



Original Article

# Role of p57kip2 immunohistochemistry in the diagnosis and classification of molar pregnancies

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## Keywords:

Complete mole, Gestational trophoblastic disease, Hydatidiform mole, p57, Partial mole.

## ABSTRACT

**Background:** Gestational trophoblastic disease is a group of benign and malignant disorders defined by abnormal trophoblastic proliferation, of which hydatidiform mole is the most common, characterized by hydropic swelling of placental villi and trophoblastic hyperplasia. It is imperative to further classify hydatidiform mole into complete mole and partial mole, as complete mole is associated with an increased risk of gestational trophoblastic neoplasia.

**Materials and Methods:** This was a cross-sectional study carried out in the Department of Pathology, 51 cases (24 complete mole, 1 partial mole, 2 hydatidiform mole - NOS, and 24 non-molar products of conception) were included in the study. Histomorphological features and the expression of IHC p57Kip2 (57P06) in cytotrophoblasts and villous stromal cells were studied.

**Results:** Histomorphological assessment of the 51 cases showed 24/51 (47%) cases of complete mole, 1/51 (2%) case of partial mole, 2/ 51 (3.9%) cases with ambiguous histology diagnosed as Hydatidiform mole-NOS, and 24/51 (47.1%) cases of non-molar products of conception. The majority of the patients [36/51 (70.6%)] were in the 21-30 years age group. Expression of p57Kip2 was found to be corroborating with histomorphological diagnosis in 48/51 (94.1%) cases, diagnostic in 2/51 (3.92 %) of cases, and non-contributory in 1/51 (1.96%) cases.

**Conclusions:** The study confirms that negative p57 IHC expression may reliably identify complete mole. However, immunohistochemistry has a limited role in discriminating partial mole from hydrops abortus and is also inconclusive in cases with discordant expression.

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## INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of benign and malignant disorders that begin during placental development and are defined by abnormal trophoblastic proliferation. They have variable tendencies for local invasion and metastases.<sup>1,2</sup> Hydatidiform mole (HM) is the most common GTD, results from abnormal fertilization and is characterized by hydropic swelling of placental villi and trophoblastic hyperplasia. It is composed of two separate entities, partial mole (PM) and complete hydatidiform mole (CHM), which are distinguished by their clinical features, chromosomal patterns, histopathology and different degrees

of risk for the development of Gestational trophoblastic neoplasia (GTN).<sup>3,4</sup> It is important to diagnose GTD as it has the potential to locally invade the uterus and metastasize. Risk of persistent GTD following complete or partial mole is detected by serum beta human chorionic gonadotrophin ( $\beta$ -hCG) which is greater in CHM as compared to PM. The risk of development of choriocarcinoma in CHM is 15-20% as compared to a 0.5-5% risk in partial moles.<sup>5-9</sup>

p57, a CDKN1C is a tumor suppressor gene which is a product of paternally imprinted and maternally expressed gene on chromosome 11p15.5.<sup>10</sup> In the placental tissue, p57 is normally present in cytotrophoblast, villous stromal cells and intermediate/extravillous trophoblasts. It is normally not expressed in syncytiotrophoblasts. Since CHMs have no maternal genome, p57 is not seen in villous stromal or cytotrophoblasts and hence p57 serves as a surrogate marker for absence of maternal genome.<sup>11</sup>

In the present study, the various histomorphological features and the role of p57 expression by immunohistochemistry (IHC) in diagnosis and subclassification of molar pregnancy were evaluated with an aim to know how ancillary studies including IHC for p57 can play a role in the confirmation of histopathological diagnosis.

## MATERIALS AND METHODS

This was a cross-sectional study carried out in the Department of Pathology, SGRRIM&HS, Dehradun, India. The study was approved by Institutional Ethical Committee. A total of 51 cases [24 cases of CHM, 1 case of PM, 2 cases of HM-NOS and 24 cases of non-molar products of conception (NM-POC)/ hydropic abortus (HA)] diagnosed on histopathology were included in this study. Exclusion criteria included inadequate specimens demonstrating only fibrin, decidua or blood clot but no viable chorionic villi. Detailed history including maternal age, presenting complaints, gestational age at time of evacuation were noted on a predesigned proforma. Serum  $\beta$ -hCG levels and ultrasonographic findings were reviewed, when available. The samples were received in 10% neutral buffered formalin and were processed in automated tissue processor. For IHC, additional sections of 2-3  $\mu$ m were taken on Poly-l-lysine coated slides and were subjected to IHC for p57.

