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TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) screening of small for gestational age and intrauterine growth restricted neonates: efficacy study in a single institute in Korea

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Purpose: Routine screening for toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex virus (TORCH) in intrauterine growth restriction (IUGR) and small for gestational age (SGA) neonates has become a common practice. However, the incidence of TORCH varies across countries, and the cost of TORCH testing may be disadvantageous compared to disease-specific screening. To evaluate the efficacy of TORCH screening, the medical charts of IUGR or SGA neonates born in a single institution in Bucheon, Korea from 2011 to 2015 were reviewed.

Methods: The clinical data of the 126 IUGR or SGA neonates were gathered, including gestational age, Apgar scores, neonatal sonographic findings, chromosome study, morbidities, developmental follow-up, and growth catch-up. Maternal factors including underlying maternal disease and fetal sonography were collected, and placental findings were recorded when available. TORCH screening was done using serum IgM, CMV urine culture, quantification of CMV DNA with real-time polymerase chain reaction, and rapid plasma reagin qualitative test for syphilis. Tests were repeated only for those with positive results.

Results: Of the 119 TORCH screenings, only one was positive for toxoplasmosis IgM. This result was deemed false positive due to negative IgM on repeated testing and the absence of clinical symptoms.

Conclusion: Considering the incidence and risk of TORCH in Korea, the financial burden of TORCH screening, and the single positive TORCH finding in our study, we suggest disease-specific screening based on maternal history and the clinical symptoms of the neonate. Regarding CMV, which may present asymptomatically, universal screening may be appropriate upon cost-benefit analysis.

Key words: Small for gestational age, Intrauterine growth retardation, TORCH

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Introduction

Growth restriction may imply a pathological restriction of the genetic growth potential[1] and intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality. Placental, maternal, environmental, and fetal factors contribute to IUGR and infection is one of the common etiologies. IUGR and small for gestational age (SGA) are often used interchangeably but are not synonymous. Because the definition of SGA does not take into account uterine growth and is solely based on birth weight, 50%–70% of SGA infants are constitutionally small and have low risk of complications.[1,2]

Congenital infection may lead to IUGR during fetal development and may present as SGA

at birth.[3] In 1971, Nahmias et al.[4] coined the acronym 'TORCH', which stands for toxoplasmosis, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV), to group perinatal infections that cause similar symptoms. Growth retardation is a common clinical manifestation of these infections and routine screening for TORCH in IUGR and SGA neonates has become common practice. Methods of TORCH screening vary. IgM level detection was one of the earlier methods for screening and remains a commonly used test.[4-6] Previously, complement fixation tests (CFTs) for CMV and HSV and hemagglutination inhibition (HI) for rubella have been used.[7] More recent studies have utilized shell vial culture for CMV and various methods of polymerase chain reaction (PCR).[8-12]

A few studies have presented the limitations of TORCH screening in IUGR and SGA neonates. With low incidence of TORCH in the general population, screening is likely to be of low utility and high expense. Studies reviewing TORCH screening have reported very low incidences of positive findings: 3 out of 23 SGA neonates in a Canadian study,[7] 9 out of 117 SGA neonates in a USA study,[9] and 1 out of 75 SGA in another USA study.[8] In addition, SGA and IUGR rarely present as unique features of TORCH infection. As de Jong et al.[6] have noted, no study has shown cost-effectiveness for a complete TORCH screening in SGA infants without other clinical signs of congenital infection.

Thus, we aimed to evaluate the efficacy of TORCH screening in SGA and IUGR neonates in Korea.

