Determining the extent of the association between TORCH infections and fetal, neonatal death at Benghazi medical Centre.

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Abstract:

Background: During the early period of pregnancy, the developing fetus may be susceptible to external and internal factors, which may lead to the undesirable gestational outcomes (preterm delivery or perinatal death). The highest rates of preterm and perinatal mortality reflect the inadequate management of pregnancy, delivery, and newborn care.

Aim: this study aimed to understand whether TORCH infection or other causes, are associated with the pregnancy complications, fetal and neonatal death.

Method: A descriptive, retrospective cross sectional study design. The data was collected by using the death certificates from the gynecology and obstetrics department at BMC and Al- Joumhouria hospital from 1-1-2019 to 31-12- 2020, in Benghazi, Libya. The total number of death cases throughout the two years of the study period were 1,070 neonates died at the neonatal unit.

Results: there were a slight predominance in male deaths (54.80%) (55.90%) over females (44.30%) (41.80%) respectively. the most frequent fetal death had shown among the age groups 29-32 weeks and 25- 28weeks during 2019 and 2020. Furthermore, the mortality rates of neonates was much higher among age group 1day to 28 days than 0 to 23 hours for the both studied years. preterm birth was the most common cause of death in 2019 and 2020. Followed by respiratory disorders, then multiple congenital malformation, sepsis, intrauterine fetal death (IUFD) after that according to the mother conditions.

Conclusion: The absence of the main causes of the fetal and neonatal death synthesize an evidence that correlate adverse perinatal outcomes with any of TORCH agents. Regular prenatal screening test is justified. It also becomes possible to speculate that heath care staff and the pregnant women in Benghazi are not familiar with the roots of TORCH transmission.

Introduction:

During the early period of pregnancy, the developing fetus may be susceptible to external and internal factors, which may lead to the undesirable gestational outcomes (preterm delivery or perinatal death) (Taye, Molla, 2019). The perinatal period starts usually from the 24th week and extending to the end of the first week of life. Whereas, Preterm birth refers to the babies who are born alive before 37

weeks of pregnancy are completed. The preterm births categorized according to the gestational age to:

 Less than 28 weeks: extremely preterm

 28 to less than 32 weeks: very preterm

 32 to 37 weeks: moderate to late preterm(WHO, 2023)

The major occurrence of   the preterm deliveries are in southern Asia and sub-Saharan Africa, since in low-income countries more than 90% of extremely preterm babies die within the first few days of life, while in high-income settings nearly 10% or less of extremely preterm babies die.(WHO, 2023).). In fact, the highest rates of preterm and perinatal mortality reflect the inadequate management of pregnancy, delivery, and newborn care. Hence, pregnancy complications or maternal diseases lead the fetuses to die intra utero, before onset of labor. (WHO, 2006)

 The Perinatal mortality includes both stillbirths or intrauterine fetal death and early neonatal deaths. (WHO, 2006) **Stillbirth**, defined as a baby who delivered with no signs of life after 24 completed weeks of pregnancy. **Intrauterine fetal death** used to describe babies with no signs of life in utero, and the death during the first hours until 28 days after the newborn baby has delivered is called as **neonatal death**.(Man J, Hutchinson J, et al, 2016)

There is an estimation that revealed; about 20% of stillborn fetuses were suffering from birth defects (BDs). Furthermore, the infant's death rate from BDs had increased in both developing and developed countries, as around 95%of all reported death from BDs had shown in the low and middle-income countries. (Taye, Molla, 2019). Actually, according to the WHO estimations, congenital disorders cannot be associated with a specific cause, although there are some known risk factors that proved to cause such defects such as one or more genetic, infectious, nutritional or environmental factors.(WHO, 2023) .