Histomorphological features observed were: mixed population or presence of 2 villous population (large hydropic and smaller fibrotic villi), trophoblastic proliferation, trophoblastic pseudoinclusions, cistern formation, scalloping of villi, stromal karyorrhexis, stromal myxoid change, presence of fetal parts, nucleated RBCs, extravillous trophoblasts, stromal vessels and abnormal villous stroma.

Grading of circumferential trophoblastic proliferation was done as follows : Grade 1 – Absent, Grade 2 – Present but less than 0.5 mm thick at its maximum intensity, Grade 3 –

Between 0.5 and 1 mm and Grade 4 – Thicker than 1mm.

Grading of villous hydrops/cistern formation was done as follows : Grade 1 – Absent, Grade 2 – Present but less than 3mm in size at its maximum intensity, Grade 3 – Between 3 and 6mm and Grade 4 – Greater than 6mm.

Grading of stromal karyorrhexis was done as follows- Grade 1 – Absent, Grade 2 – Present but inconspicuous, Grade 3 – Nuclear debris less numerous than stromal cells, Grade 4 – Nuclear debris more numerous than stromal cells.

Results of IHC were considered valid for evaluation only when internal controls (decidual cells and/or intermediate trophoblasts) showed expression of p57. The presence or absence of nuclear positivity was assessed in villous stromal cells, cytotrophoblasts, intermediate trophoblasts and maternal decidua regardless of intensity of the staining. The p57 immunostaining was interpreted as “negative” when the villous stromal cells and cytotrophoblasts were either entirely negative or demonstrated only limited expression (nuclear staining in <10% of the cytotrophoblasts and villous stroma cells). This negative result was interpreted as consistent with a diagnosis of CHM. The p57 immunostain was interpreted as “positive” when the extent of staining in these cell types was extensive or diffuse (nuclear staining in >10% of the cytotrophoblasts and villous stromal cells)

The p57 pattern was interpreted as ‘discordant’ when there was any combination /admixture of negative and positive results for villous stromal cells and cytotrophoblast within individual villi, including positive staining in cytotrophoblast and negative staining in villous stromal cells or vice versa.

The p57 expression pattern was interpreted as divergent when 2 population of villi, each with different morphologies exhibited two different staining patterns.

For analysis, SPSS v22 statistical software was used and results were presented in the form of frequency and percentage for all categorical variables. The student's t-test was used for comparison of the means of continuous variables and the chi-square test was used for comparison of discontinuous variables, with p-value of <0.05 being considered as significant. Statistical analysis for any association between p57 classification and histopathologic correlation was also done.

The study was approved by Institutional ethical committee (IEC) (Reference number- 52/21, dated 22/10/2021). Formal written informed consent was not required with a waiver by the IEC.

## RESULTS

Frequency of CHM [24/51(47.05%)] was found to be more as compared to PM [1/51 (1.96%)]. Majority of the patients 36/51 were in the age group 21-30 years (70.6%). The mean age of molar pregnancy and non-molar pregnancy was 28.2

