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ORIGINAL ARTICLE

Clinical utility of maternal TORCH screening in fetal growth restriction: A retrospective two-centre study

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Objective: The aim of this study was to evaluate the indications for maternal TORCH (*Toxoplasma gondii*, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV)) serology, with a focus on the yield in isolated fetal growth restriction (FGR).

Materials and Methods: A retrospective review of antenatal TORCH testing between January 2014 and December 2018 was carried out at two hospitals in Melbourne, Australia. TORCH testing ordered for pregnancy losses and stillbirth was excluded.

Results: Medical records of 718 pregnancies were reviewed, representing 760 fetuses. Isolated FGR was the indication for TORCH screening in 71.2% of pregnancies. Screens ordered for isolated FGR were positive in 7.4% (95% CI 5.5–10.0%). There were 49 positive maternal immunoglobulin M (CMV = 34, *Toxoplasma* = 15). Two acute maternal infections during pregnancy were diagnosed (CMV = 1, *Toxoplasma* = 1), with both screens ordered to assess symptomatic maternal illness. There was one neonatal CMV infection, born to a woman with symptomatic primary CMV. No maternal or neonatal rubella or HSV infections were identified. We found a diagnostic yield of TORCH screening for isolated FGR of 0.0% (95% CI 0.00–0.8%). An estimated AUD$64 269.75 was expended on maternal TORCH screens in this study.

Conclusion: Maternal TORCH testing for isolated FGR is of no diagnostic yield and should be abandoned.

KEYWORDS
congenital infection, cytomegalovirus, fetal growth restriction, TORCH, toxoplasma

INTRODUCTION

Toxoplasma gondii, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV), often grouped together as the TORCH infections, can cause transplacental infections and severe perinatal morbidity and mortality.[1] Congenital infection may be associated with non-specific ultrasound findings, including fetal growth restriction (FGR). FGR does not represent a single disease entity, but rather the endpoint of many possible pathologies. Older references attribute 5–10% of FGR to perinatal infections, but this prevalence is almost certainly an overestimate.[2,3]

The most recent guidance on FGR from the Society for Maternal-Fetal Medicine (SMFM)[4] recommends against routine TORCH serology for FGR in the absence of other risk factors. This recommendation is supported by a systematic review of TORCH serology that demonstrated its low clinical utility for isolated FGR.[5] However, routine maternal TORCH screening for FGR is widespread and still recommended in some guidelines.[6–8]

The Choosing Wisely campaign[9] aims to reduce unnecessary investigations, treatments, and procedures in health care. We aimed to substantiate the recent SMFM recommendations in the context of this campaign, by evaluating indications for maternal TORCH serology at two Australian hospitals, with a focus on unnecessary investigations and the diagnostic yield of maternal TORCH screens in FGR.

MATERIALS AND METHODS

Study population

This retrospective study was conducted at two hospitals in Melbourne, Australia. Hospital 1 manages pregnancies from the local area as well as tertiary referrals of high-risk pregnancies. Hospital 2 cares for low to moderate risk pregnancies for the local population. All TORCH serologies ordered between January 2014 to December 2018 at hospital 1, and January 2014 to December 2017 at hospital 2, were extracted from the respective laboratory databases. More recent data were not available due to changes in laboratory providers and data management systems. Medical records for all pregnant women who had TORCH screens in the specified period were reviewed. TORCH screens ordered for pregnancy losses were excluded. Results were also included if they were ordered on a mother in the post-natal period, prior to discharge of the neonate.

The laboratory at hospital 1 lacked a specific testing code for TORCH. TORCH screens at this site were identified by searching for requests for simultaneous *Toxoplasma* and CMV serology (immunoglobulin M (IgM) and IgG), and then additionally searching for rubella and HSV serology (any IgM or IgG) collected at the same time. TORCH serology at hospital 2 had a specific laboratory code that included *Toxoplasma* IgM and IgG, rubella IgG, CMV IgM and IgG, HSV-1 IgG and HSV-2 IgG.

