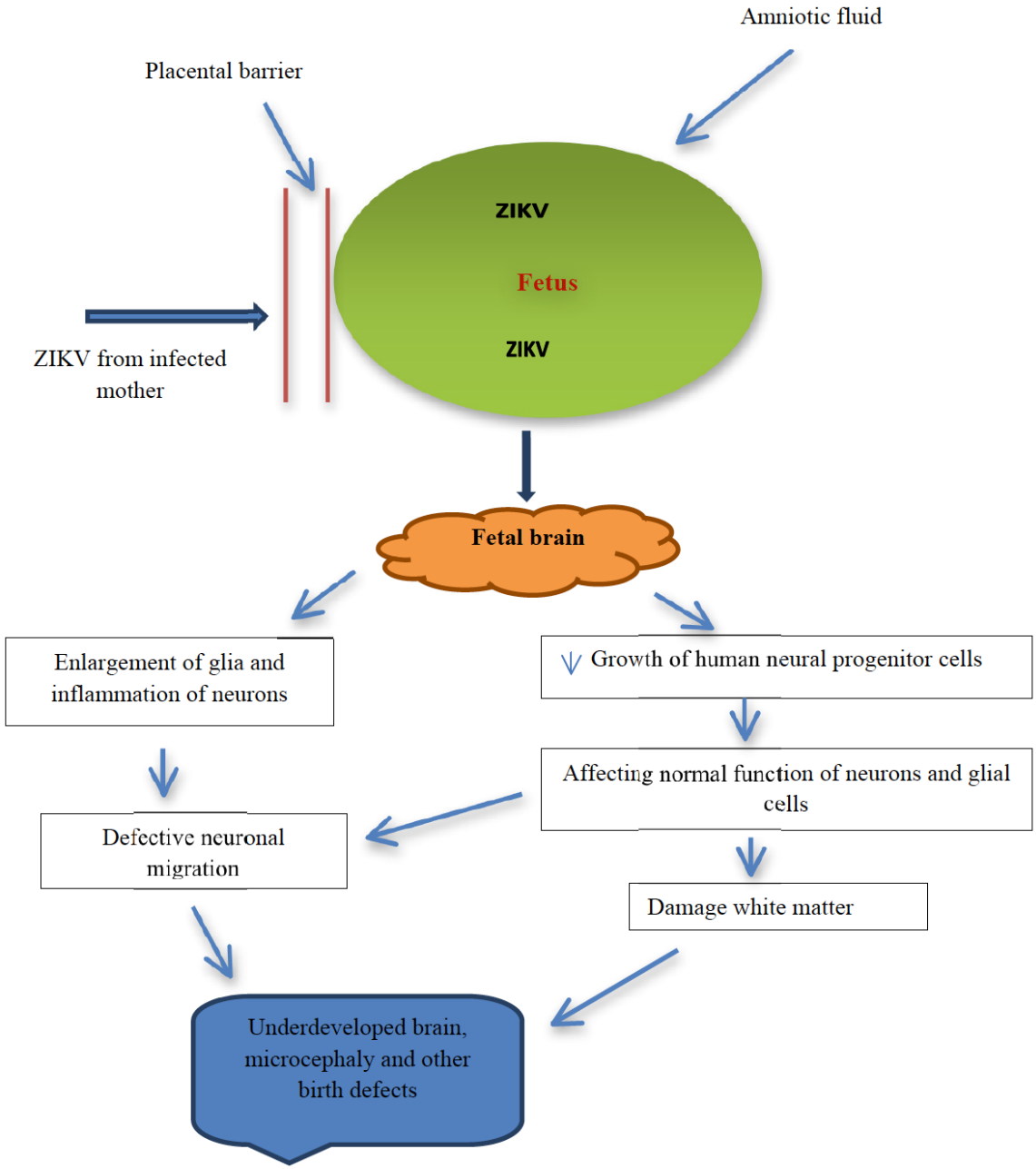

Fig. (2). Possible mechanism of ZIKV brain defects.