  Globally, Infection is an important cause of stillbirths, since each year 3.2 million stillbirths occur worldwide (Ishaque, Sidra, et al, 2011). While in low and middle-income countries infections account for about 50% or more of all prenatal death. (Goldenberg, Robert L, et al, 2010) Congenital infections in pregnancy are considered to be as major causes of maternal and fetal morbidity and mortality. Since during the first period of gestation infection is proved to cause miscarriage, stillbirth, teratogenic and mental retardation. Infections can develop in the fetus Transplacentally, prenatally (from vaginal secretions or blood) or postnatally (from breast milk). (Medscape, 2017)

It is important to take into your account that, the pregnant women and their infants with intrauterine growth retardation should be screened for TORCH infections. (Ghannad , Masoud Sabouri, et al, 2014) as these sort of infections were identified to generate congenital anomalies , birth defects , abortion, and

intrauterine fetal death if the mother contracts them during the pregnancy. The acronym (TORCH) stands for:

1. Toxoplasmosis

2. Other infections (syphilis, varicella, parvovirus "B19" infection, listeriosis)

3. Rubella

4. Cytomegalovirus

5. Herpes simplex virus (HSV). (Medscape, 2017)

These TORCH agents are different from each other in the life cycle, and their impacts have lifelong influences. (Liu Y, Wu Y, et al, 2020). The primary infection is more likely to have severe effects on fetus than recurrent infection and may cause spontaneous abortions, intrauterine fetal death, congenital anomalies, intrauterine growth retardation, prematurity, and stillbirth.(Prasoona K, Srinadh B, 2015).

Unfortunately, these group of infections occur during the period of gestations and mostly associated with congenital anomalies and possibly stillbirths (stegmann Bj, Carey JC, 2002). Nearly 80 % of stillbirths are preterm and about 50% of all stillbirths occur prior to 28 weeks. (Carlo, Waldemar A, et al, 2010)Cytomegalovirus and Rubella are accounted as dangerous viral infections to the fetus. In fact, It is estimated that CMV infects approximately 0.2% to 2% in the developed countries, and about 6–14% in the developing countries, which makes it the most common cause of intrauterine infection and prematurity (Pass RF, Arav-Boger R,2018)(Kenneson A, Cannon MJ, 2007). additionally, rubella is estimated to be around 110,000 of infants born with congenital rubella syndrome every year . More importantly, in the first period of gestation, there is a higher risk of vertical transmission (80%–90%) from a non-immune mother with primary rubella infection, and infection during this period is associated with the most severe manifestations at birth. Significant Global estimation of pregnant women with syphilis indicate that approximately 2 million women were infected in 2003 and 1.4 million cases in 2008(NEU, Natalie; DUCHON, 2015)

It is clear that TORCH infections are responsible for the major of maternal and fetal morbidity and mortality in Pregnancy, and their modes of transmissions are dangerous and unpreventable if the infection are not recognized.

Thus, this study aimed to understand whether TORCH infection or other causes, are associated with the pregnancy complications , fetal and neonatal death.

Methods:

A descriptive, retrospective cross sectional study design. The data was collected by using the death certificates from the gynecology and obstetrics department at BMC and Al- Joumhouria hospital from 1-1-2019 to 31-12- 2020, in Benghazi,

Libya. The total number of death cases throughout the two years of the study period were 1,070 neonates died at the neonatal unit.

Results:

As shown in figures, 1 &2 there were a slight predominance in male deaths (54.80%) (55.90%) over females (44.30%) (41.80%) respectively.