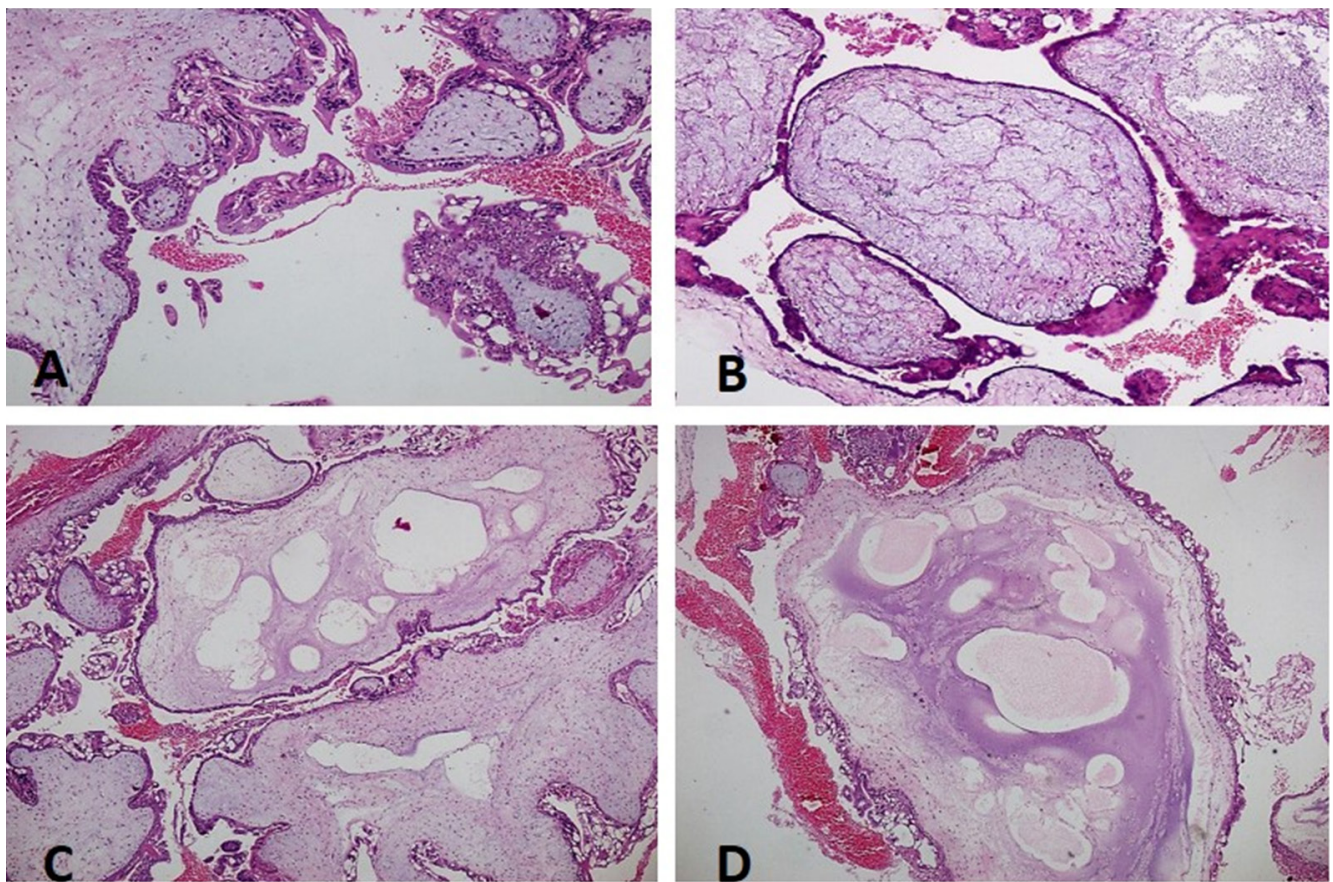
years and 28.79 years, respectively, with no statistically significant difference. Majority of molar pregnancies 9/27 (33.3%) were evacuated between 10-12 weeks of gestation. Only 7/27 (25.9%) cases of molar pregnancies presented at <9 weeks of gestation, while 20/24 (83.3%) of non-molar pregnancies presented between 4-9 weeks of gestation. Both molar and non-molar pregnancies had a similar clinical presentation, most common symptom being vaginal bleeding in 44/51 (86.3%), followed by lower abdominal pain 35/51 (68.6%).

The ultrasonographic findings were available for 44/51 (86.3%) cases and corroborated with the histologic diagnoses in most of the cases. 19/ 24 (79.2%) cases of CHM were reported as CHM on ultrasound, while the rest of the cases (5/24, 20.8%) were reported as HM. The single case of PM was reported as suspicious for GTD. One of the two cases of

HM-NOS was reported as PM and the other was reported as CHM. All the NM POC (17/17, 100%) were given as NM POC on ultrasonography.

