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Mini-commentary on 2017-SR-20765R1: Accuracy of p57KIP2 compared with genotyping to diagnose complete hydatidiform mole: a systematic review and meta-analysis

p57^{KIP2} immunostaining for diagnosis of hydatidiform mole

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Accurate diagnosis and sub-classification of hydatidiform moles (HM) and distinction from non-molar (NM) gestations is important, since risk of persistent gestational trophoblastic disease (pGTD) and therefore clinical management differ. P57^{KIP2} immunostaining has been widely described as an ancillary test to distinguish complete (CHM) and partial (PHM) hydatidiform moles, but cannot discern PHM from non-molar gestations (NM) or identify androgenetic vs biparental CHM, which may be associated with increased recurrence risk. Molecular genotyping (MG) is the gold-standard in these scenarios and also in cases with aberrant/discordant p57^{KIP2} expression, following which, CHM, PHM and NM can be reliably diagnosed.

In this systematic review Madi *et al* (BJOG 2018) compare accuracy of p57^{KIP2} immunostaining with MG for diagnosis of CHM, particularly relating to countries with limited healthcare resource. Their findings confirm the well-reported high sensitivity and positive likelihood ratio of p57^{KIP2} in correctly diagnosing CHM; CHM are almost always p57-negative (very rare CHM exhibit aberrant expression due to retention of the maternal copy of chromosome 11 and occasional PHM can demonstrate negative staining due to loss of maternal chromosome 11). p57^{KIP2} staining can therefore be a valuable adjunct in low-resource settings since it is relatively cheap, rapid, reliable

and universally available compared to MG, which is more time-consuming, expensive, technically difficult and unavailable in many laboratories.

It should be noted however that the review findings are based on results of seven studies comparing immunostaining and MG, only three of which had quantitative data for meta-analysis, all (Banet et al. Mod Pathol. 2014; 27(2):238–54; McConell et al; Am J Surg Pathol. 2009 33(6):805-17 and and Hui et al. Annu Rev Pathol. 2017; 12:449-85) from the same research group in the United States.

It has been suggested that routine microscopic evaluation by gynecologic pathologists without use of ancillary techniques has an overall accuracy for HM diagnosis of around 80%. In the setting of limited resources, use of $p57^{KIP2}$ staining can therefore reliably aid diagnosis of CHM, which has greatest risk for pGTD development, and consequently greatest clinical importance to detect. However, in clinical practice of specialist referral centres, the main diagnostic difficulty is not in identifying CHM, which is usually diagnosable morphologically, but rather in distinguishing PHM from NM. In this setting, $p57^{KIP2}$ staining is non-contributory and MG remains the optimal method. Selective MG may be performed at specialist centers on diagnostically challenging cases of possible PHM following initial screening by experienced histopathologists as an alternative, more-targeted approach (Fisher RA, et al. J Clin Pathol 2014;67:980–984). However, where genotyping is not feasible, short-term hCG follow-up represents a cost-effective and pragmatic management option.

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