Clinical demographics and definitions

Individual medical records were reviewed and data collected on maternal age, indication for TORCH testing, gestation at time of screening, extra investigations performed after a positive screen, and neonatal investigations and outcomes.

Indications for TORCH testing were classified according to fetal sonographic findings or maternal illness; only one indication was allowed per screen. The indication was classified as isolated FGR if this was the only abnormal finding on fetal sonography. Other indications were classified as central nervous system (CNS) abnormalities, echogenic bowel, and abnormal fetal fluid collections, regardless of other sonographic findings (including non-isolated FGR); and isolated polyhydramnios. Maternal illness was recorded when a TORCH screen was ordered due to symptomatic illness, rather than sonographic findings. If multiple sonographic findings were present that fit more than one classification (eg both CNS abnormalities and echogenic bowel), the indication was recorded as 'other ultrasound findings.'

Definitions of positive screens and TORCH infection

All positive or indeterminate IgM results were considered a positive screen. IgM results were classified as confirmed, probable, or possible maternal infections. A confirmed maternal infection was a consistent symptomatic illness with a positive IgM and an IgG with low avidity. A probable maternal infection was a positive IgM and low IgG avidity without a compatible symptomatic maternal illness. A possible maternal infection was a positive IgM and intermediate or high avidity IgG, without a consistent symptomatic illness. Unclassifiable IgM results either had no IgG avidity testing, or had a negative IgG.

A confirmed congenital infection was a positive polymerase chain reaction (PCR) result in a neonate <21 days of age, or on amniotic fluid.

Costs

Costs were estimated using the Medicare Benefits Schedule for items 69384 and 69396. Calculations can be found in Appendix S1.

Statistical analysis

Analysis was conducted using RStudio, version 1.3.1093 (2020). Descriptive summary statistics were performed. Testing indications at the two hospitals were compared using the χ^2 test. Point estimates were provided with 95% confidence intervals.

Ethics approval

Ethics approval was obtained from the Human Research Ethics Committee at the respective health services (hospital 1 Mercy

Health #2019-035 (clinical data), Audit/19/Austin/122 (laboratory data); hospital 2 Northern Health ALR 50.2018; combined hospitals 1 and 2 data Mercy Health #2023-023).

RESULTS

Patient population

Seven hundred and eighteen records were reviewed during the study period for a total of 760 fetuses (singleton births = 676, twin births = 42). There were 425 tests from hospital 1 and 293 from hospital 2.

The average gestation at the time of TORCH serology was 29 + 5 weeks (range: 11 weeks to 2 months post-natal). The proportion of tests done at <25 weeks, 25–32 weeks and >32 weeks were 16%, 39% and 44% respectively. The remaining 1% were tested in the post-natal period ($n = 10$) or had missing data ($n = 1$).

Indications for testing

Table 1 shows the indications for TORCH screens. The most common indication for TORCH screening was isolated FGR, performed in 511/718 women (71.2%). Hospital 2 had a higher proportion of tests ordered for isolated FGR compared with hospital 1 (82.6% vs 63.3%, $P < 0.001$), and hospital 1 had a higher percentage performed for neurological abnormalities (10.4% vs 1.7%, $P < 0.001$).

Maternal screening results

Table 2 shows the total number of infections for which screening was performed. The numbers at hospital 1 varied: 269 women (63%) had all four of CMV, toxoplasmosis, rubella and HSV ordered; 101 (24%) had three infections tested, and 55 (13%) had CMV and toxoplasmosis only. All tests at hospital 2 included all four TORCH infections. The combined cohort had a CMV IgG seroprevalence of 75.6% and a *Toxoplasma* IgG seroprevalence of 10.2%.

TABLE 2 Maternal serology tests performed

Serology	Hospital 1	Hospital 2	Total
CMV IgG and IgM	425	293	718
Toxoplasma IgG and IgM	425	293	718
Rubella IgG (± IgM)	319	293	612
HSV-1 and HSV-2 IgG	326	293	619

CMV, cytomegalovirus; HSV, herpes simplex virus; IgG, immunoglobulin G.