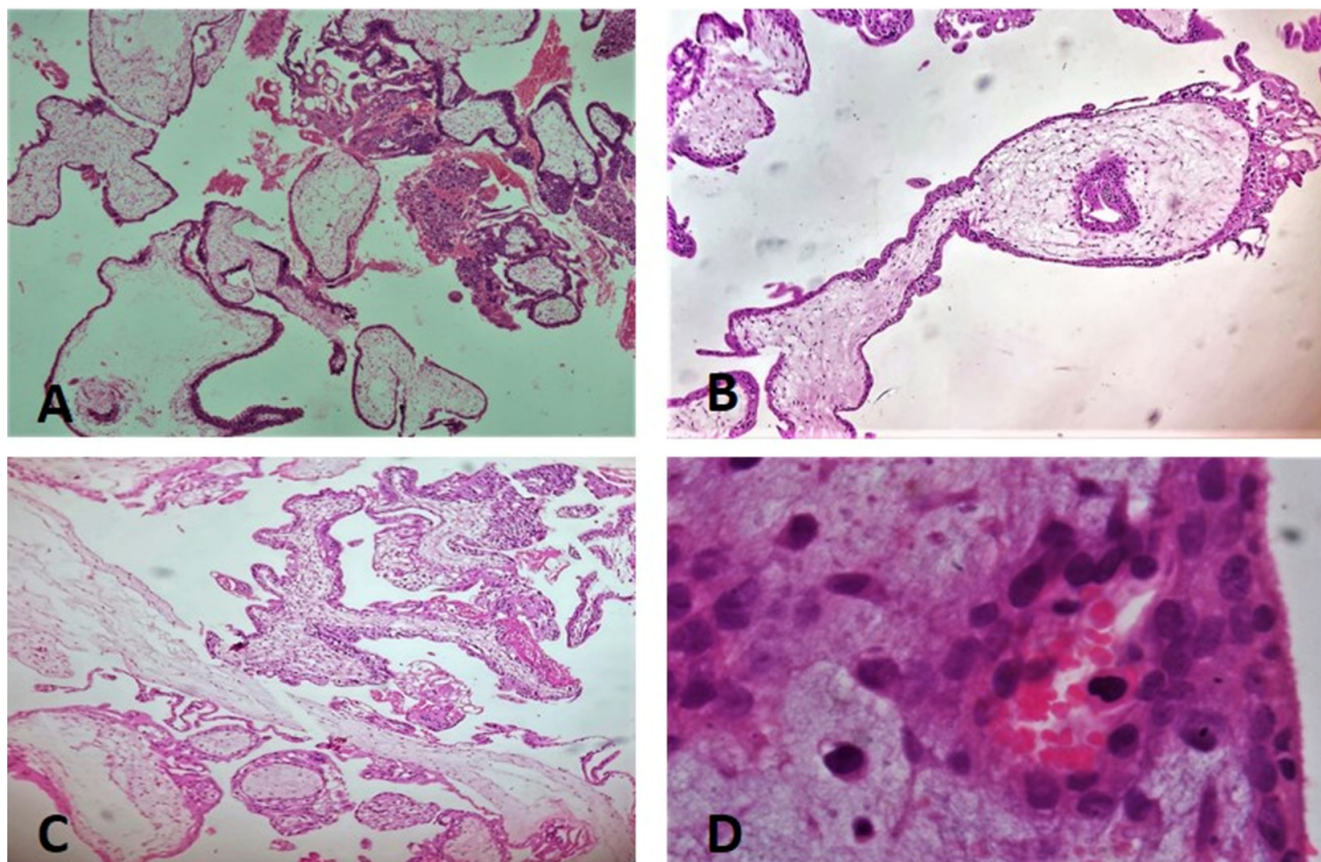
The median values of  $\beta$ -hCG in cases of molar pregnancies were significantly higher than in non-molar pregnancies (1,42,307.6mIU/mL vs. 11,564mIU/mL) with a p-value of 0.000.

Gross examination of 19/27 (70.4%) of molar pregnancies showed grape like vesicles while none of the non-molar pregnancies showed vesicles grossly. Histomorphological features exhibiting significant association with molar pregnancy included cistern formation, presence of trophoblastic proliferation, distribution of trophoblastic proliferation and absence of nRBCs. (fig.1&2).



**Figure 1:** Photomicrograph showing (A) Variably sized hydropic villi exhibiting circumferential trophoblastic hyperplasia and myxoid change in a case of CHM; (B) Hydropic villi with myxoid change; (C&D) Central cistern formation with myxoid change in a case of CHM. [H&E; 100x (A,B) and 400x (C,D)].





**Figure 2:** Photomicrograph showing (A) Two populations of villi in a case of PM (H&E, 40X); (B) Irregular trophoblastic inclusion (H&E, 100X); (C) Circumferential trophoblastic hyperplasia (H&E, 100X); (D) Nucleated RBCs (H&E, Oil immersion)- A single case of PM.