Materials and methods

The study was conducted in the Department of Pediatrics, Bucheon St. Mary's Hospital in Bucheon, Korea. The present study protocol was reviewed and approved by the Institutional Review Board of Bucheon St. Mary's Hospital, Catholic University of Korea (approval number: HC17RESI0039). A retrospective review of medical charts was completed for all IUGR or SGA neonates born at the institution's neonatal unit, or transferred there within one month of birth, from January 2011 to December 2015. IUGR in this study refers to fetus with estimated weight less than 10 percentile.[13] Diagnosis of IUGR was made by an obstetrician based on antenatal sonographic findings by calculating estimated fetal weight using the Hadlock 2 formula. SGA is defined as birth weight below the 10th percentile for gestational age.[2,13] A total of 126 IUGR or SGA neonates were included in this study with 118 meeting criteria for SGA and 95 meeting criteria for IUGR. Clinical information collected included: gestational age, birth weight, delivery mode, 1- and 5-minute Apgar scores, and whether the infant was a singleton or twin.

Maternal factors associated with IUGR considered in analyses included diseases such as preeclampsia, gestational diabetes mellitus, systemic lupus erythematosus, and renal disorder.[1,14] Fetal sonographic findings were gathered when antenatal care was done at our hospital. Fetal sonography was performed by an obstetrician to measure fetal heart rhythm, biparietal diameter, head circumference, abdominal circumference, and femur length. Fetal sonography was also used to screen for structural anomalies related to chromosomal disorders and clinical findings related to TORCH such as hepatosplenomegaly, cardiac lesions, hydrocephalus, microcephaly, and intracranial calcifications.[15] Placental biopsy findings related to IUGR such as placental abruption, extensive infarction, and placenta previa were gathered when available.[14]

Clinical abnormalities related to TORCH (e.g., prematurity, hearing impairment, patent ductus arteriosus, thrombocytopenia[2]) found during the neonatal period were recorded, as were neonatal sonographic findings and chromosome study results. To determine long-term outcomes of SGA and IUGR, developmental follow-up data were reviewed for all patients who attended the pediatric or rehabilitation out-patient clinic. Korean-Ages & Stages Questionnaires was used for developmental assessment. Developmental follow-up less than 1 year was categorized as follow-up loss.

Total serum IgM level of toxoplasma (Access Toxo IgM II, Beckman Coulter, Brea, CA, USA), rubella (ARCHITECT Rubella IgM Reagent Kit, Abbott, Dublin, Ireland), CMV (CMV IgM, Abbott, Chicago, IL, USA), HSV (Liaison HSV-1/2 IgM, DiaSorin, Saluggia, Italy) was determined by chemiluminescence immunoassay. CMV urine culture was performed by shell vial culture (D3 DFA CMV Immediate Early Antigen ID Kit, Quidel, San Diego, CA, USA) and CMV real time PCR (AccuPower Quantitative PCR Kit, Bioneer, Daejeon, Korea) was performed with urine and blood sample. For syphilis, rapid plasma reagin (RPR) qualitative test (Mediace RPR, Sekisui Chemical Co., Ltd, Tokyo, Japan) was performed. Initial tests were performed within 1 week of admission and follow-up tests were done only when initial test results were positive.

Results

1. Patient characteristics

A total of 2,168 patients were treated at the neonatal intensive care and neonatal inpatient units at Bucheon Saint Mary's Hospital during the study period. Among these, 126 neonates who met criterion for IUGR or SGA were included in our study. Eighty-seven neonates (69%) met criterion for IUGR and SGA, 8 (6%) were IUGR but not SGA, 8 (6%) were SGA but not IUGR, and 23 (18%) were SGA but could not determine state of IUGR due to insufficient antenatal data. Of the 95 IUGR neonates, 51 were symmetric and 44 were asymmetric. Neonatal characteristics are shown in Table 1. Average gestational age at birth was 37 weeks and 3 days with a greater portion of term compared to preterm neonates. The earliest gestational age was 29 weeks and the latest was 41 weeks and 3 days. Birth weight average was 2,128 g with the smallest infant

Table 1. Neonatal characteristics (n=126)

Characteristic	Value
Male sex	53 (42)
Preterm	39 (31)
Average gestational age (wk)	37.4±2.4
Average birth weight (g)	2,128±504
Delivery mode: Cesarean delivery	78 (62)
5-Min Apgar less than 7	7 (5)
Twin	16 (13)

Values are presented as number (%) or mean±standard deviation.

