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**Title:**

Low-risk Gestational Trophoblastic Neoplasia – Twenty years' experience of a State Registry

**Running Title:**

Low-risk GTN

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Low-risk gestational trophoblastic neoplasia – Twenty years' experience of a State Registry

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***ABSTRACT***

**Background:** Gestational trophoblastic disease (GTD) is an uncommon but highly treatable condition. There is limited local evidence to guide therapy.

**Aims:** to report the experience of a statewide registry in the treatment of low-risk Gestational trophoblastic neoplasia (GTN) over a twenty-year period.

**Materials & Methods**: A retrospective review of the prospectively maintained, gestational trophoblastic disease registry database was conducted. 144 patients with low-risk GTN were identified, of which, 115 were analysed. Patient demographics, treatment details and outcomes, including development of resistance, toxicity or relapse were reviewed.

**Results:** The incidence of GTD was 2.6/1000 live births. There was 100% survival. The mean time from diagnosis to commencing treatment was 1.9 days (range 0-29 days). 77.0% of patients treated with methotrexate achieved complete response. Thirteen patients (11.3%) required multi-agent chemotherapy, for the treatment of resistant or relapsed disease. There was a higher rate of treatment resistance in those with WHO risk scores 5-6 (OR 6.56, 95%CI 1.73 – 24.27, *P*=.005) and those with pre-treatment HCG >10,000 (OR 4.00 95%CI 1.73 -24.27 *P*=.007). Four patients (3.5%) were diagnosed with choriocarcinoma after commencing treatment. Nine patients (7.8%) had successful surgical treatment for GTN, both alone and in combination with chemotherapy. The relapse rate was 4.3% all treated successfully with a combination of chemotherapy and surgery. 93.9% of patients completed follow up through the registry.

**Conclusions:** Methotrexate is a highly effective treatment for low-risk GTN, especially with WHO risk score ≤4. The optimal treatment for those with risk score of 5-6 requires further investigation.

## ***INTRODUCTION***

GTD is a spectrum of disorders relating to tumours of the placental trophoblast. It comprises premalignant conditions (complete and partial molar pregnancies), and malignant conditions including invasive mole, gestational choriocarcinoma (CC), placental site trophoblastic tumours (PSTT) and epithelioid trophoblastic tumours (ETT). Gestational trophoblastic neoplasia (GTN) is the term that encompasses these malignant pathologies, as well as persistent trophoblastic disease (PTD), which occurs when the HCG fails to fall appropriately, most commonly after a molar pregnancy. GTD is an uncommon condition, affecting 1-3/1000 pregnancies (1). In most cases, surgical evacuation of a molar pregnancy is definitive treatment. Post molar GTN occurs in 15-20% of complete moles and 0.5-4% of partial moles (2,3).

GTN is a highly chemo-sensitive condition, with survival rates approaching 100%. After a diagnosis of a molar pregnancy, women undergo HCG tracking, to detect cases of PTD.

Globally there are several national GTD registries, that provide centralised care for this uncommon condition. Our centre provides a state registry for Victoria. This service provides follow up and oversees the treatment of all women with GTN in the state, many of whom receive their treatment on site.

Here we report the largest, single centre experience in Australia of the management of GTD. We hope to contribute the outcomes of this cohort to the international literature.

## ***MATERIALS & METHODS***

All women registered with GTD in Victoria between the years 2000-2019 who developed low-risk GTN, were identified and included in this study. Data was gathered from the gestational trophoblastic disease registry database, a prospectively maintained data set, and from review of the patient's history.

Information retrieved included demographic and clinical details, HCG levels, imaging findings and histopathology. For each patient, FIGO stage and WHO score were calculated. Treatment outcomes (development of resistance, relapse, or significant toxicity), as well as completion of follow up and subsequent pregnancy outcomes were recorded.

To estimate the incidence of GTD in Victoria, the number of live births recorded by the Registry of Births, Deaths and Marriages (BDM) Victoria, was used as a surrogate marker for total pregnancies, as demonstrated in other epidemiological studies (4,5). This information was available from 2010 onwards.

PTD was diagnosed by either a rise in HCG (increase by 10% or more for two consecutive weeks) or an inadequate fall in HCG (less than 10% decline over three consecutive weeks) after a molar pregnancy (3,6). The diagnosis of GTN was made with histological evidence of CC or PSTT, after review by an experienced pathologist from our centre or with evidence of invasive or metastatic disease on imaging. Women with PTD or GTN underwent a clinical examination, chest x-ray and pelvic imaging

(either doppler USS or MRI). Further imaging of the chest and brain was performed for women with pulmonary metastases on chest x-ray or other clinical indication. A risk score was assigned, based on the modified WHO prognostic staging system for GTN.