Histomorphological features with poor diagnostic significance were scalloping of villi, stromal myxoid degeneration and stromal karyorrhexis. None of the non-molar pregnancies showed trophoblastic proliferation, while 20/27 (74.1%) molar pregnancies showed Grade 2 trophoblastic proliferation and 7/27 (25.9%) showed Grade 3 trophoblastic proliferation. Non-molar products of conception with hydropic changes were preferentially included in the study. 21/24 (87.5%) of non-molar pregnancies exhibited Grade 2 hydropic change and only 2/24 (8.3%) cases exhibited Grade 3/ 4 hydropic change. However, 20/27 (74.1%) cases of molar pregnancy showed Grade 3/ 4 hydropic change. Of the 22 cases exhibiting grades 3/4 hydrops, 20 (90.9%) were that of molar pregnancies, while only 2 (9.1%) cases of non-molar pregnancies showed grades 3/4 hydrops. This difference was statistically significant with a p-value of 0.000.

24/27 (88.9%) cases of molar pregnancies and (17/24) 70.84% cases of non-molar pregnancies showed grade 2 karyorrhexis. Rest of the cases did not show stromal karyorrhexis.

Two populations of villi (small and large), a feature of PM was also noted in 2/24 (8.3%) cases of CHM and 12/24 (50%)

cases of NM-POC due to hydropic change not involving all the villi universally. However, these small villi did not show fibrosis of the stroma. Hydropic change was noted in cases of HA, though cistern formation was seen in only 1 of the 24 cases (4.16%) of non-molar pregnancies.

Trophoblastic proliferation (circumferential and multifocal) was noted in all the cases of molar pregnancy and was found to be more specific. 22/24 (91.6%) of CHMs showed circumferential proliferation, while 2/24 (8.4%) cases showed non-circumferential proliferation, which were differentiated from polar syncytial knots seen in 8 of the 24 (33.3%) non-molar products of conception. None of the non-molar products of conception exhibited trophoblastic proliferation. Two pitfalls while evaluating trophoblastic proliferation are trophoblastic proliferation associated only with fibrin (False positive) and artefactual separation of proliferating trophoblasts from villi, which can be misidentified as intermediate villi with absent proliferation (False negative). Presence of nRBCs, a feature of PM was also noted in 3 of 24 cases (12.5%) of CHM, though these were few in number and prominent presence of nRBCs was not compatible with a diagnosis of CHM (Table 1).

**Table 1 showing clinical, ultrasonographic, and pathological findings of cases (n=51).**

| Features                                           | Complete hydatidiform mole (n=24) | Partial hydatidiform mole (n=2) | Discordant (n=1) | Non-molar pregnancies/ Hydropic abortus (n=24) | p-value* |
|----------------------------------------------------|-----------------------------------|---------------------------------|------------------|------------------------------------------------|----------|
| Maternal age (mean)                                | 28.17                             | 22.00                           | 26.00            | 28.79                                          | 0.487    |
| Parity (Median)                                    | 0                                 | 1                               | 2                | 2                                              | 0.587    |
| Gestational age(weeks) (median)                    | 11.50                             | 8.50                            | 15.00            | 8.00                                           |          |
| Pre-evacuation $\beta$ -hCG levels (IU/L) (median) | 240005.00                         | 77749.25                        | 24751.00         | 11564.00                                       | 0.000    |
| Two populations of villi                           | 02(8.3%)                          | 2(100%)                         | 1(100%)          | 12(50%)                                        | 0.000    |
| Villous hydrops Grade 1                            | 0                                 | 0                               | 0                | 1(4.16%)                                       | 0.303    |
| Grade 2                                            | 06(25%)                           | 1(50%)                          | 0                | 21(87.5%)                                      | 0.000    |
| Grade 3                                            | 16(66.67%)                        | 1(50%)                          | 1(100%)          | 2(8.34%)                                       | 0.000    |
| Grade 4                                            | 2(8.4%)                           | 0                               | 0                | 0                                              |          |
| Cistern formation                                  | 22(91.6%)                         | 2(100%)                         | 1(100%)          | 1(4.16%)                                       | 0.004    |
| Stromal myxoid change                              | 7(29.16%)                         | 1(50%)                          | 1(100%)          | 6(25%)                                         | 0.457    |
| Stromal karyorrhexis                               | 21(87.5%)                         | 2(100%)                         | 1(100%)          | 17(70.84%)                                     | 0.363    |
| Circumferential Trophoblastic proliferation        | 22(91.6%)                         | 2(100%)                         | 1(100%)          | 0                                              | 0.012    |
| Scalloping of villi                                | 18(75%)                           | 2(100%)                         | 1(100%)          | 8(33.33%)                                      |          |
| Pseudoinclusions present                           | 18(75%)                           | 1(50%)                          | 1(100%)          | 5(20.8%)                                       |          |
| Presence of capillaries                            | 13(54.1%)                         | 0                               | 0                | 17(70.8%)                                      | 0.753    |
| Presence of fetal elements                         | 0                                 | 0                               | 0                | 3(12.5%)                                       | 0.897    |
| Presence of nRBCs                                  | 3(12.5%)                          | 1(50%)                          | 0                | 16(66.66%)                                     | 0.457    |