Table 2. Maternal factors related to intrauterine growth restriction (n=123)

Underlying disease	No. (%)
None	83 (67)
Pregnancy-induced hypertension	29 (24)
Chronic hypertension	3 (2)
Gestational diabetes	12 (10)
Systemic lupus erythematosus	1 (1)
Renal disease	2 (2)

weighing 880 g at birth. Average Apgar scores at 1 and 5 minutes were 7 and 8, respectively; seven neonates had a 5-minute Apgar score under 7. There were 110 singleton neonates and 16 twins. Of the 16 twins, 3 pairs were included and the other 10 twins had siblings who did not meet the SGA or IUGR criteria of our study.

2. Maternal disorders

Underlying maternal disorders are described in Table 2. Due to our inclusion of 3 twin pairs, the number of mothers included in this study was 123. No mother had a history of smoking, alcohol, or drug use during pregnancy. Pregnancy-induced hypertension was observed in 29 (23%), chronic hypertension in 3, gestational diabetes in 12 (9.7%), systemic lupus erythematosus in 1 and renal disease (IgA nephropathy, membranoproliferative glomerulonephritis) in 2. Seven mothers had multiple disorders. Notably, one mother showed serological testing of rubella IgM (+) and rubella IgG (+) 6 months prior to pregnancy. Repeated tests during pregnancy and over the next 3 years showed consistently positive IgM and IgG levels whereas repeated rubella reverse transcription PCR were all negative, suggesting false positive serological testing results or persistent IgM response. The mother did not show any symptoms or signs of rubella infection and prior immunization history of MMR could not be checked due to insufficient data.

Fetal sonography findings were used to determine status of IUGR and no other structural abnormalities were noted except for 1 patient with duodenal atresia.

Placenta findings were recorded in 81 mothers, and 11 had abnormalities related to IUGR. Eight had extensive infarction, 3 had placenta abruption, and 1 had placenta previa (1 mother had both placenta abruption and placental previa).

3. Imaging and chromosome studies

Neonatal sonography was performed in 76 out of 126 neonates included in our study (60%), and none showed findings related to TORCH such as hydrocephalus, intracranial calcification, and hepatosplenomegaly. Chromosome study was done in 6 neonates (5%) and abnormalities were found in 2 (46, XY inv(9)(p12q13) and 21 trisomy).

4. Clinical findings

Clinical findings were normal in 90 neonates and 36 (28%) presented abnormalities during the stay in the neonatal care unit. Among the 36 neonates with abnormal findings, 24 showed clinical manifestations that could be related to TORCH infection. These are described in Table 3.[15,16] No neonate had a positive TORCH result. Follow-up periods varied from 4 to 36 months. Developmental follow-up was done in 41 neonates (32%) and of these, 27 showed normal development and 14 showed developmental delay. Patient 18 in Table 3 showed impaired hearing of the right ear on an automated brainstem response test done 3 weeks after birth. TORCH screening test results were negative for this patient, including CMV urine culture and blood PCR. Further follow-up of CMV was not done. One-month follow-up of the automated brainstem response test showed normal results for both ears. At 24 months of age the patient showed delayed expressive speech and hearing was tested again with auditory brainstem response threshold test which showed normal results for both sides and otoacoustic emission test which showed right side impairment. At the most recent follow-up at 36 months, the patient showed normal development in all dimensions and had no hearing deficit.

5. TORCH screening

Of the 126 IUGR or SGA neonates, 121 neonates (94.4%) had TORCH screening workup. Toxoplasmosis was tested with serum IgM in 113 patients, rubella was tested with serum IgM in 113 patients, and HSV serum IgM was tested in 114 patients. CMV was tested with serum IgM in 76 patients, urine culture in 76 patients, urine PCR in 3 patients, and blood PCR in 75 patients. Syphilis was tested in 19 patients with RPR titer test. Only one positive finding of toxoplasmosis IgM was found. Repeated testing of toxoplasmosis IgM and IgG revealed negative findings. This patient had no clinical findings and follow-up until 4 years showed no comorbidities.

