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What is the optimal duration of human chorionic gonadotrophin surveillance following evacuation of a molar pregnancy? A retrospective analysis on over 20,000 consecutive patients

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HIGHLIGHTS

- The risk of pGTN after normal hCG is extremely low for a partial mole.
- For a partial mole, one urine hCG at a month after hCG normalisation is now advised.
- The risk of pGTN after normal hCG is higher for a complete mole (CHM).
- First normal hCG after 56 days increases the risk of pGTN 3.8-fold for a CHM.
- The current hCG surveillance protocol following a CHM remains unchanged.

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ABSTRACT

Objective. To quantify the risk of developing post-molar gestational trophoblastic neoplasia (pGTN) beyond the first normal human chorionic gonadotrophin (hCG) in women who have had a complete (CHM) or partial molar pregnancy (PHM) and to re-evaluate the current UK Hydatidiform mole hCG surveillance guidelines.

Methods. The Charing Cross Hospital Trophoblast Disease Centre database was screened to identify all registered cases of hydatidiform mole (HM) between 1980 and 2009.

Results. We identified 20,144 cases of HM, comprising 8400 CHM, 9586 PHM, and 2158 cases of unclassified hydatidiform mole (UHM). Twenty-nine cases (20 CHM, 3 PHM and 6 UHM) developed pGTN after the first normal hCG. For CHM the risk of pGTN at the point of hCG normalisation was 1 in 406, and fell rapidly in the first six months of monitoring. For PHM the risk of pGTN at the point of hCG normalisation was 1 in 3195. Women with CHM where hCG normalisation occurred beyond 56 days after uterine evacuation of molar tissue were found to have a 3.8-fold higher risk of pGTN.

Conclusions. Our results show that pGTN can occur after hCG normalisation following PHM but the risk is extremely low. Women with CHM have a comparatively higher risk of pGTN after hCG normalisation. Those with CHM where hCG normalises within 56 days have a lower risk of pGTN. We have revised the current UK hCG surveillance protocol for PHM to a single additional confirmatory normal urine hCG measurement one month after first normalisation. The protocol for CHM remains unchanged.

1. Introduction

In the UK, human chorionic gonadotrophin (hCG) surveillance is performed on all registered women with hydatidiform molar pregnancies (HM) in three regional trophoblastic disease units (London, Sheffield and Dundee). The majority fall into two groups; those who develop post-molar gestational trophoblastic neoplasia (pGTN) prior to hCG normalisation and require chemotherapy, and those with HM that undergo spontaneous resolution without requiring treatment. There is also a third, much rarer outcome where HM appears to undergo spontaneous resolution, with normalisation of serum hCG, but subsequently relapse and develop pGTN. This risk is much higher for a complete hydatidiform mole (CHM) than a partial hydatidiform mole (PHM) [1]. pGTN is potentially life threatening malignancy, but has a

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cure rate in the UK of around 100% [1]. This is dependent on early detection of relapse and prompt initiation of chemotherapy. Once hCG levels normalise, surveillance continues to ensure that any subsequent relapse is detected and treated promptly.

A key issue is how long this surveillance is required. Following evacuation of a HM, the UK hCG surveillance policy has been to measure serum hCG with a centralised assay every two weeks until hCG normalisation. Following hCG normalisation urinary hCG is then monitored with a centralised assay every four weeks and continues for six months from the date of hCG normalisation. If urinary hCG remains within the normal range, surveillance is then discontinued. Where hCG normalisation occurs within 56 days the risk of subsequent relapse is thought to be lower. In this sub-group, hCG surveillance is shortened to six months from the date of evacuation rather than from hCG normalisation. The same protocol applied to cases of both CHM and PHM.

Previous research has suggested that the risk of developing pGTN after the first normal hCG is zero for women with a PHM and very low with a CHM [2]. It has been proposed that hCG surveillance can be shortened to perhaps just the first normal hCG value, however this is based on data from comparatively small case series subject to case ascertainment bias [2]. Using a 56 day cut-off to define a sub-group at lower risk of pGTN originates from research in a small data set (4205 women), which found that where hCG fell to normal within 56 days, there were no cases of pGTN [3]. Here we have re-evaluated the current hCG surveillance protocol [4] in a very large population based cohort and present the evidence to support a revised UK hCG surveillance protocol.