There were 49 positive maternal IgM results from 46 women: 34 CMV IgM and 15 *Toxoplasma* IgM, including results from three women who tested positive for both CMV and *Toxoplasma*. The percentage of positive IgM results for each indication is seen in Table 3.

Rubella IgG was performed in 612 (85.2%) women, of whom 506 (84.3%) had prior evidence of immunity to rubella on their routine antenatal bloods. There were no cases of positive rubella IgM.

HSV-1 and HSV-2 IgG were performed in 619 women. Seroprevalence for HSV-1 was 60.9%, and 4.4% for HSV-2.

Maternal and neonatal infections

There were two confirmed maternal infections (one CMV, one *Toxoplasma*; Fig. 1); both of these women underwent testing to investigate symptomatic maternal infection. There was one probable maternal infection and 25 possible maternal infections. Twenty cases with positive IgM could not be classified.

The woman with confirmed toxoplasmosis had TORCH testing ordered to investigate cervical lymphadenopathy and fevers. She had positive *Toxoplasma* IgM and IgG with low IgG avidity; repeat testing three weeks later demonstrated a positive IgM and IgG

TABLE 1 Indications for TORCH testing by hospital[†]

	Total $n = 718$	Hospital 1 $n = 425$	Hospital 2 $n = 293$	*P*-value
Isolated FGR	511 (71.2%)	269 (63.3%)	242 (82.6%)	<0.001
CNS abnormality	49 (6.8%)	44 (10.4%)	5 (1.7%)	<0.001
Echogenic bowel	25 (3.5%)	15 (3.5%)	10 (3.4%)	1.0
Abnormal fluid collection	22 (3.1%)	13 (3.1%)	9 (3.1%)	1.0
Isolated polyhydramnios	39 (5.4%)	29 (6.8%)	10 (3.4%)	0.07
Other ultrasound finding[‡]	38 (5.3%)	28 (6.6%)	10 (3.4%)	0.089
Maternal illness[§]	22 (3.1%)	17 (4%)	5 (1.7%)	0.126
Other[¶]	12 (1.7%)	10 (2.4%)	2 (0.7%)	0.156

CNS, central nervous system; FGR, fetal growth restriction.
[†]Only one indication was allowed per TORCH screen.
[‡]'Other ultrasound findings' included defects in long bone development, intrahepatic lesions, vascular abnormalities outside the CNS, talipes, and oligohydramnios.
[§]All women who had a TORCH test to investigate maternal illness had normal fetal ultrasound at the time of TORCH screen.
[¶]'Other' included patient request, maternal exposure without symptoms, reduced fetal movements, and no clear indication in medical record.

TABLE 3 Positive maternal IgM results by indication for testing

Indication	Total, *n*	Positive IgM, *n* (%)	95% CI	CMV IgM, *n* (%)	*Toxoplasma* IgM, *n* (%)
Isolated FGR	511	38 (7.4)	5.5–10.0	26 (5.1)	12 (2.3)
CNS abnormality	49	2 (4.1)	1.1–13.7	2 (4.1)	0
Echogenic bowel	25	1 (4.0)	0.7–19.5	1 (4)	0
Abnormal fluid collection	22	1 (4.5)	0.8–21.8	1 (4.5)	0
Isolated polyhydramnios	39	4 (10.3)	4.1–23.6	2 (5.1)	2 (5.1)
Other ultrasound findings[†]	38	1 (2.6)	0.5–13.5	1 (2.6)	0
Maternal illness	22	2 (9.1)	2.5–27.8	1 (4.5)	1 (4.5)
Other[‡]	12	0	0–24.4	0	0
Total	718	49 (6.9)	6.8–8.9	34	15

CMV, cytomegalovirus; CNS, central nervous system; FGR, fetal growth restriction; IgM, immunoglobulin M.
[†]'Other ultrasound findings' included defects in long bone development, intrahepatic lesions, vascular abnormalities outside the CNS, talipes, and oligohydramnios.
[‡]'Other' included patient request, maternal exposure without symptoms, reduced fetal movements, and no clear indication in medical record.