Total of fetal and neonatal death in 2019

0.87%

44.30%

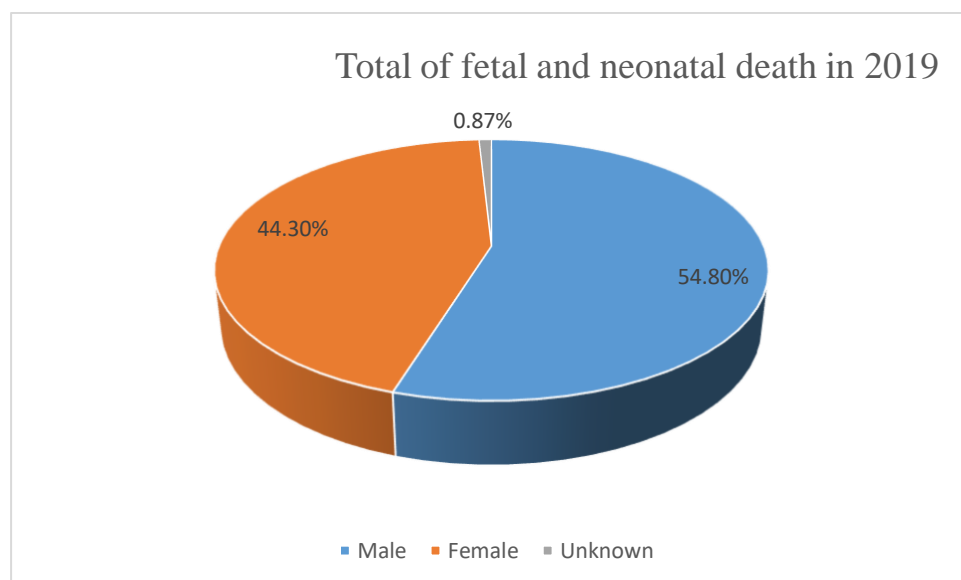54.80%

■ Male ■ Female ■ Unknown

Fig. (1) Distributions of fetal and neonatal death according to the gender during 2019

The pie-chart showing the total of fetal and neonatal death in 2019. 54. 80 % of the participants who died were male. While 44.30 % of them were female and 0.87 were unknown.
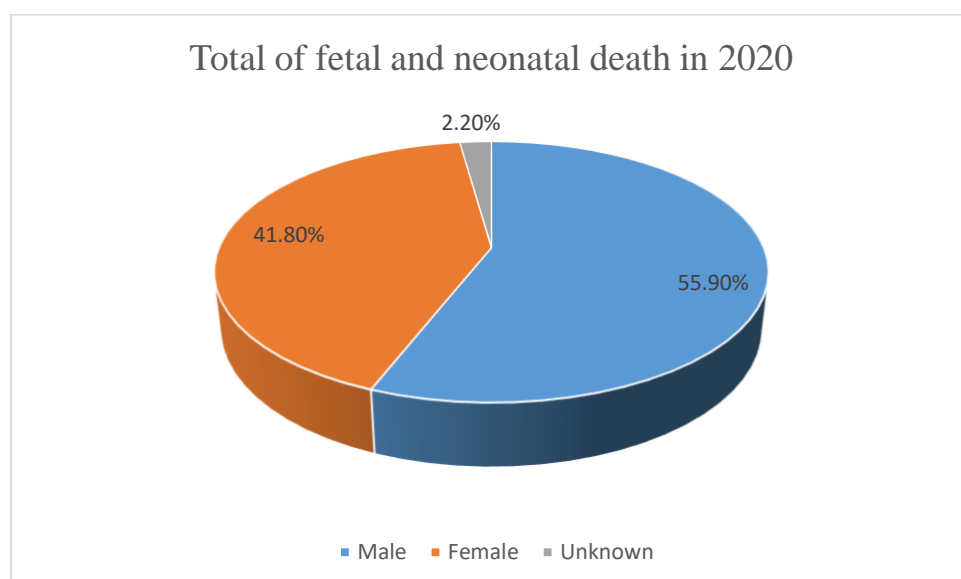

Total of fetal and neonatal death in 2020

2.20%

41.80%

55.90%

■ Male ■ Female ■ Unknown

Fig. (2) Distributions of fetal and neonatal death according to the gender during 2020

The pie-chart showing total of fetal and neonatal death cases from 1-2-2020 to 31-12- 2020. More than half of 55.90% cases who died were male. Whereas, 41.80 % of them were female. 2.20% of participants were died.

Table 1 Distribution of fetal death according the age in weeks during (2019 & 2020)

Age in weeks of fetal death cases	Number of death cases (%)	
	2019	**2020**
13-16	1 (0.22%)	-
17-20	7 (1.5%)	3 (0.66%)
21-24	57 (12.9%)	22 (4.8%)
25-28	103 (23.4%)	76 (4.8%)
32-29	119 (27.1%)	131 (28.9%)
33-36	73 (16.6%)	61 (13.4%)
37-42	45 (10.2%)	44 (9.7%)
Un known	34 (7.7%)	115 (25.4%)
Total	439	452

Table 1 shows the age in weeks of fetal death cases during 2019 & 2020. Regarding year of 2019, the greatest proportion of the participants was died at 32-29 weeks (27.1%).Whereas the lowest proportion of the participants was died at 13-16 weeks (0.22%). While 10.2% of them were died without any unknown.

