ORIGINAL ARTICLE

# Differential expression of P63, P27, P57, Ki-67, and CD146 in hydropic and molar pregnancies

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## Abstract

**Objective:** To investigate the expressions of immunohistochemical markers P63, P27, P57, Ki-67 and CD146 in hydropic and molar specimens in order to explore their role in the pathogenesis of molar gestations.

**Method:** The retrospective study was conducted at the Kırıkkale Medical University, Turkey, and comprised data from 2011 to 2018 related to patients with a definitive pathological diagnosis of hydropic abortus, complete hydatidiform moles and partial hydatidiform moles. Immunoreactivity using antibodies against P63, P27, P57, Ki-67 and CD146 was scored by evaluating the percentage of distinctly stained cells. Data was analysed using SPSS 15.

**Results:** Of the 37 specimens, 10(27%) were hydropic abortus, 17(46%) partial hydatidiform moles and 10(27%) complete hydatidiform moles. Patients with complete hydatidiform moles severe cytologic atypia in CD146-positive extravillous trophoblastic column and florid syncytiotrophoblast proliferation. P57 immunostaining was negative in 9(90%) patients with complete hydatidiform moles, whereas all patients in the two other groups showed positive immunostaining, and they also showed P63 and Ki-67 overexpression in cytotrophoblasts. P27 was expressed in differentiated, non-dividing syncytiotrophoblasts but did not yield any diagnostic aid.

**Conclusion:** The proliferative activity location varied between molar and nonmolar pregnancies.


**Keywords:** Hydatidiform mole, Hydropic abortion, P63, P27, P57, Ki-67, CD146. (JPMA 71: 796; 2021)

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## Introduction

Traditionally, hydatidiform moles (HMs), which are rare abnormal pregnancies due to genetic fertilisation disorders, are subdivided into complete hydatidiform moles (CHMs) and partial hydatidiform moles (PHMs). CHMs are androgenic in origin which means that all the genetic material is paternally-derived. In most cases, they result from an enucleated egg that is fertilised by either two sperms or a haploid sperm which then duplicates. The excess paternal genetic material leads to excessive growth of trophoblastic tissues compared to foetal tissues. In contrast, PHMs are biparental and generally dispermic triploids. They develop from an ovum that is fertilised by two sperms, leading to a paternal-to-maternal chromosome ratio of 2:1 and is a diagnosis of molar pregnancy.[1]

Subdividing HMs into CHMs and PHMs is important for determining the risk of gestational trophoblastic neoplasia and its clinical management. Studies have reported that malignant change occurs in ~15-20% of CHMs and <1-5% of PHMs.[2]

Morphologic examination of conception products is the main diagnostic tool used for differential diagnosis of a complete mole (CM) and a partial mole (PM). However, the histopathological criteria for molar and nonmolar hydropic pregnancies are subjective and show considerable inter- and intra-observer variability.[3] With early diagnosis and evacuation of molar pregnancies, their differentiation from early nonmolar placentation, especially hydropic abortus (HA) with an abnormal villous pattern, becomes complicated.[1,3]

Numerous ancillary techniques have been used to improve HM diagnoses, including immunohistochemistry (IHC) for $P57^{kip2}$, which is a strongly paternally imprinted, cyclin-dependent kinase (CDK) inhibitor, being expressed from the maternal allele. $P57^{kip2}$ is absent or markedly underexpressed in cytotrophoblasts (CTs) and mesenchyme of CHMs compared to PHMs, having biparental genomes, but it cannot help distinguish a PHM from an HA.[3-6]

HMs are characterised by abnormal proliferating trophoblasts. The transcription factor P63 plays a crucial role in stem cell maintenance, in addition to its tumour suppressor and oncogenic roles. The cell-cycle-controlling molecule P27, which belongs to the Kip/Cip family of CDK inhibitors, can mediate gap 1 (G1) arrest.[6-10]

The current study was planned to investigate the expressions of IHC markers P63, P27, P57, Ki-67, and melanoma cell adhesion molecule CD146 in hydropic and molar specimens in order to explore their role in the pathogenesis of molar gestations.