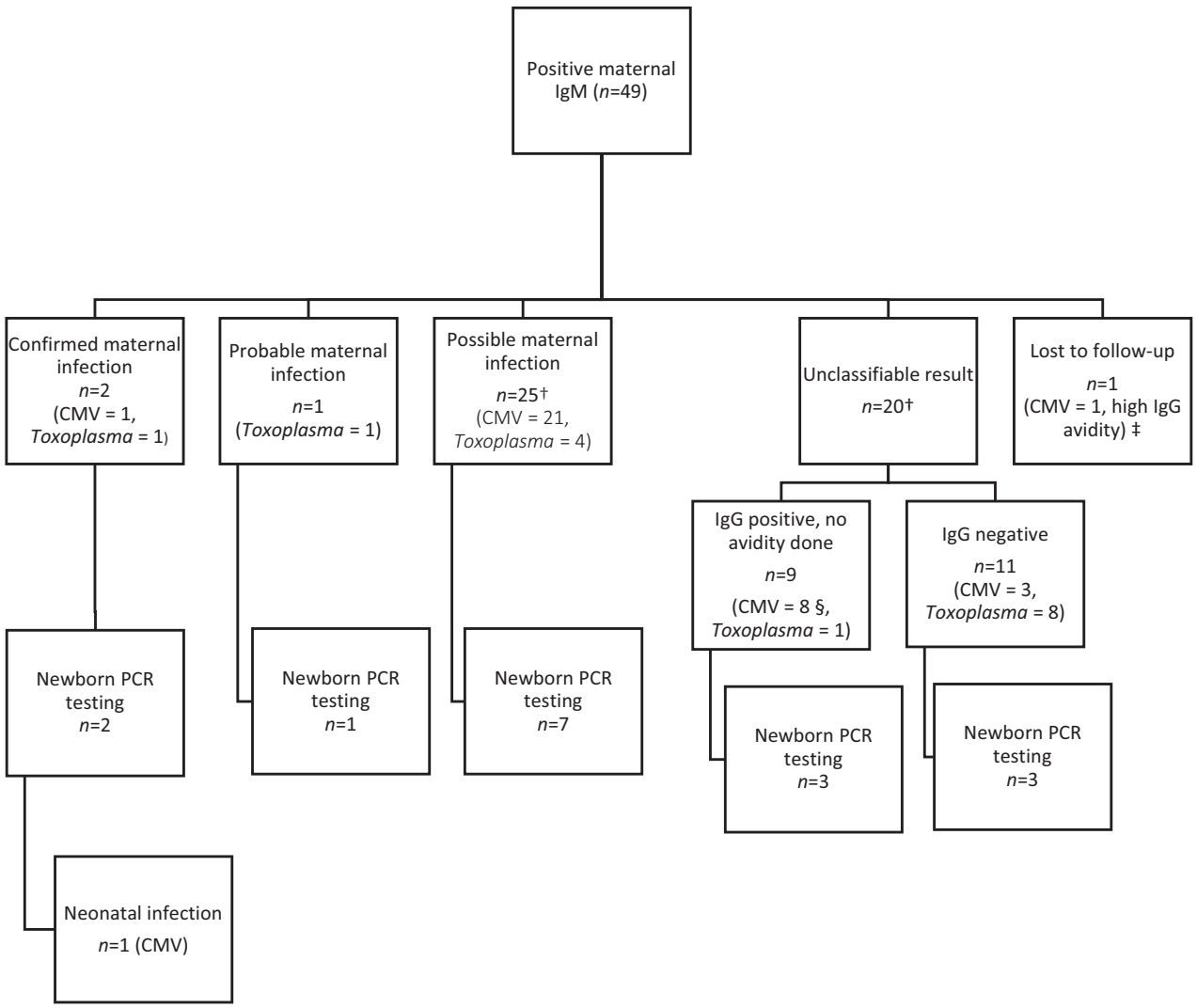

FIGURE 1 Classification of positive maternal immunoglobulin M (IgM) results and newborn polymerase chain reaction (PCR) testing. [†]Three women had both a positive cytomegalovirus (CMV) IgM (possible infection, *n* = 2; unclassifiable, *n* = 1) and *Toxoplasma* IgM (unclassifiable, *n* = 3). Testing of infants born to women who were positive for both CMV and *Toxoplasma* was counted once for each positive maternal IgM, so that the total number of neonatal results is equal to the number of positive maternal IgM. [‡]One woman was lost to follow-up after TORCH (*Toxoplasma gondii*, rubella, CMV, and herpes simplex virus (HSV)) serology was ordered to investigate isolated fetal growth restriction (FGR). [§]One pregnancy was terminated following TORCH screening for an unrelated reason.