2. Methods

The electronic database at Charing Cross Hospital was screened to identify all registered cases of HM for hCG surveillance between 01st of January 1980 and 31st of December 2009. This period was chosen because of the availability of centralised pathological review and to allow time for subsequent cases of pGTN to be captured. Cases were excluded where a diagnosis was reclassified as non-molar after central pathology review and where chemotherapy was administered prior to hCG normalisation. Cases of HM were identified as CHM, PHM and unclassified hydatidiform mole (UHM). The time from uterine evacuation of the molar tissue to hCG normalisation was recorded. These cases were screened to identify women who underwent hCG normalisation and subsequently developed pGTN. The ongoing risk of pGTN according to the duration of hCG monitoring was also calculated.

It is likely that the majority of cases of UHM represent unidentified cases of CHM which were diagnosed prior 2003, when $p57^{KIP2}$ staining became available. We therefore undertook a combined analysis for these cases to determine the rates of pGTN beyond hCG normalisation following CHM.

The data was examined to determine the risk of being diagnosed with pGTN where hCG fell to normal within 56 days to re-evaluate the importance of the 56-day cut off to define high and low risk groups. Where no date of hCG normalisation was available it was assumed that this occurred prior to registration and therefore within 56 days. Significance testing was undertaking using Fisher's exact test or Pearson's Chi-square test with Yates correction according to the sample size. This study complied with local regulations and was approved by the

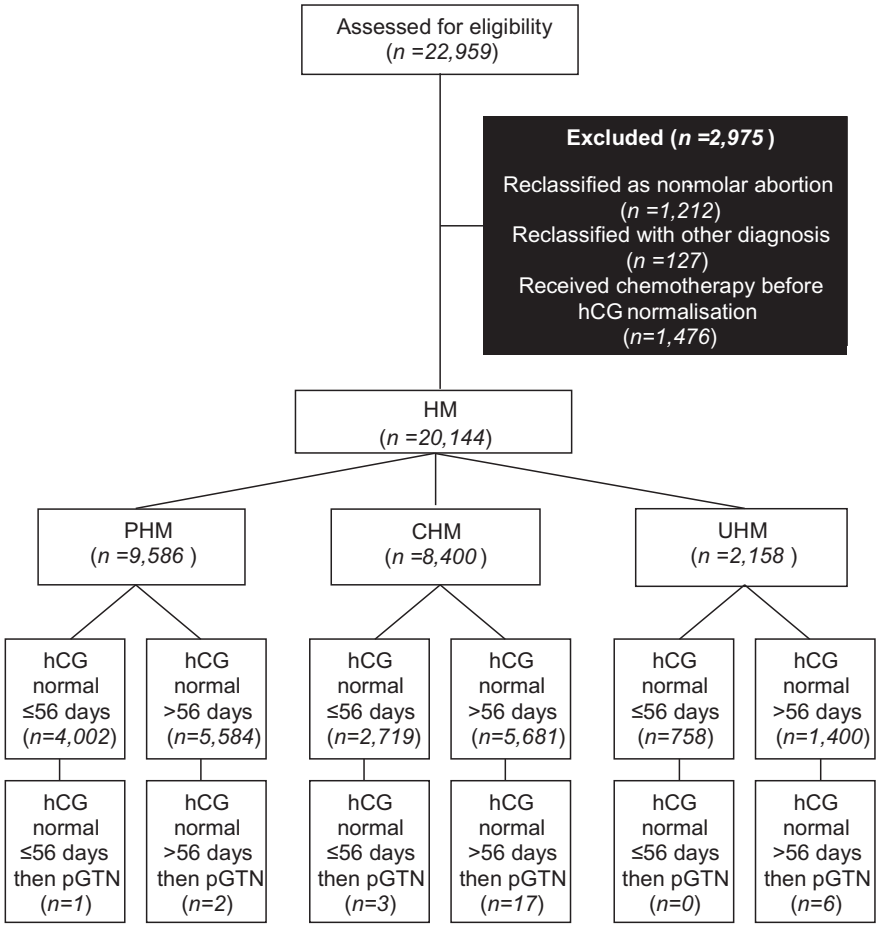

Fig. 1. Women with HM identified between 1980 and 2009 according to subtype, and the timing of hCG normalisation (≤56 days, or >56 days after evacuation of uterine molar tissue).

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