Regarding year of 2020, The highest percentages of the participants was died at 32-29 weeks (28.9%%).Whereas the lowest percentages of the participants was died at 17-20 weeks (0.66%). While no death was happen at13-16 10.2% of them were died without any un-known

Table 2 Distribution of neonatal death according the age in days during 2019 & 2020

Age in days of neonatal death cases	Number of death cases (%)	
	2019	**2020**
1 hour- 23 hours	47 (35.6%)	6 (12.8%)
1 day- 28 days	85 (64.4%)	41 (87.2%)
Total	132	47

Table 2 displays the age in days of neonatal death cases in both of year (2019 & 2020). First year 2019, more than half (64.6%) of participate were died between 1 day- 28 days . Whereas,35.6% of them were died between 1 hour- 23 hours. Second year 2020, the majority of cases(87.2%) were died between 1 day- 28 days . Whereas,12.8% of them were died between 1 hour- 23 hours.

Table (3) Describes the number of fetal mortality rates according to the causes of death in 2019 and 2020

Causes of death	Number of death cases during 2019	Number of death cases during 2020
Prematurity	352	290
Respiratory disorders*1	131	160
Sepsis	49	72
Congenital anomalies*2	91	75
Metabolic disorders*3	15	6
IUFD*4	84	118
Cardiopulmonary arrest	89	31
Maternal conditions*5	57	67

*1 (Respiratory distress syndrome, Hyaline membrane disease, pneumothorax)

*2 (Congenital heart diseases, congenital head and brain disorders, multiple congenital malformation)

*3 (Down syndrome, Edward syndrome, potter and Golden har syndrome)

*4 intrauterine fetal death

*5(Placenta abruption, birth asphyxia, hypo and hyperglycemia, etc.)

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There was more than one cause of death for each case

Table 3shows the number of fetal and neonatal mortality rates according to the causes of death, in 2019 and 2020 the highest rate was prematurity, as shown their total numbers were higher in 2019 (352) than were reported in 2020(

290). The second most common cause of death was respiratory disorders also for the two studied period. Whereas, metabolic disorders had lowest numbers of cases of death in 2019 and 2020.

Discussion:

This paper was conducted to understand the main cause of death that contributes to the fetal adverse outcomes. This can be seen clearly from the connection with previous studies that have been done in the literature and neighboring areas. The current study findings revealed that number of fetal and neonatal death among males were (54.8%, 55.9%) much higher than females (44.3%, 41.8%) during the years 2019 and 2020 respectively. There are several studies previously conducted have nearly similar results. As a study in 2019 by ABD-ELGAWAD, S; and MOHAMED, H. Was conducted in the same current study departments of Benghazi Medical Centre. They had found number of died males more than females from 2014 to 2018[14].

 Also, Csermely, G, et al, in 2015 were indicated that male fetuses are more vulnerable to miscarriages than female fetuses especially in the early pregnancy. Similarly, another study showed that the congenital anomalies were significantly more prevalent in the male fetuses than female fetuses. (Peter W.G, et al,)

Another study emphasized that male infants are at greater risk than females in occurring the birth defects (Lary JM, Paulozzi LJ, 2001). much more studies come in line with these findings, one study by (Chowdhury .P, et al, 2017)conducted in India about congenital malformation at birth, the incidence of congenital anomalies was more in male preterm babies and stillborn than female babies. Another study by (Lawal. T, et al, 2017) showed an increase in number of male babies with congenital malformations to about 77.6% in comparison to the female babies. Also Sokal et al in 2014; were found that the prevalence of congenital anomalies was 26% higher in boys compared with girls. In addition to another study done by Ndibazza and others in 2011, the percentage of total anomalies was higher in males than in females. Moreover, Sarkar.S et al in 2013. Identified that the congenital malformations affected significantly higher proportion of male babies (2.9%) than female babies (1.5%) did.

In fact, it is not surprising to say that some studies were able to demonstrate these differences in the vulnerability to risk agents, since it found that male embryos are subject to stronger intrauterine selection forces than females (Vatten LJ, Skjaerven R.2004). This agreed with (AL-EZZY, A. 2015) findings, that demonstrated C. trachomatis and TORCH agents play a substantial role in hormonal disturbances, that lead to sperm abnormalities and consequently to infertility issues.