IHC corroborated with histopathological diagnosis in 48/51 (94.1%) cases, was diagnostic in 2/51 (3.92 %) of cases, and was of no significant value in 1/51(1.96%) cases. In 23/24 (95.8%) cases of CHM, the majority of morphological features were evident, including enlarged villi with cistern formation and trophoblastic proliferation. These were categorised as CHM based on morphology alone and subsequently were also confirmed by the absence of p57 by IHC.

In a single case (1/24, 4.2%), multifocal trophoblastic proliferation was noted along with 2 populations of villi and subtle hydropic change; however, no fetal parts were seen. This case was signed out as PM on morphology, which was subsequently confirmed by a positive expression of p57 by IHC.

In two cases (2/51,3.9%), subtyping of molar pregnancy was not possible by histomorphological examination alone, and these were signed out as HM-NOS. p57 expression of IHC was found to be useful in diagnosing molar pregnancy (Table 2).

**Table 2 showing results of immunohistochemical analysis of p57 expression**

| Histomorphological Diagnosis                  | Results of immunohistochemistry for p57 |           |            |                |
|-----------------------------------------------|-----------------------------------------|-----------|------------|----------------|
|                                               | Positive                                | Negative  | Discordant | Unsatisfactory |
| Complete hydatidiform mole (n=24)             | 01                                      | 23        | -          | -              |
| Partial hydatidiform mole (n=1)               | 01                                      | -         | -          | -              |
| Hydatidiform mole – NOS (n=2)                 | -                                       | 01        | 01         | -              |
| Non-molar pregnancy / Hydropic abortus (n=24) | 24                                      | -         | -          | -              |
| <b>Total</b>                                  | <b>26</b>                               | <b>24</b> | <b>01</b>  | <b>0</b>       |

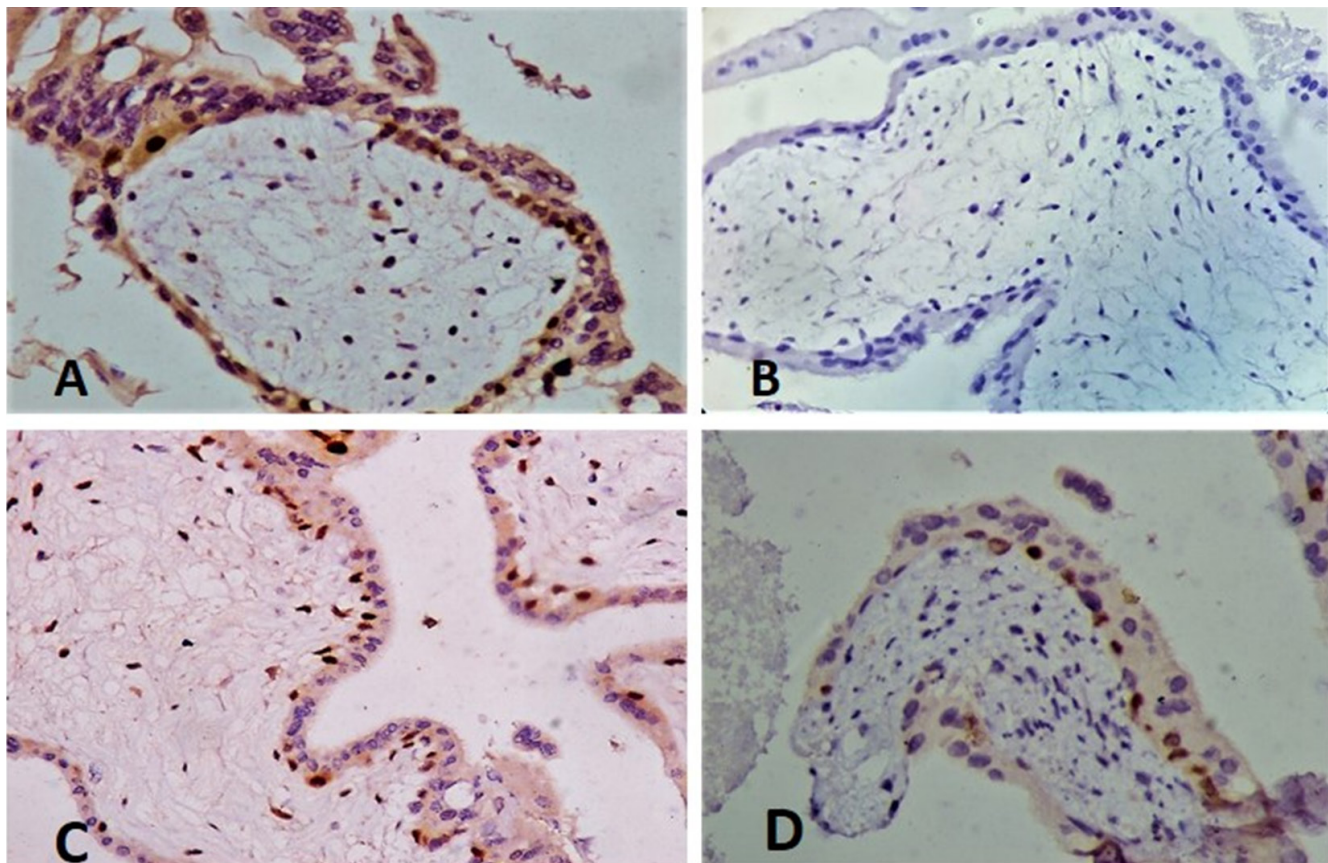
IHC enabled a definite diagnosis in one of these two cases with ambiguous morphology (Table 3).