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**Table-1:** P27, P57, Ki67, P63, and CD146 expression with respect to maternal and gestational age among the groups.

| | Maternal age (Mean ± SD) | Gestational age (Mean ± SD) | P27/ST (Mean ± SD) | P57 (Mean ± SD) | Kİ-67/CT (Mean ± SD) | Kİ-67/TC (Mean ± SD) | P63 (Mean ± SD) | CD146 (Mean ± SD) |
|---|---|---|---|---|---|---|---|---|
| Total (n = 37) | 27.9±6.7 | 9.3±1.0 | 3.1±1.0 | 2.7±1.6 | 3.0±0.9 | 3.8±0.5 | 2.8±1.2 | 4.0±0.0 |
| Hydropic abortus (n = 10) | 31.6±5.4 | 9.7±0.9 | 3.1±1.0 | 3.4±1.1 | 2.9±0.9 | 4.0±0.0 | 3.0±1.1 | 4.0±0.0 |
| Complete mole (n = 10) | 25.3±5.8 | 8.7±1.1 | 3.5±0.8 | 0.5±1.1 | 3.7±0.7 | 3.3±0.7 | 1.6±0.7 | 4.0±0.0 |
| Partial mole (n = 17) | 27.2±7.2 | 9.4±0.9 | 2.9±1.1 | 3.6±0.7 | 2.8±0.9 | 4.0±0.0 | 3.5±0.9 | 4.0±0.0 |
| Kruskal–Wallis test *p*-value | 0.043* | 0.020* | 0.395 | 0.001* | 0.029* | 0.001* | 0.001* | >0.999 |

*Statistically significant; ST: Syncytiotrophoblast; CT: Cytotrophoblast; TC: Trophoblastic column; SD: Standard deviation

**Table-2:** Pairwise comparisons in terms of clinical variables and immunohistochemical markers between the groups.

| | Maternal age (Mean ± SD) | Gestational age (Mean ± SD) | P27/ST (Mean ± SD) | P57 (Mean ± SD) | Kİ-67/CT (Mean ± SD) | Kİ-67/TC (Mean ± SD) | P63 (Mean ± SD) | CD146 (Mean ± SD) |
|---|---|---|---|---|---|---|---|---|
| Hydropic abortus (n = 10) | 31.6±5.4 | 9.7±0.9 | 3.1±1.0 | 3.4±1.1 | 2.9±0.9 | 4.0±0.0 | 3.0±1.1 | 4.0±0.0 |
| Complete mole (n = 10) | 25.3±5.8 | 8.7±1.1 | 3.5±0.8 | 0.5±1.1 | 3.7±0.7 | 3.3±0.7 | 1.6±0.7 | 4.0±0.0 |
| Mann–Whitney U test *p*-value | 0.012* | 0.007* | 0.340 | 0.001* | 0.032* | 0.005* | 0.006* | >0.999 |
| Hydropic abortus (n = 10) | 31.6±5.4 | 9.7±0.9 | 3.1±1.0 | 3.4±1.1 | 2.9±0.9 | 4.0±0.0 | 3.0±1.1 | 4.0±0.0 |
| Partial mole (n = 17) | 27.2±7.2 | 9.4±0.9 | 2.9±1.1 | 3.6±0.7 | 2.8±0.9 | 4.0±0.0 | 3.5±0.9 | 4.0±0.0 |
| Mann–Whitney U test *p*-value | 0.063 | 0.143 | 0.719 | 0.827 | 0.663 | >0.999 | 0.164 | >0.999 |
| Complete mole (n = 10) | 25.3±5.8 | 8.7±1.1 | 3.5±0.8 | 0.5±1.1 | 3.7±0.7 | 3.3±0.7 | 1.6±0.7 | 4.0±0.0 |
| Partial mole (n = 17) | 27.2±7.2 | 9.4±0.9 | 2.9±1.1 | 3.6±0.7 | 2.8±0.9 | 4.0±0.0 | 3.5±0.9 | 4.0±0.0 |
| Mann–Whitney U test *p*-value | 0.528 | 0.076 | 0.185 | 0.001* | 0.012* | 0.001* | 0.001* | >0.999 |

**Statistically significant: ST: Syncytiotrophoblast; CT: Cytotrophoblast; TC: Trophoblastic column; SD: Standard deviation.