The number of fetal death according to the age groups. It is clear that the most frequent fetal death had shown among the age groups 29-32 weeks and 25-28weeks during 2019 and 2020. Furthermore, table 2 indicates that, the mortality rates of neonates was much higher among age group 1day to 28 days than 0 to 23

hours for the both studied years. As there was not any medical cause proved for their death, the authors speculated their cause of death could probably belongs to any of TORCH infection agents. As Ishaque et al, in 2011 focused on a noticeable association between infection and gestational age they explained that the earlier the fetal death during gestation, the more likely to be caused by an infection. A study revealed that 19% of fetal deaths less than 28 weeks were associated with an infection, while only 2% of term stillbirths were infection-related (Waiswa ,P, et al, 2010).

Another supportive study highlighted that toxoplasmosis causes premature birth at the age of 36 weeks (70%) and at the age of 13 weeks (15%), hence, these results indicated to the possibility of presence of toxoplasmosis(Soltani S, et al, 2021). One more study in Egypt also agreed with the hypothesis, Their outcomes revealed that 75% of preterm neonates (most of them at gestational age ≤ 34 weeks) had toxoplasmosis. (Kieffer F, and Wallon. M,2013)

Likewise,(Mrisho, et al, 2012) they studied the effect of infection on the neonatal death. They used Verbal Autopsy (VA) interview that confirmed the most common causes of neonatal death that were prematurity (33%), birth asphyxia (22%) and infections (10%). In fact, the elevated number of the neonatal death each year needs to be of much concern and understanding why newborn babies die can be improved by using the WHO verbal autopsy tools. These tools can professionally provide good estimates of the most common causes of newborn death especially in countries with higher neonatal mortality rates. This tool adopts that each cause of death has a set of clear signs that can be recognized by the primary caregivers (usually mother) and that the characteristics of one cause of death can be distinguished from other. (Aggarwal. A, et al in 2013).

Whereas (Zhang L, et al, 2022),they found the same rate of hospitalization from congenital CMV infections among the 29 d–<1 y group and the 0–28 d group, they verified that most of the cases with congenital CMV infection were asymptomatic at birth and were not admitted until a noticeable clinical manifestations occurred, such as liver damage. Moreover, study proved that among asymptomatic congenital CMV infections, about 5% to 20% of neonates whose mothers infected with primary CMV infection may be obviously symptomatic at birth and their death rates reaches to 30%, and about 80% might suffer from severe neurologic disorders. (Morsy T A, et al, 2022)

This demonstrates importance of the findings introduced by (Kalane SU, et al, 2022), that emphasized on the importance of maternal and neonatal screening for CMV infection among the babies delivered <34 weeks of gestation.AS the American Academy of Pediatrics (AAP) claimed that mothers who deliver infants at <32weeks of pregnancy can be screened for CMV. As well as, the American College of Obstetricians and Gynecologists (ACOG) stated that pregnant women must be screened for rubella and syphilis when they go for the first prenatal visit.

While other countries recommend screening for Toxoplasmosis. (Morsy T A, et al, 2022)

Regarding the cause of death, this study found that preterm birth was the most common cause of death in 2019 and 2020. Followed by respiratory disorders, then multiple congenital malformation, sepsis, intrauterine fetal death (IUFD) after that according to the mother conditions.

These findings were highly consistent with those from the neighboring areas, in one order or another. As study in Benghazi children hospital found higher predominance of preterm neonates over term, which accounted for 35% of the total neonatal death. The most common causes were lung diseases of prematurity (29%), sepsis (25%), Congenital Heart Diseases (12.5%), post-operative intestinal obstruction (7%), multiple congenital anomalies (7%), intractable convulsions (6.5%). (Rajab, A., et al, 2020). Actually, these results support the fact that says; around 13 million infants are born yearly before 37 completed weeks of gestation. Therefore, the Complications from these preterm births are the well-established leading cause of neonatal death. (Lawn JE,2005)(Alburke S, et al, 2015)