Table 2. Birth defects associated with ZIKV.

Birth Defect	Countries	References
Microcephaly	Brazil, Columbia, Hawaii	[25, 46]
Ocular abnormalities	Brazil	[26]
Guillain-Barré syndrome	Brazil, Columbia, French Polynesia	[46, 47]
Hydrops fetalis and Hydranencephaly	Brazil	[31]

in Brazil revealed its association with optic nerve anomalies and ocular lesions [26]. A review also discussed the link between maternal ZIKV infection, microcephaly, and eye lesions in new born [42]. The infection has also been shown to increase the risk of developing GBS [43]. ZIKV infection has been shown to cause severe fluid accumulation in fetal compartment and fetal death [31]. The possibility of developing meningoencephalitis and hypertensive iridocyclitis in adults from ZIKV infection has also been reported [44, 45]. Acute myelitis has also been associated with ZIKV infection following the admission of a teenager to a hospital in Guadaluope [46].

Mechanisms that May be Related to ZIKV Associated Birth Defects

ZIKV has been reported to cause several birth defects such ocular abnormalities and neurological complications following in utero exposure of the fetus [26, 41]. A recent study conducted in mice reported that ZIKV is capable of causing inflammation of the cornea, retina, and the optic nerve; which may result in eye damage/ blindness of the fetus or new born [48]. Infection of the fetus by ZIKV can be classified under non-immune causes of Hydrops fetalis in the fetus/neonate [49]. It involves the abnormal movement of fluid between the plasma and tissues, which may obstruct oxygen delivery to tissues, increase oxygen extraction, cause redistribution of blood flow to organs, with subsequent renal tubular damage, increased cardiac output (CO) and activation of renin angiotensin system (RAS) [50, 51]. These processes can lead to interstitial fluid accumulation in the fetus, a condition known as hydrops fetalis. Decrease in the growth of progenitor cells and stem cells have been associated with reduction in the number of neurons generated during neurogenesis which can lead to cell death, reduced brain volume, and subsequent microcephaly [37]. These possible mechanisms have been summarized in the Fig. (**3**).

DIAGNOSIS

The incubation period for ZIKV is usually 4-10 days, associated with symptoms such as headache, fever, rashes, conjunctivitis, muscle and joint pain [52]. Diagnosis of this infection can be confirmed only *via* laboratory testing for the presence of viral RNA in body fluids such as serum, saliva, and urine [19, 22, 23, 29]. There are specific tests used to confirm the presence of ZIKV, RT-PCR has been used to detect the virus in serum [53]. RT-PCR can detect RNA viruses in serum during the first seven days of infection; however a serological test may be conducted over 5 days to rule out flavivirus infection, when RT-PCR results are negative [54]. ZIKV has also been detected in urine using RT-PCR method 10 days after infection, a period longer than that of blood [29]. Specific tests such as immunoglobulin enzyme linked immunosorbent assay (Ig-ELISA) are carried out to detect the presence of abovirus antibodies like immunoglobulin-M and -G (Ig-M/G) [54]. Plaque reduction neutralization test (PRNT) is specific for differentiation of flavivirus that are closely related, and can be carried out in addition to Ig-ELISA test [55]. ZIKV has been shown to persist in semen for 55 - 65 days from first onset of symptoms, RT-PCR method has been used to confirm the presence of the virus in semen [18]. The tests mentioned previously are also used to diagnose ZIKV infection in pregnant women, but onset, duration, and incubation period of the virus can affect the accuracy of these tests [40]. Tests are also carried out on pregnant women exposed to ZIKV on the safety or otherwise of their fetuses, as a result of strong evidences associated with Zika virus infection and birth defects. Prenatal ultrasonography is carried out to evaluate microcephaly in fetuses from exposed or infected mothers [32,38]. ZIKV has also been detected in fetal brain using RT-PCR test [38].