Women with FIGO stage 1-3, low-risk GTN (Score <7), were treated with single agent chemotherapy. First line treatment was an eight-day methotrexate regimen, with intramuscular injection of methotrexate on alternate days with oral folinic acid rescue. After 2012, a fixed dose of 50mg methotrexate was used (prior to this the dose was 1mg/kg). The alternative single agent regimen was intravenous actinomycin D 1.25mg/m$^2$ every fourteen days. Both treatments were administered until the HCG normalised. After normalisation, consolidation cycles were administered. From 2016 the number of consolidation cycles recommended increased from two to three, consistent with change in international practice guidelines. After normalisation of HCG, follow up testing was performed weekly for four weeks, then monthly for one year. During this time the patient was advised to avoid pregnancy.

Treatment regimens were changed in the event of treatment resistance (rising or plateauing HCG), or significant toxicity. Second line regimens were single agent actinomycin D, for those with low levels of HCG or the multi-agent treatment regimen (EMA-CO), for those with higher HCG or according to clinician discretion.

Some patients with GTN also underwent surgical treatment. Hysterectomy was offered to patients with Stage I disease, who had completed their family.

Statistical analysis was performed to compare those who had complete response to primary chemotherapy, to those who developed treatment resistance. Binary univariate logistic regression was undertaken with the outcome of treatment resistance to chemotherapy. HCG and WHO risk score were stratified and treated as categorical variables. Odds ratios (with 95% confidence intervals) and p-values were calculated with a p-value below 0.05 defined as statistically significant. Data was analysed using IBM SPSS Statistics (version 14).

Ethics Approval was obtained for this study (AQA 20/01) from the Royal Women's Human Research Ethics Committee.

## ***RESULTS***

During the study period, 2,905 cases of GTD were managed through the gestational trophoblastic disease registry. Table 1 shows the distribution of cases. Of these, 159 cases of GTN were identified (5.5%), of which, 144 women had low risk GTN. Twenty-nine women had incomplete or undocumented staging investigations, so were excluded from further analysis.

From 2010-2019 there were 775,524 live births in Victoria (7) in which time there were 2010 cases of GTD. The incidence of GTD was 2.6 cases per 1000 live births.

In Victoria during the study period, the incidence of GTN after CHM was 11.35% (138/1216) and PHM was 0.61% (10/1626).

Table 2 shows the baseline characteristics of patients with low-risk GTN, and the elements of the WHO risk score.

**Treatment & Response**

One hundred and fifteen patients with low-risk GTN received treatment. All patients achieved normal HCG and there were no deaths. Figure 1 shows an overview of treatment pathways and outcomes for these women.

**First line treatment**

Of the 113 women treated with methotrexate, 87 (77.0%) achieved complete response. The average number of cycles required to achieve normalisation of HCG was 4.3 (range 1 – 12). Ninety-four (83.2%) of these women received chemotherapy within two days of diagnosis of PTD, 81 (71.7%) on the same day.

Twenty-one women (18.6%) were diagnosed with treatment resistance to methotrexate. Five more (4.4%) developed significant toxicity, requiring a change in regimen. The most common toxicity requiring regimen change was pleuritic chest pain, which occurred in three women, another woman developed severe mucositis, the toxicity in the remaining patient was not documented as she was treated at another centre.

**Second and third lines of treatment**

Twenty-seven women (23.5%) required second-line treatment. Eighteen were treated with actinomycin D, of which fifteen (83.3%) had complete response. Three women (15.8%) developed resistance to actinomycin D; one had previously responded to methotrexate but changed regimen due to toxicity. She was successfully rechallenged with methotrexate, avoiding multi-agent therapy. Overall, 89.6% of patients had complete response to single agent therapy.

Nine patients (7.8%) required treatment with multi-agent EMA-CO to achieve primary complete response. This includes two patients who were diagnosed with choriocarcinoma on histopathology after adjuvant hysterectomy. One of these patients originally declined further treatment after one cycle of second line actinomycin D and represented two years later with a haemoperitoneum secondary to invasive uterine disease.

**Treatment Resistance**

Table 3 compares the baseline characteristics of the population that had complete response to first line chemotherapy and those who developed treatment resistance. Patients who developed treatment toxicity (n=5), or who did not receive any chemotherapy (n=2), were excluded from this analysis. The odds of developing treatment resistance were significantly higher with HCG >10,000 and WHO risk score 5-6, however increasing age and the presence of metastatic disease did not have a significant effect.

**Consolidation Cycles**

Of the 87 women who responded to treatment with methotrexate, 47 received three consolidation cycles. No woman who received three consolidation cycles had disease relapse during follow up. Thirty-two women received two consolidation cycles, of which one experienced relapse during the follow up period. Three women received only one consolidation cycle, and of these, two relapsed. Three women had no consolidation cycles, and two women had an unknown number of consolidation cycles as they completed their treatment overseas, none of these women experienced relapse. Consolidation cycles were withheld in the event of toxicity, patient choice or at clinician discretion.

**Relapse**

Five patients had disease relapse during their follow up, three who had had complete response to methotrexate, two after complete response to actinomycin D. The average time to relapse during follow up was twelve months. Four women required multi-agent therapy in the treatment of relapsed disease; one responded to second line actinomycin D. All patients ultimately had complete response to treatment.