Similarly, in Misruta, about the vast majority of death was among preterm(71%) and the main reported causes of deaths during the first 24 hours until the first week of their life were respiratory distress syndrome 48%, congenital malformation 22%, neonatal sepsis 12%, Congenital Heart Disease 12% and birth asphyxia 4%. Whereas, the main causes of late neonatal deaths (from the first week to 28 days of life) were neonatal sepsis 59%, congenital malformation 17%, birth asphyxia 12%, Congenital Heart Disease 6% and intravascular haemorrhage 6%. (Alburke S, et al, 2015)

Moreover, in Tripoli approximately (52.3%) of neonatal deaths were among premature babies, then respiratory distress (HMD) (40.4%), congenital malformation (19.6%), neonatal infections (18.5%) and asphyxia (15.8%). Those died premature babies with extremely and very low birth weight were mainly attributed to insufficient respiration, necrotizing enterocolitis and infections. The majority of deaths (63.1%) occurred during the early neonatal period. (Abushhaiwia A.M.E, et al 2010)

Additionally, in Misurata Central Hospital, The leading causes of neonatal deaths in 2014 were prematurity (37.5%), birth asphyxia (20%), neonatal sepsis (18%) congenital malformations (10%) and other different reasons (13.7%). The majority of deaths (88%) occurred during the early neonatal period.(Ashour, B. M., et al, 2014) This is the pointer that reflects the inadequate obstetric and neonatal care, and improving these will reduce the death that mainly due to prematurity and infection. This was clearly noticeable from the largely high rates of survival for very low birth weight newborns in Japan that was around 90%. This improvement of survival of such infants reflects the better knowledge of the pathophysiology of the neonate and improvement in the medical care (Abushhaiwia A.M.E, et al 2010) the enhanced

More importantly, it was reported that infectious agents are responsible for up to 30% of stillbirths; these infectious agents represent TORCH infection that globally associated with low birth weight, preterm birth, stillbirth, neurological and developmental disorders in addition to hearing and vision loss. Unfortunately, TORCH infections affect widely low and middle-income countries (Lynn M.K, et al 2023). However, in Libya no concern were given to the issue of TORCH infections and the related outcomes.

This can be illustrated from a study by (Abd-elgawad. S, et al, 2022) that showed the most frequent cause of miscarriage(among pregnant women with a history of repeated miscarriages and stillbirths) was from TORCH infections at about(23.1%) with the age groups of 31-40 years. Nevertheless, the respondents who stated TORCH as a cause for their miscarriages did not have any knowledge about TORCH adverse outcomes, they know only Toxoplasmosis but by the name (disease of the cat), they do not have any idea about TORCH infections and their adverse consequences on the pregnancy.

This can be clarified by the findings of Abdelgawad,S and others 2020) which highlighted that there is a large gap in the knowledge of the obstetricians and neonatologists regarding TORCH infections. As the study revealed that knowledge of the staff about TORCH infections and related outcomes differed according to the years of experience, since those with more than 20 years working were better than those with the least experience were.

When comparing these findings with those who have positive results of TORCH in the previous mentioned study. Certainly, this indicates to the presence of TORCH infections cases in Benghazi, AS according to the death certificates that were used in this research; they were not any case reported with any agents of TORCH infections nor from the study conducted by Abdelgawad, S, and Mohamed H from 2014 until 2018. Particularly, it was observed that the higher rate of fetal and neonatal death with the similar complications connected with TORCH infections.

An outstanding study by (Wang Y, et al, 2019) emphasizes this theoretical fact, since they explored the correlation between TORCH infections and abnormal pregnant outcomes. They proved that TORCH infection was the main risk factor that lead to severe damage to the fetus, especially congenital malformations in china. Since congenital malformations was much higher among TORCH infected patients than those without TORCH infection. Their findings explained that, The IgM antibodies were positive for TORCH infections and the rate showed a significant increase in patient with upper respiratory tract infection (14.6%, 32/219) or with a history of pregnancy complications (4.8%, 70/1464). Among 85 ToRCH infected women , the adverse outcome of pregnancy were observed in 57 cases which included abortions (31.8%, 27/85), premature births (8.2%, 7/85), congenital malformations (12.9%, 11/85), and stillbirths (9.4%, 8/85).