**Table 3 showing role of immunohistochemistry for p57 in the diagnosis of molar pregnancy.**

| Histopathological diagnosis      | No of cases | Post IHC p57 diagnosis (N)        | Contribution of IHC p57                                                           |
|----------------------------------|-------------|-----------------------------------|-----------------------------------------------------------------------------------|
| Non-molar products of conception | 24          | Non-molar POCs (N= 24)            | Corroborating with morphological diagnosis                                        |
| Complete hydatidiform mole       | 24          | Complete hydatidiform mole (N=23) | Corroborating with morphological diagnosis.                                       |
|                                  |             | PM (N=01)                         | Aided, in diagnosis which was revised after IHC.                                  |
| Partial hydatidiform mole        | 01          | Partial hydatidiform mole (N=01)  | Corroborating with morphological diagnosis                                        |
| Hydatidiform mole (NOS)          | 02          | Complete hydatidiform mole (N=01) | Aided in diagnosis which was revised after IHC.                                   |
|                                  |             | Discordant villi (N=01)           | Diagnosis not confirmed even after IHC. Ploidy and molecular studies recommended. |

Diagnosis could not be confirmed even with the use of IHC in a case which showed ambiguous morphology on histopathological examination and discordant expression by IHC. IHC expression. (fig.3)



**Figure 3:** Photomicrograph showing (A) Positive p57 immunexpression in villous stromal cells and cytotrophoblasts in a case of Hydropic abortus (IHC, 400X); (B) Negative p57 immunexpression in cytotrophoblasts and villous stromal cells in a case of Complete hydatidiform mole (IHC, 400X); (C) Positive p57 immunoexpression in villous stromal cells and cytotrophoblasts in a case of Partial hydatidiform mole (IHC, 400x); (D) Discordant p57 expression by IHC between cytotrophoblasts (15%) and villous stromal cells (<10%).

## DISCUSSION

In the present study, the majority of the patients were in the 21-30 years age group, accounting for 70% of the cases, and only 6% of cases were over 40 years of age. The mean age was 28.17 years in cases of CHM, which was similar to other studies where the majority of cases were <40 years of age.<sup>12-14</sup>

In the present study, 57.7% of molar pregnancies and 92% of non-molar pregnancies were evacuated in the first trimester. Similarly, Kumar et al. and Awosusi et al. found that the majority of molar pregnancies were evacuated/presented at 8-10 weeks of gestation.<sup>14,15</sup>

Vaginal bleeding was the most common presentation in molar pregnancies (82% cases) followed by pain in abdomen (34% cases) similar to previous studies.<sup>12,16</sup> However, there was no

statistically significant difference between presentations of molar and non-molar pregnancies in the present study.

One of the hallmarks of molar pregnancy is a high  $\beta$ -hCG level which was available in 32 cases. The pre-evacuation median level of  $\beta$ -hCG in cases of CHM was 2,23,000 mIU/ml, highest being 24,32,400 mIU/ml and the lowest being 96,549 mIU/ml. Triratanachat et al. also found a median level of 2,10,000 mIU/ml in cases of CHM.<sup>12</sup>

Triratanachat et al. evaluated 107 cases of CHM and 20 cases of PM to define morphological features that could differentiate between CHM and PM. They found 2 populations of villi in 15 of the 20 (75%) cases of PM and 29 of the 107 (27%) cases of CHM.<sup>12</sup>

Due to early radiological diagnosis, the classical histomorphological features are also not fully developed. Grape-like vesicles on gross examination are rarely seen in early evacuations, with only subtle hydropic change appreciated by histopathological examination. Moreover, many non-molar abnormal pregnancies evacuated in the first trimester have hydropic change with mild trophoblastic proliferation, adding to the diagnostic dilemma. Histomorphological diagnosis and subtyping of molar pregnancy has high interobserver and intraobserver variability.<sup>17</sup> Morphological diagnosis is further limited by imperfect defining features of CHM and PM and subjectivity in the application of these.<sup>18</sup>

p57 immunostaining is a cheap and veritable ancillary option to differentiate between CHM and PM especially when encountered with features of early CHM. Our findings of cases classified as CHM on morphology alone were confirmed by a negative immunohistochemical staining of the cytotrophoblast and villous stromal cells. Similarly, a single case morphologically diagnosed as PM stained positive for p57 in the cytotrophoblasts and villous stromal cells. Thus, IHC corroborated morphological diagnosis in 48 of 51 cases (94.1%).

A single case of molar pregnancy evacuated at 9 weeks 3 days with USG features of snowstorm appearance and a pre-evacuation  $\beta$ -hCG level of 1,50,000 mIU/ml, suggestive of CHM, exhibited variably sized villi, circumferential trophoblastic proliferation along with cistern formation, and no fetal parts. Considering the clinicroadiological findings and morphology, the case was signed out as CHM. IHC for p57 in this case showed immunoexpression in 30% of cytotrophoblasts and 50-60% of villous stromal cells. Sections were reviewed, and a few small fibrotic villi were noted. No nRBCs were seen. Correlating histomorphology with IHC, the diagnosis was revised to PM.

Another case of molar pregnancy evacuated at 8 weeks 3 days with a pre-evacuation  $\beta$ -hCG level of 3,72,000 mIU/ml and USG suggestive of partial mole did not show any grape-like vesicles on gross examination. Though microscopic

examination showed stromal myxoid degeneration along with stromal karyorrhexis (features consistent with very early CHM), trophoblastic proliferation was not circumferential in all the villi, and there was the presence of scalloping and two types of villi. The dilemma could not be resolved by histomorphology, and a morphological diagnosis of HM-NOS was rendered. IHC showed no expression of p57 in stromal cells or cytotrophoblast, confirming the diagnosis of CHM.

Hence, in the above 2 cited cases (3.92%), p57 expression by IHC helped in establishing a conclusive diagnosis.

However, one case (1.96%) with a pre-evacuation  $\beta$ -hCG of 24,751 mIU/mL and morphological diagnosis of HM-NOS exhibited predominantly discordant villi on p57 IHC (positive staining of cytotrophoblasts and negative staining of stromal cells). A few villi with negative expression of p57 in both cytotrophoblast and stromal cells were also noted. Molecular studies were advised for biparental/androgenetic mosaicism or chimeric conceptions.

The study confirms that negative p57 IHC expression may reliably identify CHM. However, IHC has limited role in discriminating PM from hydrops abortus (HA) and is also inconclusive in cases with discordant expression. Molecular ploidy studies play an imperative role in cases where the diagnosis remains discordant despite the use of both morphological study and IHC. The present study was limited by a lack of molecular ploidy studies and very few cases of PM.

## CONCLUSIONS

Morphological differentiation between CHM and PM can be difficult in the absence of fetal parts and is aided by the use of IHC. IHC for p57 expression in stromal cells and cytotrophoblasts is a fairly decisive technique to differentiate CHM from PM and HA. IHC has both a corroborative and diagnostic role in assessing evacuated products of conception, especially in cases of very early CHMs, which can be a diagnostic challenge for histopathologists. However, IHC has a limited role in discriminating between PM and HA and is also inconclusive in cases with discordant expression between stromal cells and cytotrophoblast.

**Conflicts of interest: None**

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