INPLASY

The Diagnostic Utility of p57Kip2 Immunostaining in Complete Molar Pregnancy: A Systematic Review and Meta-Analysis

INPLASY202680023

doi: 10.37766/inplasy2026.8.0023

Received: 5 August 2026

Published: 5 August 2026

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ADMINISTRATIVE INFORMATION

Support - The authors declare that they did not receive any funding for this research.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202680023

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 5 August 2026 and was last updated on 5 August 2026.

INTRODUCTION

Review question / Objective This systematic review and meta-analysis aims to evaluate the diagnostic performance of p57 immunohistochemistry (IHC) in the diagnosis of complete hydatidiform mole (CHM) among women of reproductive age.

The specific objectives are:
1. To derive pooled estimates of diagnostic accuracy for p57 IHC in CHM detection, including sensitivity, specificity, diagnostic odds ratio, positive likelihood ratio, and negative likelihood ratio.
2. To investigate whether diagnostic accuracy varies according to the type of reference standard employed, specifically comparing histopathological assessment alone with histopathology complemented by molecular genotyping.
3. To examine the influence of predefined study-level covariates on test performance, including the immunohistochemical positivity cut-off, mean maternal age, mean gestational age at diagnosis, and the number of pathologists involved in IHC interpretation.
4. To evaluate study quality and risk of bias using the QUADAS-2 tool.

Rationale CHM is a subtype of gestational trophoblastic disease and carries a well-established risk of malignant sequelae, necessitating structured post-evacuation human chorionic gonadotropin surveillance. Accurate identification of CHM is therefore essential for appropriate clinical management and risk stratification. Histopathological examination remains the cornerstone of diagnosis; however, morphological overlap with non-molar hydropic abortions and partial moles frequently complicates interpretation, even for experienced gynecological pathologists. In this context, p57Kip2 immunohistochemistry has emerged as a valuable ancillary diagnostic tool. This imprinted gene product is paternally silenced and maternally expressed. Consequently, its nuclear staining is absent in CHM tissues because of the androgenetic origin of the molar genome, while it is

retained in non-molar specimens and partial moles. Despite its biological rationale and widespread adoption in many diagnostic laboratories, the reported diagnostic accuracy of p57 immunohistochemistry varies considerably across published studies. Discrepancies may arise from differences in staining protocols, antibody clones, interpretation thresholds, or population characteristics such as maternal age and gestational age. By systematically collating and synthesizing all available high-quality primary studies, this review will provide robust summary estimates of p57 IHC diagnostic performance, while also exploring potential sources of heterogeneity through predefined subgroup analyses and meta-regression. The synthesized evidence will offer clinicians and pathologists a clear, evidence-based benchmark for p57 interpretation, support more confident decision-making in equivocal cases, and potentially reduce over-reliance on costly molecular genotyping. Ultimately, this work aims to contribute to the standardization of diagnostic practice and to improve the accuracy and safety of early gestational trophoblastic disease diagnosis.

Condition being studied The condition being studied is complete hydatidiform mole (CHM), a benign form of gestational trophoblastic disease characterized by abnormal proliferation of trophoblastic cells and hydropic degeneration of chorionic villi. CHM results from a diploid conception in which the vast majority of cases are androgenetic in origin, meaning that all chromosomes are paternally derived, typically arising from fertilization of an empty ovum by a single sperm with subsequent chromosome duplication (resulting in a 46,XX karyotype in approximately 90% of cases) or, less frequently, by two sperms (yielding a 46,XY karyotype in about 10% of cases).

METHODS

Search strategy A comprehensive literature search was conducted across three electronic databases – PubMed, Journals@Ovid (OVFT) and Google Scholar – from inception through August 26, 2026. The search strategy combined free-text keywords and database-specific subject headings using the following Boolean logic: ("p57" OR "p57KIP2" OR "p57kip2") AND ("complete mole" OR "hydatidiform mole" OR "complete hydatidiform mole" OR "molar pregnancies" OR "trophoblastic diseases" OR "molar diseases"). To minimize irrelevant records, studies focusing on twin pregnancies, NLRP7 mutations, mosaicism, ectopic or extrauterine gestations, invasive mole, choriocarcinoma or gestational neoplasia were excluded during screening. No language restrictions were applied. Reference lists of included studies and relevant review articles were manually screened to identify additional eligible records.