Discussion

To our knowledge, this is the first study in South Korea to evaluate the efficacy of TORCH screening in SGA and IUGR neonates. In our

Table 3. Neonates with abnormal clinical findings that could be related to TORCH infection (n=24)

Patient	Gestational age (wk)	Birth weight (g)	Maternal disease	Clinical findings	Follow-up
1	36^{+2}	1,940	GDM	Prematurity	Loss
2	32^{+3}	1,120	PIH	Thrombocytopenia, prematurity	Expired
3	34^{+5}	1,640	PIH	Prematurity	FTT
4	34^{+1}	1,780	PIH, IgAN	Prematurity	Normal
5	40^{+0}	2,760	Nonspecific	PDA	Loss
6	35^{+1}	1,260	PIH	Prematurity	Loss
7	32^{+6}	1,320	Nonspecific	Prematurity	Normal
8	32^{+0}	1,040	PIH	Prematurity	Normal
9	36^{+6}	2,180	Nonspecific	Prematurity	Normal
10	40^{+4}	2,980	Nonspecific	PDA	Normal
11	33^{+6}	1,380	Nonspecific	Prematurity	Loss
12	30^{+1}	980	Nonspecific	Prematurity	Loss
13	30^{+1}	940	GDM	Prematurity	Normal
14	35^{+1}	1,400	Placenta abruption	Prematurity	GDD
15	33^{+4}	1,460	PIH	Prematurity	GDD
16	36^{+3}	2,220	Nonspecific	Prematurity	Loss
17	34^{+2}	1,520	PIH	Prematurity	GDD
18	33^{+6}	1,580	PIH	R/O Hearing impairment, prematurity	Normal
19	39^{+4}	2,620	Nonspecific	Hearing impairment	Loss
20	31^{+6}	1,160	Nonspecific	Prematurity	GDD
21	36^{+0}	1,560	PIH	PDA, prematurity	Loss
22	36^{+4}	1,600	Nonspecific	Prematurity	Loss
23	33^{+1}	1,630	Nonspecific	Prematurity	Expired
24	29^{+0}	880	PIH, GDM	PDA, prematurity	GDD

TORCH, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; IgAN, IgA nephropathy; FTT, failure to thrive; PDA, patent ductus arteriosus; GDD, gross developmental delay.

study of TORCH screening results from SGA and IUGR neonates, we found only one positive toxoplasmosis IgM finding, which did not correlate with the patient's clinical symptoms. Further, SGA and IUGR neonates who showed clinical symptoms related to TORCH infection all tested negative on TORCH screening.

The positive toxoplasmosis IgM finding was considered to be false positive based on negative result of repeated serologic IgM and lack of clinical symptoms. Direct detection of the parasite with highly specific PCR assay of placenta, blood, CSF, or urine would have been instrumental in clarifying the diagnosis.[17]

Our study finding correlates with previous studies that showed few positive results of TORCH screening in IUGR or SGA neonates. In a study by Kahn, 75 SGA infants were evaluated for TORCH with only one positive urine CMV culture.[8] A study by Abdel-Fattah et al.[18] showed that among 38 IUGR cases, none were positive for infectious etiology. A Dutch study of TORCH screening in 112 SGA neonates found only 2 patients with evidence of congenital CMV infection.[11] In a study by Wei et al.[9] of 117 SGA infants in whom TORCH titer testing was done, only two infants showed positive results (each positive for CMV IgM and HSV IgM).

An early study in 1978 by Matthews and O'Herlihy[5] in which the investigators measured cord IgM levels in 969 SGA infants found 5 cases of proven intrauterine infection with rubella, syphilis, and toxoplasmosis all of which had elevated cord IgM levels. However, these cases were related to premature rupture of membrane and chorioamnionitis and the authors suggest that elevated cord IgM levels may be related to such clinical findings rather than to intrauterine infections. This study concluded that determination of cord IgM levels in SGA infants did not significantly help clinical management of these infants.[5] A study by Primhak and Simpson[7] in 1982 performed TORCH screening in 23 severe SGA infants (body weight percentile less than 3%) and found 2 positive cases of rubella HI and 1 positive case of CMV CFT. One positive case of rubella HI showed no clinical signs of infection and was normal at follow-up, and the other 2 cases expired.[7] These authors suggested that IUGR as a sole manifestation of TORCH is rare and thus close clinical investigation of IUGR infants is more appropriate than TORCH screening.[7]