## Materials and Methods

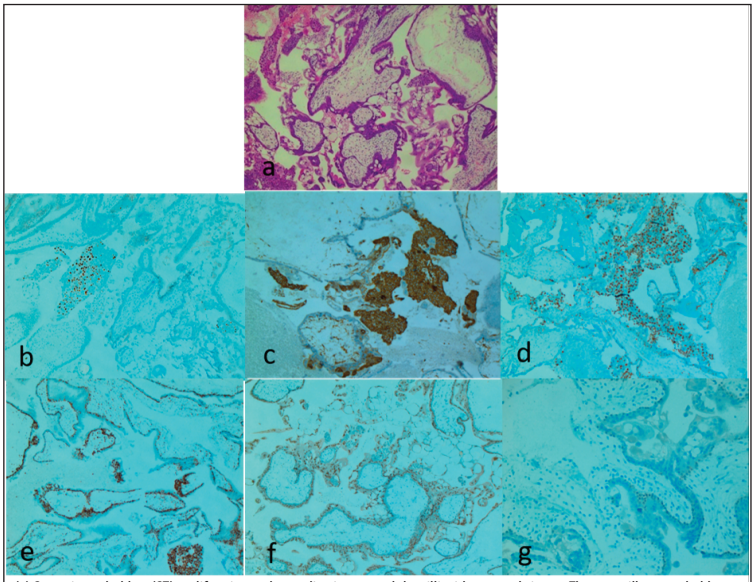
The retrospective study was conducted at the Kırıkkale Medical University, Turkey, and comprised data from 2011 to 2018 related to patients with a definitive pathological HA, CHM and PHM diagnosis. The diagnoses were based on the analysis of haematoxylin and eosin (H&E)-stained slides of formalin-fixed and paraffin-embedded tissues of retrieved from the pathology archives. Two pathologists re-evaluated the diagnoses, and their findings showed no conflict. Extravillous and syncytiotrophoblast (ST) proliferation, ST vacuolisation and cytologic atypia were graded as mild, moderate or severe. P63, P27 a,d P57 expression patterns were noted and IHC analysis for Ki-67 was done as a proliferation control in line with literature.[8,11-13] CD146, which is expressed in mature extravillous-type trophoblasts, was used to determine proliferating cell compartment.[14]

Immunoreactivity, using antibodies against P63, P27, P57, Ki-67, and CD146, was scored using a semiquantitative scoring method based on the percentage of distinctly stained cells. Scoring estimates were based on the number of stained trophoblast nuclei: 0 = no staining, 1+ = 1-10% staining, 2+ = 11-25% staining, 3+ = 26-50% staining, and 4+ = >50% staining.

Data was analysed using SPSS 15. Mann-Whitney U test and Kruskal-Wallis test were performed to evaluate possible associations between nonparametric terms between two groups and among three or more groups, respectively. P<0.05 was considered statistically significant.

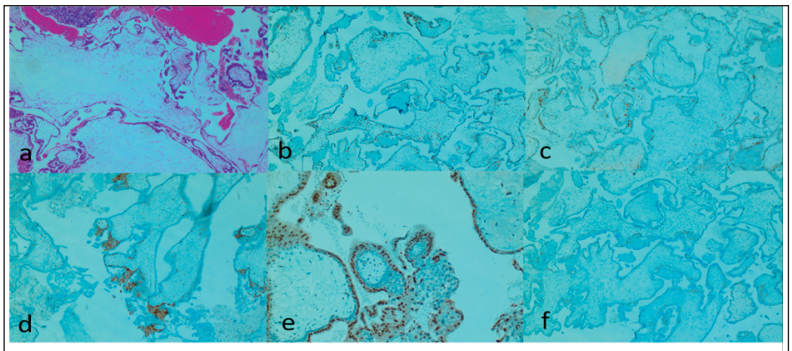
## Results

Of the 37 specimens, 10(27%) were HAs, 17(46%) PHMs and 10(27%) CHMs. Data was compared with respect to



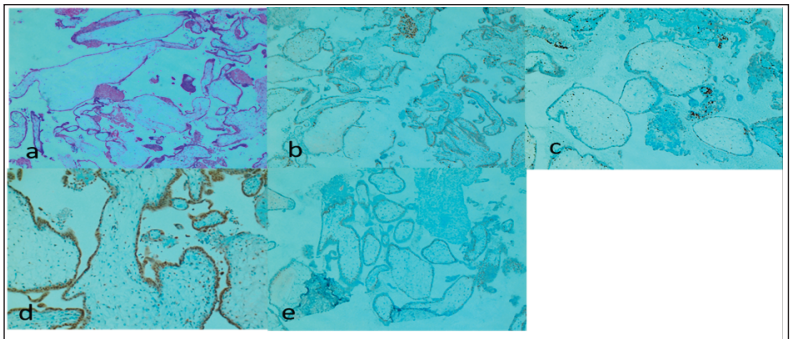

(a) Syncytiotrophoblast (ST) proliferation and vacuolization around the villi with a central cistern. The extravillous trophoblasts, forming plates that show nuclear atypia, are on the left side (HE X40). (b) P57 is expressed in extravillous trophoblast islands in CHM (X40). (c) A strong membranous staining with CD146 in extravillous trophoblasts in all patients (X40). (d, e) Ki-67 immunoreactivity was marked in extravillous trophoblasts and villous cytotrophoblasts (CTs) in CHM (X40). (f) All STs showed P27 nuclear positivity in CHM patients (X40). (g) Rare cells displayed weak and moderate staining with P63 in CHM patients (X100).

**Figure-1:** Histopathological features and immunohistochemical staining patterns of complete hydatidiform moles (CHM) cases.




(a) Molar villi with scalloped edges and moderate extravillous trophoblastic proliferation (HE X40). (b) P57 expression in cytotrophoblasts and villous stromal cells in PHM (X40). (c) Molar villi with 2+ and 3+ CT Ki-67 staining in PHM patients (X40). (d) Trophoblastic columns (TCs) stained diffusely with Ki-67 in PHM patients (X40). (e) Syncytiotrophoblasts (STs) showed strong nuclear expression of P27 in PHM patients (X100). (f) Basal CTs have a 2+ and 3+ immune score with P63 in PHM patients (X40).

**Figure-2:** Histopathological features and immunohistochemical staining patterns of partial hydatidiform moles (PHM) cases.




(a) HA patients with edematous villi and intervillous fibrinoid material (HE X40). (b) P57 expression in cytotrophoblasts (CTs), villous stromal cells, and extravillous trophoblasts in HA patients (X40). (c) CTs showed mostly a 2+ immune score with Ki-67 (X40). (d) P27 expression in syncytiotrophoblasts (STs) in HA patients (X100). (e) Basal CTs displayed a 4+ score with P63 in HA patients (X100).

**Figure-3:** Histopathological features and immunohistochemical staining patterns of hydropic abortus (HA) cases.

**Table-3:** Statistical analysis of histopathological features between the groups.

| | Proliferating EVTs (Mean ± SD) | ST vacuolization (Mean ± SD) | ST proliferation (Mean ± SD) | Cytologic atypia (Mean ± SD) |
|---|---|---|---|---|
| Total (n = 37) | 2.0±0.7 | 1.5±0.8 | 1.8±0.8 | 1.7±0.8 |
| Hydropic abortus (n = 10) | 1.7±0.5 | 1.0±0.0 | 1.5±0.5 | 1.1±0.3 |
| Complete mole (n = 10) | 2.6±0.5 | 2.5±0.7 | 2.4±0.8 | 2.7±0.5 |
| Partial mole (n = 17) | 1.9±0.7 | 1.3±0.5 | 1.7±0.8 | 1.5±0.5 |
| Kruskal–Wallis test *p*-value | 0.007* | 0.001* | 0.047* | 0.001* |

**Statistically significant; ST: Syncytiotrophoblast; EVT: Extravillous cytotrophoblast.

maternal and gestational age (Table 1) and in terms of clinical variables and IHC markers (Table 2). There were no significant differences related to maternal age and gestational week among the groups ($p>0.05$). All HM and PHM patients (100%) showed positive immunostaining for P57, which was absent in 9(90%) CHM patients. The remaning 1 (10%) patient fitted morphologically with a CHM diagnosis but tested positive for P57 in a few villous CTs.