**Surgical treatment of Low Risk GTN**

Seven women underwent hysterectomy as treatment for low-risk GTN. Three women with Stage 1 disease (all aged over 50 (range 50-52)), were treated with primary hysterectomy. Two patients did not require additional chemotherapy, whilst one patient was treated with adjuvant methotrexate. Four hysterectomies were performed in the management of relapsed or resistant disease. In two patients, choriocarcinomas were diagnosed on histopathology. Both women were treated with multi-agent therapy post-operatively with complete response.

Two uterine wedge resections were performed in the management of low-risk GTN. One was for a 29-year-old patient who presented to a rural hospital with a haemoperitoneum secondary to invasive disease at diagnosis; she was treated with postoperative methotrexate and achieved complete response. The other was performed in a 24-year-old woman with locally recurrent disease that was resistant to EMA-CO. Histopathology revealed a choriocarcinoma, which was treated with EMA-EP post operatively. This patient went on to achieve a subsequent normal pregnancy, delivered overseas via Caesarean section at term.

**Follow up**

Seven patients (6.1%) were lost to follow up within 6 months of achieving a normal HCG. One-hundred and two patients (88.7%) completed at least six months follow up, and of these, 92 patients (80%) completed the recommended twelve months follow up. Seven patients fell pregnant during the follow up period.

**Subsequent Pregnancies**

According to registry data, 20 women (17.4%,) achieved normal pregnancies after successful treatment of low-risk GTN. Three women also reported miscarriages following treatment.

***DISCUSSION***

In this study, we report 20 years of experience of management of low-risk GTD through the gestational trophoblastic disease registry in Victoria. This is the largest cohort of its kind in the Australian setting. The findings support that GTN is a highly treatable, chemo-sensitive condition, with a 100% survival

rate in this population. The condition remains uncommon, requiring specialist supervision and multidisciplinary coordination for optimal management.

The incidence of GTD in Victoria was 2.6/1000 live births. The true incidence of GTD per pregnancy is difficult to ascertain, as there is no statewide database to record each pregnancy, and so live births is used as an imperfect surrogate for this population. This is comparable to international findings in Canada and Denmark (5,8).

There was a high rate of complete response to first line methotrexate in this population, approaching 80%. This is significantly higher than reported by Hao et al. in their meta-analysis, who reported a primary remission rate of only 65.1% with methotrexate, compared to 80.2% with actinomycin D for low-risk GTN (9). This may be due to the wide variation in methotrexate regimens used globally and included in the study, the majority of which were less intensive than the regimen used in our centre - which may underestimate the effectiveness of the drug.

There is ongoing debate as to the optimal first line single agent therapy for low-risk GTN. The 2016 Cochrane review reports that actinomycin D probably has a higher chance of achieving a primary cure in women with low-risk GTN and is less likely to result in treatment failure (10). However, internationally, many centres use methotrexate as first line therapy. Prospective randomized trials comparing the two treatments, are scarce. In Schink et al.'s recent multi-centre trial to address this, methotrexate (IM or IV preparation) achieved complete response for 88% of patients, compared to 79% for actinomycin D, however the results were underpowered due to low accrual, and the study was closed after achieving only 15% of the intended sample size (11). The individual's choice between the two therapies is likely to be multi-factorial, as both treatments are effective, with tolerable side effects. Access and geographic location are likely to have a significant impact on an individual's decision. In some Australian centres, actinomycin D may be preferred, due to geographical barriers to accessing multi-day treatments (12).

Established risk factors for treatment resistance include increasing WHO risk score, clinicopathological diagnosis of choriocarcinoma, higher pre-treatment HCG and presence of metastatic disease (13,14). In our cohort, patients with WHO risk scores of 5-6 had a significantly higher rate of treatment resistance following methotrexate, with only 45.5% (5/11) of the patients in this subgroup responding to this treatment. Of the six patients who developed resistance, only two responded to actinomycin D (overall 63.6% response to single agent chemotherapy). The optimal first line treatment for this subgroup requires further research, to establish if there are better predictors of treatment resistance or a superior single agent chemotherapy regimen, that would reduce the need for multi-agent treatment. In our population, higher pre-treatment HCG also correlated with the development of treatment resistance, however the complete response rates were similar in both non-metastatic and low-risk metastatic disease.

Overall, the rate of relapse was low in this population, occurring in 4.2% of patients. There was a trend to reduced relapse rate with increased use of consolidation courses, with no patients relapsing after three consolidation courses. This is consistent with Lybol et al. who suggested a rate of relapse of 4% with three consolidation courses, compared to 8% with only two (15). Management of relapsed GTN

is highly individualized, and requires repeat imaging, centralized review of pathology and multidisciplinary care.

This study highlights the benefits of a disease registry for coordination of treatment for this uncommon condition. Of particular benefit there was minimal delay to commencing treatment, with most patients starting chemotherapy on the day of their diagnosis. