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

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Highlights

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

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 8,400 CHM, 9,586 PHM, and 2,158 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 3,195. 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 represent a group with 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.

KEYWORDS: Molar pregnancy, complete hydatidiform mole, partial hydatidiform mole, gestational trophoblastic disease, post-molar gestational trophoblastic neoplasia, human chorionic gonadotrophin.

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 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 (4,205 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.

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 to the availability of $p57^{KIP2}$ staining. 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 institutional review boards of Imperial College London. Patient details were anonymised and therefore patient consent was not required.

RESULTS:

We identified 20,144 women registered with HM between 1980 and 2009, comprising of 9,586 PHM, 8,400 CHM and 2,158 UHM. Figure 1 shows the cases identified and the reasons for exclusions. There were 29 women who developed pGTN after hCG normalisation. 14 women developed pGTN within, and 15 women beyond, the time limits of the current surveillance protocol.

PHM

There were three women with PHM that developed pGTN after the first normal hCG. For women with PHM the risk of pGTN developing at the point of hCG normalisation was very low at 1 in 3,195. This risk of pGTN developing was reduced three-fold after six months to 1 in 9,584. Table 1 summarises the risks of pGTN developing from hCG normalisation for PHM.

CHM

There were 20 women with CHM that developed pGTN after the first normal hCG. For women with CHM the risk of pGTN developing at the point of hCG normalisation was 1 in 420. This risk halved after four months to 1 in 839 and halved again after twelve months to 1 in 1,677. Table 2 summarises the risks of pGTN developing over the first 12 months from hCG normalisation for CHM.

UHM

There were six women with UHM that developed pGTN after the first normal hCG. For women with UHM the risk of pGTN developing at the point of hCG normalisation was 1 in 360. This risk halved after 12 months to 1 in 718. Table 3 summarises the risks of pGTN developing over the first 12 months from hCG normalisation for UHM.

CHM and UHM combined

In view of the similar risks of pGTN seen with UHM and CHM, it seems likely that most UHM were in fact CHM. Indeed there was no significant difference between the risk of pGTN developing in women with CHM and UHM at the time of hCG normalisation [Odds-ratio (OR) 0.86, 95% confidence interval (CI) 0.34-2.13]. When the data for CHM and UHM are combined there were 26 women that developed pGTN after the first normal hCG. For women with CHM or UHM the risk of pGTN at the point of hCG normalisation was 1 in 406. This risk was reduced at six months to 1 in 753. Table 4 summarises the risks of pGTN developing in the first 12 months from hCG normalisation for CHM and UHM combined.

Risk of pGTN where hCG normalisation occurs within 56 days of uterine evacuation of molar tissue

Overall, there were 7,479 women with HM where hCG normalisation occurred within 56 days and of these, only four women subsequently developed pGTN. There were 12,665 women with HM where hCG normalisation occurred after 56 days and of these 25 subsequently developed pGTN. Table 5 summarises the risks of developing pGTN for each subtype of HM according to whether hCG normalisation occurred within or after 56 days. No significant difference in the risk of pGTN in cases of PHM undergoing hCG normalisation before and after 56 days was detected. For women with CHM (or UHM) undergoing hCG normalisation within 56 days had a significantly lower risk of developing pGTN than women undergoing hCG normalisation after 56 days (OR 0.27 95% CI 0.08-0.88, *p=0.03*).

DISCUSSION:

Previous research has suggested that the risk of developing pGTN after the first normal hCG is zero for women with a PHM (2). Our results are based on a much larger population and show that pGTN can occur after hCG normalisation following PHM but the risk is greater than seven fold lower than after CHM (or UHM). For PHM, whatever cut off for hCG surveillance is used, the risk of pGTN remains very low. Extending surveillance doesn't necessarily catch all relapses as some can occur very late. We have revised the current UK hCG surveillance protocol for PHM to one urine hCG measurement at a month

after hCG normalisation. This is to ensure that the first normal value was correct and not a laboratory or sample error.

For women diagnosed with CHM (or UHM), the risk of pGTN after hCG normalisation has been confirmed to be small but real and falls rapidly in the first six months of monitoring. In cases of CHM (or UHM) where hCG normalisation occurred beyond 56 days, the risk of pGTN was 3.8-fold higher than where hCG normalised within 56 days. This provides evidence from a large data-set to support the current hCG surveillance protocol following CHM, which remains unchanged.

This is a large population based study, and therefore not subject to case-ascertainment bias. Other strengths include central pathology review and the use of a single well characterised hCG assay. A potential limitation of the study is that the classification of UHM is based on morphological rather than cytogenetic criteria and therefore, whilst the majority of cases are likely to represent unestablished CHM this remains unproven. Furthermore, despite the large number of cases, the actual number developing pGTN following a normal hCG is very small so the study might be viewed as underpowered.

The optimal duration of hCG monitoring beyond normalisation should minimise the risk of missed relapses but should not cause unnecessary delay to those hoping to try for a child or prolong the anxiety associated with monitoring. Future surveys could help to establish the acceptable period of hCG surveillance for women with CHM who intend to attempt to have further children. This research provides tables describing the estimated risk of pGTN following hCG normalisation for CHM and PHM which have not existed previously. These tables could be used to empower patients to choose their own duration of surveillance.

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Conflict of interest statement

The authors declare no competing financial interests

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References

1. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. In: The Lancet. 2010. p. 717–29.
2. Wiesma S, Kerkmeijer L, Bekkers R, Pyman J, Tan J, Quinn M. Persistent trophoblast disease following partial molar pregnancy. Aust New Zeal J Obstet Gynaecol. 2006;46(2):119–23.
3. Bagshawe KD, Dent J, Webb J. HYDATIDIFORM MOLE IN ENGLAND AND WALES 1973-83. Lancet. 1986;328(8508):673–7.
4. Sebire NJ, Foskett M, Short D, Savage P, Stewart W, Thomson M, et al. Shortened duration of human chorionic gonadotrophin surveillance following complete or partial hydatidiform mole: Evidence for revised protocol of a UK regional trophoblastic disease unit. BJOG An Int J Obstet Gynaecol. 2007;114(6):760–2.

Figure 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).

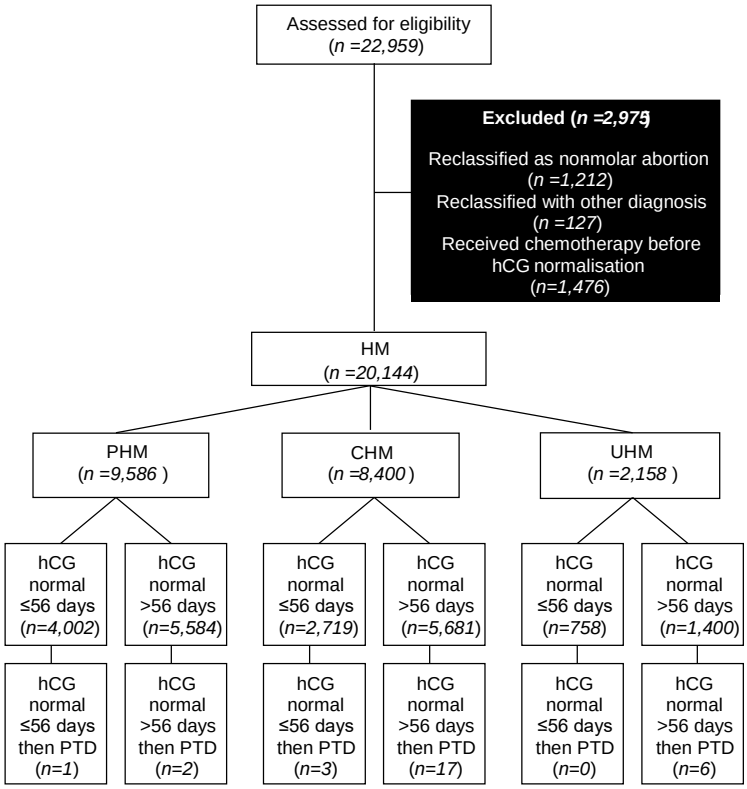

Table 1: Calculated risks of pGTN from hCG normalisation for PHM

Months after hCG normalisation	Cases in remission (hCG normal)	Cumulative cases of pGTN (*total n=3*)	Remaining risk of pGTN after this time point
0	9,586	0	1 in 3,195
4	9,585	1	1 in 4,793
6	9,584	2	1 in 9,584
8	9,583	3	0

Table 2: Calculated risks of pGTN in the first 12 months from hCG normalisation for CHM

Months after hCG normalisation	Cases in remission (hCG normal)	Cumulative cases of pGTN (*total n=20*)	Remaining risk of pGTN after this time point
0	8,400	0	1 in 420
1	8,395	5	1 in 560
2	8,391	9	1 in 763
4	8,390	10	1 in 839
7	8,389	11	1 in 932
8	8,388	12	1 in 1,049
10	8,387	13	1 in 1,189
12	8,385	15	1 in 1,677

Table 3: Calculated risks of pGTN in the first 12 months from hCG normalisation for UHM

Months after hCG normalisation	Cases in Remission (hCG normal)	Cumulative cases of pGTN (*total n=6*)	Remaining risk of pGTN after this time point

0	2,158	0	1 in 360
5	2,157	1	1 in 431
6	2,156	2	1 in 539
12	2,155	3	1 in 718

Table 4: Calculated risks of pGTN in the first 12 months from hCG normalisation for combined CHM and UHM

Months after hCG normalisation	Cases in remission (hCG normal)	Cases of pGTN (*total n=26*)	Remaining risk of pGTN after this time point
0	10,558	0	1 in 406
1	10,553	5	1 in 503
2	10,549	9	1 in 621
4	10,548	10	1 in 659
5	10,547	11	1 in 703
6	10,546	12	1 in 753
7	10,545	13	1 in 811
8	10,544	14	1 in 879
10	10,543	15	1 in 958
12	10,540	18	1 in 1,318

Table 5: Cases of HM according to subtype and whether hCG normalises before of after 56 days.

Subtype	**Time to hCG normalisation**	**Number reaching normal hCG**	**Subsequent cases of pGTN**	**Risk of pGTN**	**Odds ratio** (95% CI)	***P value***
PHM	≤56 days	4,002	1	1 in 4,002	**0.6976** (0.0632-7.696)	***0.6227***
	>56 days	5,584	2	1 in 2,792		
CHM (and UHM)	≤56 days	3,477	3	1 in 1,159	**0.265** (0.0795-0.8832)	***0.0344***
	>56 days	7,081	23	1 in 308		