with rising avidity, suggesting periconceptional infection. She received treatment with spiramycin. Fetal sonography was normal, and amniocentesis returned a negative *Toxoplasma* PCR. She received increased antenatal surveillance. She had a live-born infant at 38 weeks (weight 3690 g). Placental *Toxoplasma* PCR and immunohistochemistry were negative and neonatal serological testing revealed negative *Toxoplasma* IgM and IgG.

The woman with confirmed CMV had TORCH testing due to an influenza-like illness at 28 weeks, returning a positive CMV IgM and IgG with low avidity. Serology retrospectively performed on stored sera collected at ten weeks gestation was CMV IgM and IgG negative, confirming seroconversion during pregnancy. Fetal sonography was normal. She was referred to a maternal-fetal medicine specialist for pregnancy management with increased antenatal surveillance. Amniocentesis was declined. She had a live infant born at 37 weeks (weight 3070 g). Newborn testing with urine PCR was CMV positive and the baby was referred for paediatric review and antiviral treatment, cranial ultrasounds, and audiometry follow-up.

The woman with a probable maternal infection had positive *Toxoplasma* IgM and IgG, with low IgG avidity, but did not have a compatible illness. TORCH testing was ordered to investigate FGR. She had increased fetal surveillance but declined amniocentesis. Her baby was born at 37 weeks (weight 2290 g). Placental *Toxoplasma* PCR and immunohistochemistry were negative, and neonatal serological testing was IgM and IgG negative. Repeat maternal *Toxoplasma* serology after delivery remained IgM and IgG positive, with low IgG avidity.

Positive IgM results for nine women were not followed up by the treating team, including one result classified as a possible infection, three results with a positive IgG where avidity testing was not performed, and five results which did not have a positive IgG.

Follow-up testing of neonates born to women with a positive IgM varied (Fig. 1).

There were no cases of confirmed maternal or congenital infection detected after TORCH testing for isolated FGR. The diagnostic yield of TORCH screening for isolated FGR was therefore 0.0% (95% CI 0.0–0.8%).

Clinical costings

The estimated cost of initial TORCH screens alone was AUD$64 269.75.

DISCUSSION

In this two-hospital study of 718 TORCH screens, we found no confirmed cases of maternal or congenital infection among 511 pregnancies where testing was performed for isolated FGR. We identified only one case of congenital CMV in the cohort, born to a woman with symptomatic primary CMV in the second trimester. No other maternal TORCH result changed maternal or fetal outcomes.

Infections by TORCH pathogens are associated with distinct sonographic findings in the fetus, but are uncommon causes of isolated FGR. However, clinical experience suggests that a TORCH screen is routinely ordered in the workup in this setting[6,7]; indeed, some guidelines continue to recommend its use.[8] A recent systematic review reported low utility of TORCH serology for isolated FGR, with a diagnostic yield of 0.4% (2/496) for congenital CMV when performed for this indication.[5] The combined diagnostic yield of CMV serology for isolated FGR from that review and this report combined is 2/1007 (0.2%, 95% CI 0.05–0.7%), which is not higher than the background 0.48% CMV birth prevalence in high income countries.[10] This low diagnostic yield has also been observed in studies of small for gestational age newborns.[11–13]

Although a TORCH screen is often considered a single test by clinicians, it represents a combination of investigations, requiring specific follow-up tests such as avidity or repeat serology. In our study, there was considerable heterogeneity in which tests were ordered at hospital 1, where it was not possible to order a combined TORCH panel. This is consistent with previous studies which have demonstrated significant variation among clinicians in the overall assessment and management of FGR.[14] The inefficiency of ordering a TORCH panel as a single test was also seen in our study, in the frequent re-ordering of rubella serology. In our study, 84.3% of women who had rubella serology ordered as part of a TORCH screen had previously documented immunity to rubella earlier in their pregnancy.