Certainly, upper respiratory infections and influenza proved to cause congenital malformation by various pathways either directly via placenta or indirectly via the

toxic metabolites that induced by the fever (hyperthermia) or drugs that used to treat such infections.(Edwards MJ, 2006)(Chughtai et al.2023). Hyperthermia causes damage to the cells leading to congenital anomalies, and this risk reported to be increased in the first trimester following respiratory infections. (Chughtai et al.2023).

Moreover, Abu-Madi, et al, in 2010 found that about 43 cases of toxoplasmosis acquired during pregnancy (with history of miscarriages would be expected to result in 11-21 cases of congenital toxoplasmosis. Also another study demonstrated that miscarriages, stillborn, and congenital malformation of the head can be seen as a result of the earlier toxoplasma transmission.(Morsy T A, et al, 2022) Also, in a study by (Ghasemi et al, 2016) which evaluated the role of toxoplasmosis in etiology of abortion and stillbirth, the results showed that the IgG seroprevalence was 25.5% in the case group (26.8% in abortion and 21.4% in stillbirth).

In India, it is proved that among women who undergone to fetal congenital malformation in their previous pregnancy. They reported 61% to seropositivity of HSV. (Baghel S, Inamdar SA, 2020)

In study by (Mohammad E and Salman Y, 2014), perinatal outcomes showed a high frequency of stillbirths (94.11%), IUFD (80%), abortion (70%), and congenital malformation (63%).

The current results showed higher numbers of IUFD in 2020. Even though the main cause of death was unknown, it was only written in the death certificates IUFD. which differed from a study in Japan by (Takita.H, et al, 2018) that stated the most common leading cause of IUFD in 2001–2007 was fetal abnormalities (43.2%), they highlighted the main cause that contributed to 56% of IUFD was related to chromosomal abnormalities.

Whereas, Ghannad, et al in 2014, reported that CMV is the most common cause of intrauterine infection. They also stated in Guinea-Bissau, stillbirth rates were increased 4- to 9-fold if the mother was infected with rubella during her pregnancy. Additionally, Howard, J. 2009, reported that 9% of blood samples taken from stillbirths by cardiac puncture were PCR positive for CMV. Moreover, a recent study from Greece showed significantly increased levels of CMV (16%) in the placentas of stillbirths compared to controls (3%) (Dhiman Chaudhury, et al, 2019)

According to Lynn M.K, et al 2023, about 10% of symptomatic CMV neonates at birth and toxoplasmosis shows Jaundice, hepatosplenomegaly, petechiae, microcephaly, intrauterine growth restriction, retinitis. Another study also supported this evidence, which found 50% of neonates with CMV develop jaundice 67%, hepatosplenomegaly 60%, petechial rash 76% (Boppana et al, 1992). which corresponds to the findings from a study conducted in Benghazi Children Hospital that proved the most common cause of neonatal admission were

jaundice, followed by prematurity (Alharam Z M, et al, 2020) . Nevertheless, it was not clear what is the cause of jaundice and prematurity in their study nor any other study in the same area; they only focused on leading cause of admission or death, without mention to the etiology. Actually understanding the etiological factors that causes infant morbidity and mortality is critical to reduce this burden in the community.

Conclusion:

The clearest evidence of impact in fetal and neonatal death reduction is adequate prevention and treatment of maternal infections such as TORCH. At present, large gaps exist in the growing list of pregnancy adverse outcomes and risk factors. The absence of the main causes of the fetal and neonatal death synthesize an evidence that correlate adverse perinatal outcomes with any of TORCH agents. Regular prenatal screening test is justified. It also becomes possible to speculate that heath care staff   and the pregnant women in Benghazi are not familiar with the roots of TORCH transmission. Thus,

- improving the awareness of the staff and women especially pregnant regarding TORCH infections and their consequences, the main transmission routes, and associated risk factors, this can surely decline the rate of seroprevalence.

- More efforts should be also made to raise awareness of the staff on better reporting for the causes of death in attempt to control the causes leading to the congenital anomalies and intrauterine fetal death and prematurity. This could be simply achieved by using WHO verbal autopsy tools.

-Health officials should regard the screening test for TORCH infections before marriage or pregnancy as a routine test.

CONFLICT OF INTEREST:

None declared.

ETHICAL APPROVAL:

Ethical approval was obtained from the Ethics Committee of faculty of public health.

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