PREVENTION

Several guidelines have been set by world protection agencies on how to prevent ZIKV infection and transmission. Mosquito breeding can be prevented by avoiding dark areas and stagnant waters, while bites can be prevented by using overall clothing, treated mosquito nets, and use of insect repellants [56]. Human transmission can be prevented by protecting one's self from mosquito bites and by avoiding any sexual relationship with ZIKV suspected individual [57]. Partners or spouses of pregnant women suspected with the disease should abstain or use other protective methods such as condoms to reduce the risk of fetal and human to human exposure [57, 58]. Travelling to endemic areas should be restricted, especially by pregnant women or those who want to

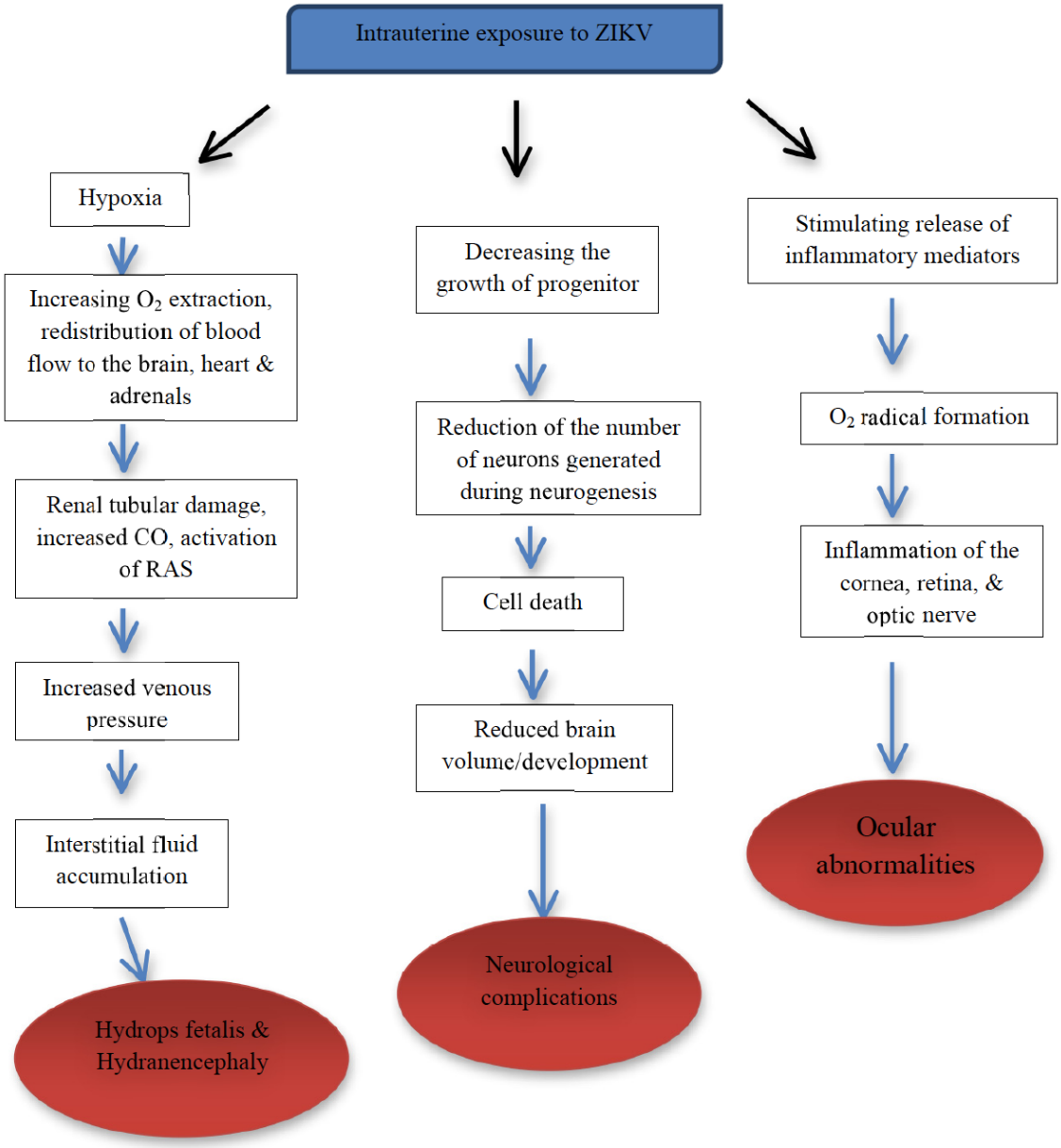

Fig. (3). Mechanisms that may be related to ZIKV associated birth defects.