The incidence of TORCH infections have decreased over the 4 decades since routine TORCH screening for IUGR and SGA neonates was first introduced. The seroprevalence of toxoplasmosis has

decreased in USA and similar trends have been observed in France and Sweden.[19] Rubella cases dropped significantly in the USA after the introduction of the rubella vaccination in 1969.[20] Also, TORCH infection rates vary widely between different populations. The incidence of toxoplasmosis is highest in Middle Eastern countries and low-income African countries[21] and CMV seroprevalence has higher rates in South America, Africa, and Asia.[22] Rubella cases have decreased significantly in the USA but developing countries with lower rates of vaccination show a wide range of susceptibility.[17]

In Korea, the toxoplasmosis seroprevalence rate was 0.88% to 3.7% in one study of 5,725 pregnant women,[23,24] showing relatively low rates compared to Europe and America.[24] Toxoplasma prevalence of the general Korean population range from 8% to 25.8% but positive findings are markedly higher in groups of older age, explaining the relatively low rates of toxoplasmosis seroprevalence in pregnant women.[25,26] From 2001 to 2009, only 3 confirmed cases of congenital rubella syndrome were reported to the Korea Centers for Disease Control and Prevention.[27] The seroprevalence of rubella IgG among females of childbearing age ranges from 90%–100%, contributing to a significant decrease in primary rubella infections during pregnancy.[27] A study in 2009 showed that the seroprevalence of CMV IgG and IgM were 98.1% and 1.7%, respectively in pregnant women, demonstrating a low risk of CMV primary infection during pregnancy among Korean women.[28] However, caution needs to be taken because congenital infection resulting from nonprimary maternal infection is common, especially in populations with high maternal seroprevalence.[17] The prevalence of syphilis in Korean adults decreased significantly from 2.5% in 1977 to 0.2% in 2000.[29] Regarding herpes simplex, a study during the period of 2009–2010 showed 17% of pregnant women tested positive for herpesvirus 2 antibody[30] which is comparative to 15.7% in the USA from 2005–2010.[17]

The above review of prevalence of TORCH infection in Korea suggests that screening toward each disease entity should be individualized. Low toxoplasmosis seroprevalance rate in pregnant women suggests lower risk of congenital infection, but higher seroprevalence in older aged Koreans shows that precaution should be taken to avoid consumption of food related to toxolasmosis infection during pregnancy. High seroprevalence of rubella IgG of childbearing age females demonstrates protection against congenital rubella infection and effort to keep immunization rates high should be maintained. Significantly decreased prevalence of syphilis over 3 decades is evidence of lower risk of congenital syphilis infection, but sexual transmission risk needs to be educated. Comparative to the lowered risk of toxoplasmosis, rubella, and syphilis, neonatal screening for CMV should be focused on risks of congenital infection due to maternal reinfection and reactivation.[17]

However, high proportions of congenital infections show no clinical symptoms at birth which increases the risk of unforeseen congenital infections. Silent infections in the infant are more common than symptomatic infections in congenital rubella infection, 80%–90% of congenital toxoplasmosis have no symptoms, 90% of congenital CMV infections are subclinical, and two-thirds of congenital syphilis neonates are asymptomatic at birth.[17] To screen for these asymptomatic cases of congenital infection, disease specific screening would be more effective than universal TORCH screening in SGA, IUGR neonates. The scope of this paper is too limited to make specific recommendations but suggestion in the literature is as follows.