We also found that 83% of TORCH screens were ordered after 24 weeks gestation, when serology is less clinically helpful for timing infection. A high IgG avidity at this gestation does not exclude primary infection in early pregnancy as it only excludes recent infection within the last three months. Positive IgM from an infection earlier in pregnancy may be lost when assessed at a later gestation. Further, there are differences in risk of perinatal transmission according to pregnancy gestation. The risk of *in utero* transmission of CMV and *Toxoplasma* increases as a pregnancy progresses[15,16]; however, the risk of symptomatic neonatal CMV or *Toxoplasma* infection decreases with later transmission.[16] Similarly, 90% of congenital rubella occurs due to transmission in the first trimester.[17] HSV is distinct from other TORCH infections in that most vertical transmission occurs in the intrapartum and neonatal period rather than during pregnancy.[18] If maternal infection is suspected, the diagnosis should be made by PCR testing of herpetic lesions or bodily fluids, rather than serology. There is little utility in performing investigations for HSV during the third trimester unless there are additional maternal clinical features or fetal ultrasound findings suggestive of HSV. Given the low risk of symptomatic neonatal infection occurring due to third trimester transmission for any of the four infections in our study, the high percentage of tests ordered after 24 weeks is not likely to be clinically useful.

The interpretation of serology can be challenging in pregnancy. A positive IgM is often non-specific, with frequent false positives. It also cannot exclude reactivation of latent infections. A careful

clinical history coinciding with IgG seroconversion, or positive IgM with a low IgG avidity is required to establish the timing of maternal infection, often requiring review by an infectious diseases physician or maternal-fetal medicine specialist. In our study, IgG avidity was not ordered in nine women with positive IgG and IgM, which may have resulted in missed infections. There was also variable follow-up of neonates born to women with possible infections (only seven of 25 neonates tested), highlighting the inconsistent management of positive maternal serology during pregnancy. Negative IgG and IgM serology may have clinical utility for excluding infection as a cause for an ultrasound finding, thus removing the need to perform testing on amniotic fluid. It was not clear from the medical records whether this 'rule-out' purpose was used in our cohort.

There is significant cost associated with routine TORCH screening as seen in our study, with an estimated minimum AUD$64 269.75 in laboratory costs. Indiscriminate testing can also result in increased maternal anxiety and utilisation of medical services. With a growing focus on Choosing Wisely,[9] the importance of targeted investigations is crucial.

Our cohort is larger than any of the published studies included in a recent systemic review of pregnancy outcomes following maternal TORCH screening.[5] A limitation is that our cohort did not include all pregnancies in which isolated FGR was diagnosed, but only those for whom a TORCH screen was ordered. Therefore, the rate of TORCH positivity in FGR may be limited by this bias. However, it is likely that management at these two centres is reflective of wider Australian practice, so these results are useful in informing the clinician of the utility of TORCH screens when performed for FGR.

As our study relied on results from hospital laboratories, we could not identify women managed at these hospitals who had pathology performed at external laboratories, or women managed in the community, for example as part of a shared-care model. While this may bias our results by detecting excessive investigations in hospital settings, we may anticipate that specialist investigation and management is more selective in tertiary centres with fewer unnecessary tests. This is supported by the higher proportion of tests performed for a fetal CNS abnormality at hospital 1.

In conclusion, there is a low utility in screening for TORCH infections in isolated FGR, particularly in the third trimester. This, along with the complexities of interpreting serology, and the heterogeneity of clinical management demonstrated in our study, highlights the need for concise guidelines and clinician education in the investigation of FGR. This study demonstrates that maternal TORCH testing for isolated FGR is of no diagnostic yield and should be abandoned.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Estimation of cost of TORCH screening using Medicare Benefits Schedule.