Participant or population Women of reproductive age with a confirmed diagnosis of complete hydatidiform mole following histological examination of tissue obtained after spontaneous miscarriage or hysterectomy.

Intervention Immunohistochemical assessment of nuclear p57 protein expression in cytotrophoblast cells and stromal cells of chorionic villi, performed on tissue from spontaneous miscarriages, diagnostic uterine curettage procedures, or hysterectomy specimens.

Comparator Histological examination performed independently by two or more surgical pathologists with subspecialty expertise in gynecological pathology or in the diagnosis of hydatidiform mole; genetic analysis using STR (short tandem repeat) typing; karyotyping and FISH analysis, used in conjunction with the histological examination described above.

Study designs to be included Consecutive case series, cross-sectional studies, randomized trials.

Eligibility criteria Included studies are not restricted by geographical location or type of healthcare facility. All studies meeting the inclusion criteria will be considered, regardless of country, disease prevalence, or clinic type.
Excluded: retrospective studies, case–control studies, review articles, commentaries, and studies published only as abstracts. Studies in which the diagnosis of complete hydatidiform mole was based on the results of the index test.

Information sources Google Scholar, PubMed, Journals@Ovid (OVFT) from inception to August 26, 2026.

Main outcome(s) Sensitivity and specificity of p57Kip2 immunohistochemistry for the diagnosis of complete hydatidiform mole. No time-point restrictions apply, as p57Kip2 is assessed on diagnostic archival tissue. Effect measures will be pooled sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio, with 95% confidence intervals, using a bivariate random-effects model.

Quality assessment / Risk of bias analysis Methodological quality and risk of bias will be evaluated independently by two reviewers using the QUADAS-2 tool, which assesses four domains: patient selection, index test, reference standard, and flow and timing. Potential publication bias due to missing or unpublished studies will be examined using Deeks' funnel plot asymmetry test, with a p-value of less than 0.05 considered indicative of significant asymmetry.

Strategy of data synthesis Pooled estimates of diagnostic accuracy (sensitivity, specificity, likelihood ratios, diagnostic odds ratio, and AUC) will be calculated using STATA v.16 with the MIDAS and METADTA packages. A bivariate random-effects model will account for the expected correlation between sensitivity and specificity. Heterogeneity will be quantified with the I^2 statistic, with values ≥50% considered substantial.
To investigate sources of heterogeneity, subgroup analyses are planned according to comparator pathology, reference standard type (histology alone vs combined with genotyping), p57 positivity threshold, mean maternal and gestational age, and the number of pathologists who assessed the IHC results. Meta-regression will be used to assess the influence of study-level covariates.
Robustness of the pooled estimates will be evaluated through leave-one-out sensitivity analysis. Results will be presented using forest plots and summary ROC curves.
Publication bias will be examined using Deeks' funnel plot asymmetry test ($p < 0.05$ considered significant). If fewer than four studies are available for a given outcome, a narrative synthesis will replace the meta-analysis.

Subgroup analysis Where data permit, subgroup analyses will be conducted to examine potential drivers of heterogeneity in diagnostic performance. Planned stratifications may include:

Reference standard type: histology alone versus histology combined with genotyping

p57 positivity threshold: predefined versus unspecified or variable

Mean maternal and gestational age: dichotomized by the median value across included studies

Number of pathologists: single versus two or more assessors

Stratum-specific pooled estimates with 95% confidence intervals will be calculated when at least two studies contribute to a subgroup. Given the anticipated limited number of studies per stratum, these analyses are considered exploratory and hypothesis-generating.

Sensitivity analysis A leave-one-out sensitivity analysis will be conducted to assess the influence of individual studies on pooled estimates. Additional pre-specified sensitivity analyses include restriction to studies using genotyping-confirmed reference standards, studies with clearly defined p57 positivity thresholds, and studies at low risk of bias, to evaluate the robustness of the findings.

Language restriction No language restrictions willbe applied.

Country(ies) involved Russian.

Keywords Molar pregnancy; P57; Gestational Trophoblastic Desiese; Sensitivity and specificity.

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