Laboratory diagnosis for congenital toxoplasmosis is recommended when maternal infection during pregnancy has been documented or suspected and when the neonate shows clinical symptoms suspicious of toxoplasmosis and the mother has not been tested for toxoplasmosis during pregnancy. When information of maternal infection during pregnancy is available, IgM and IgA should be tested on peripheral blood and PCR on placenta or cord blood (when placenta is not available). When no information is available regarding infection during pregnancy, maternal serology testing should be done first.[17]

Congenital rubella infection should be considered in infant born to a mother diagnosed or suspected of rubella during any time of pregnancy and any newborn with suspicious symptoms. Fetal derived rubella specific IgM antibody could be tested or IgG level of infant can be monitored consecutively over months to see if it persists. Reverse transcriptase PCR may also be used.[17]

Congenital CMV infection should be tested when infants show suspicious clinical symptoms, and maternal history of seroconversion or mononucleosis like symptoms during pregnancy exist. CMV culture of tissue or PCR may be done.[17] Recent study results show that saliva real-time PCR identifies more infants with congenital CMV compared to tissue cultures.[31] In a consensus recommendation reported by the International Congenital Cytomegalovirus Recommendations Group (ICCRG), real-time PCR of saliva, urine, or both, as soon as possible after birth, within first 3 weeks of life, with saliva as the preferred sample is recommended for diagnosis of congenital CMV in neonates.[32] Screening for CMV in newborns who have failed hearing screening tests is recommended[17] but whether universal CMV screening for all infants should be done remain controversial.[32] Considering that 10%–15% of asymptomatic congenital CMV infected neonates develop sequelae such as sensorineural hearing loss beyond the neonatal period,[31] the ICCRG recommends universal neonatal CMV screening to enable early detection and intervention.[32]

Due to difficulty of diagnosing congenital syphilis and severe consequences when left untreated, "evaluate and treat when uncertain" approach is recommended. The evaluation should start with serological evaluation of the mother.[17]

HSV infection is transmitted to the neonate most commonly through intrapartum contact and in utero transmission is very rare. Differing from other TORCH infections, asymptomatic cases

are uncommon and clinically suspected infants should undergo evaluation regardless of maternal history. Virus isolation and PCR of assay for CNS involvement are gold standard diagnostic methods.[17] Any vesicular rash in a neonate should be considered for HSV infection and infants younger than 4 weeks with CNS infection or sepsis should be evaluated for HSV, preferably with a PCR assay and assessment of plasma and blood samples for HSV DNA.[33]

Intrauterine infections account for around 5% of IUGR cases.[34,35] When investigating causes of IUGR, other factors also need to be considered. In our study, 38 mothers had diseases that could result in reduced uteroplacental perfusion and 11 had placental factors related to IUGR. There were 16 twins and 2 chromosome abnormalities. Reduced uteroplacental perfusion associated maternal vascular diseases contribute to 25%–30% of IUGR cases.[34] Multiple gestations account for 3% and chromosome abnormalities for 7%–19% of IUGR newborns.[35]

Limitations of our study include small number of participants in a single institution, data based on retrospective review of medical charts, and lack of targeted screening based on preset study indications. Also, regarding CMV screening, saliva real-time PCR would have been the preferred method of screening which could detect more neonates at risk of congenital CMV infection. For HSV screening, viral isolation, PCR assay, or assessment of HSV DNA should have been used because commercial assays of IgM antibodies are not validated in infants.[33]

Taking into account the incidence and risk of TORCH in Korea, financial costs of a TORCH screening battery, the invasiveness of blood sampling, and only one positive finding of TORCH in our study which did not present clinical symptoms for 4 years of follow-up, we suggest that decision to perform diagnostic tests for TORCH should be made based upon maternal history of possible infection during pregnancy, infection related clinical symptoms of neonates rather than the universal TORCH screening approach for SGA and IUGR newborns. Regarding CMV, which may present asymptomatically, universal screening could be considered after cost-benefit analysis.

A larger, prospective study of SGA and IUGR neonates in South Korea screened according to disease specific indications would provide insight into the true prevalence of TORCH infection among SGA and IUGR neonates. Also, a study evaluating the efficacy of universal screening test for CMV in neonates in Korea would help improve early detection and intervention of asymptomatic congenital CMV infected neonates.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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