Histopathological features and IHC staining patterns were analysed for CHMs (Figure 1), PHMs (Figure 2) and HAs (Figure 3).

Inter-group (Table 3) and pair-wise (Table 4) analyses of histopathological findings were also done.

## Discussion

P57 loss is a valuable tool for CHM diagnosis, but it cannot distinguish PHM from HA. In the current study, only one patient showed aberrant P57, possibly due to some other pathogenesis that retained the maternal allele.

The current study analysed the expression patterns of key cell-cycle checkpoint proteins Ki-67 and $P27^{kip1}$ using IHC to measure the proliferative status in molar, less molar, or nonhydropic pregnancies. PHM and HA patients showed high Ki-67 expression in TCs, but Ki-67 positivity was marked in extravillous cytotrophoblasts (EVTs) in CHM patients. CTs are considered trophoblast stem / progenitor cells. PHM and HA patients had more villous CTs staining strongly for P63 compared to CHM patients. We believe the proliferation / differentiation ratio indices increase during differentiation into CD146-positive extravillous trophoblast and ST cell lines in CHM patients. Therefore, ST hyperplasia was more likely the result of abnormal trophoblastic maturation rather than proliferation of these cells.

In the current study, Ki-67 was not expressed in STs in all patients. STs have non-dividing properties and display CDK inhibitor P27 expression, indicating cell-cycle arrest in the G1 phase. Alwaqfi et al. found that the Ki-67 proliferative index was higher in CHM patients compared to PHM and HA patients, and also stated that PHM patients tended to have higher Ki-67 expression compared to HA patients.[15] In the current study, CT proliferation, including EVTs, was marked in CHM patients. Missaoui et al. observed that P63 and Ki-67 were significantly expressed in CHM patients compared to PHM and HA patients.[13] According to studies, nuclear immunoreactivity of P63 is higher in molar than in nonmolar pregnancies and in PHM than in CHM patients.[7,16] Erfanian et al. detected STs that stained positive for Ki-67 and P63.[16] We believe that the proliferative activity location varies between molar and nonmolar pregnancies. PHM and HA patients have more

**Table-4:** Pairwise comparisons of histopathological findings between the groups.

| | Proliferating EVTs (Mean ± SD) | ST vacuolization (Mean ± SD) | ST proliferation (Mean ± SD) | Cytologic atypia (Mean ± SD) |
|---|---|---|---|---|
| Hydropic abortus (n = 10) | 1.7±0.5 | 1.0±0.0 | 1.5±0.5 | 1.1±0.3 |
| Complete mole (n = 10) | 2.6±0.5 | 2.5±0.7 | 2.4±0.8 | 2.7±0.5 |
| Mann–Whitney U test *p*-value | 0.002* | 0.001* | 0.016* | 0.001* |
| Hydropic abortus (n = 10) | 1.7±0.5 | 1.0±0.0 | 1.5±0.5 | 1.1±0.3 |
| Partial mole (n = 17) | 1.9±0.7 | 1.3±0.5 | 1.7±0.8 | 1.5±0.5 |
| Mann–Whitney U test *p*-value | 0.528 | 0.062 | 0.678 | 0.029* |
| Complete mole (n = 10) | 2.6±0.5 | 2.5±0.7 | 2.4±0.8 | 2.7±0.5 |
| Partial mole (n = 17) | 1.9±0.7 | 1.3±0.5 | 1.7±0.8 | 1.5±0.5 |
| Mann–Whitney U test *p*-value | 0.012* | 0.001* | 0.053 | 0.001* |