conceive. Possible quarantine of people travelling from infected to non - infected areas may be employed until they are diagnosed ZIKV free. The major preventive measure should be complete eradication of the vector Aedes mosquito and also development of vaccines.

ZIKV VACCINE

There are no available specific treatments for ZIKV infection. Treatments are directed towards visible symptoms such as headache, fever, rashes, joint pain and conjunctivitis [10, 13]. Vaccines are available for some flavivirus such as yellow fever, West Nile virus and Dengue, which are in the same genus with ZIKV and are transmitted by same mosquitoes [59, 60]. Viruses from flaviviridae family are positive stranded RNA viruses with three important structural proteins, capsid (C), envelope (E), and membrane (M) [58]. In developing immunity against flavivirus infection, the presence of virus neutralizing antibodies, which inhibit normal molecular functioning of the virus with E-protein as the main target plays a very important role [61]. Phagocytosis and clearance of infected cells *via* Fc-γ receptors by antibodies against a non-structural protein (NS1) produced by these cells has been related to protection against flavivi-

rus infection [62, 63]. Flavivirus are considered to be related antigenically, which indicate the possibility of cross neutralization of antibodies as well as cross protection [64]. Degree of neutralization and protection depends on similarity in amino acid sequence in E-protein, which is higher among serocomplexes [58]. Infection with a particular serotype has been shown to produce immunity against other serotypes such as dengue virus [65, 66]. Cross reactivity of these viruses and functions of antibodies may be effective in prophylaxis and treatment, following results obtained from a study conducted using an E protein domain III protected mice model which reported efficacy against ZIKV infection [67].

There are three lineages of ZIKV based on geographical location; Asian, East African, and West African [68]. The virus is antigenically related to Spondweni serocomplexes, which belong to the same flavivirus genus and is transmitted by *Aedes* mosquitoes [69, 70]. Some level of cross reactivity has been reported between ZIKV and other flavivirus from serologic tests carried out [53]. No vaccine against ZIKV is available, though, it is still under development. World Health Organization (WHO) has identified two candidates for ZIKV vaccine from the United States and India, which are DNA and inactivated product vaccines. Promising results of vaccine research on animals, especially mice have been reported. Two approaches with 95% success rate have been reported in Brazil; genetic control of the vector and developing species resistant to infection due to abovirus [71, 72]. The mosquito species are fed with supplement capable of repressing the effect of the lethal gene such as tetracycline; when they mate with females they produce offspring that lack the lethal gene, hence survival to the adult stage is made difficult. Another method of minimizing the ability of abovirus to replicate within a vector by the use of endosymbiotic bacteria has been implemented and successful for dengue, chikungunya, and yellow fever, hence may be effective for ZIKV [73]. Recently in Brazil, a full length pre-membrane and envelop DNA vaccine has provided complete protection against ZIKV in mice evidenced as absence of viremia following challenge [74]. The same group of scientists also showed possibility of passive protection from adoptive transfer of purified IgG from vaccinated mice.

CONCLUSION AND RECOMMENDATION

ZIKV infection is a major public health problem as a result of the increasing number of reported cases and complications associated with the virus. The virus can be transmitted to humans *via* several modes including sexual and prenatal. It has also been associated with fetal abnormalities and exacerbation of certain congenital conditions. Laboratory confirmatory tests are available in addition to physical symptoms for effective diagnosis. Measures to avoid infection and transmission should be employed especially among children and pregnant women. More researches should be carried out to develop standard antiviral treatments and vaccines to manage symptoms and minimize the rapid spread of the virus around the world.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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