**Statistically significant; ST: Syncytiotrophoblast; EVT: Extravillous cytotrophoblast; SD: Standard deviation.

progenitor cells, which express the highest levels of P63 compared to CHM patients. P63 is expressed only in CTs and completely excluded from both STs and EVTs. CHM patients are nearly devoid of P63-positive cells, but have Ki-67-positive cells. P63(ΔNp63), a P53 family member, is a master regulator of epithelial morphogenesis and stemness. In the absence of P63 or under conditions of P63 inactivation, stem cells may shift toward mesenchymal morphology and an increase in motility in primary keratinocytes and squamous cell lines. The loss of endogenous P63 expression results in up-regulated genes associated with invasion and metastasis, predisposing the body to a loss of epithelial and acquisition of mesenchymal characteristics. In addition, P63 is one of the most down-regulated transcription factors during epithelial-to-mesenchymal transition in human prostate cells.[17,18] We believe this transition can be applied to transforming EVTs from CTs. In the current study, P63 was lost or weakly expressed in CHM patients, but Ki-67-proliferating cells retained an extravillous compartment that selectively expanded and also had invasive properties. In contrast, in PHM and HA patients, these cells remained undifferentiated.

Abdou et al. compared P57 and P27 expression among molar pregnancies and choriocarcinoma,[10] and claimed that P27 expression by stromal cells and total trophoblastic population at a 7.5% cut-off point could discriminate between PMs and CMs.[10] However, in the current study, P27 was limited to STs and showed no oncogenic role in either trophoblastic atypia or proliferation.

One of our histopathological findings was extravillous trophoblasts having prominent atypia in CHM patients. This was like a highly polyploid nuclei arising through deoxyribonucleic acid (DNA) duplication without the accompanying nuclear division.[19] Extravillous trophoblasts expressed P57 in all patients in the current study and synchorously showed Ki-67 overexpression in CHM patients. P57 is a CDK inhibitor and functions as a negative regulator of cell proliferation. The maternally expressed P57 gene is believed to be gained by epigenetic relaxation in extravillous trophoblasts in CHM patients, but might have deficient activity, resulting in incomplete nuclear mitosis. Nearly half of the Beckwith–Wiedemann syndrome patients carry germline mutations in the coding sequence of the maternally expressed CDK inhibitor 1c (p57$^{KIP2}$) gene. Studies have reported that these patients' placentae with aberrant imprinting centere-2 (IC2) methylation lead to abnormal P57 expression and have a striking excess of extravillous trophoblasts.[20] The P57 mutant placenta shows overgrowth with trophoblast overproliferation, diffuse EVT cytomegaly with polyploidy, and reduced diameter of mutant foetal capillaries.[21,22] So mega nuclei are associated with the absence of P57. This is a pathological guideline in either floating extravillous trophoblasts or implantation site-invasive trophoblasts in CHM patients.

In our study, Ki-67 proliferation was distinct in extravillous trophoblasts in CHM patients, while it was more prominent in TCs in PHM and HA patients. Based on expression of the P63 location, PHM and HA cases remained a steady state with slow cycling speed limited to basal CTs that might have enough time to mature gradually by gestational age. In contrast, in CHM patients, transition from stem cells to specialized cells is supposed to be faster, resulting in abnormal differentiated cell types.

The histopathological criteria used in the current study allowed for reliable distinction between molar and nonmolar pregnancies. However, no significant differences were observed between CMs and PMs, and we focussed on ST vacuolisation indicative of impaired fluid transportation, especially when evaluating early molar placentation.

The major limitation of the current study is its small sample size which was due to the decision of some molar cases to have a second opinion on the demonstrative paraffine blocks at some other centres. Also, we tried to select less bloody samples to reduce interference with IHC antibodies.

## Conclusion

Ki-67 proliferation rate vastly shifted from TC to villous and extravillous sides in CHM disease. P63 deficiency, like P57 deficiency, induced exaggerated proliferation and differentiation and could be used as an ancillary diagnostic tool for CHM diagnosis.

**Disclaimer:** None.

**Conflict of Interest:** None.

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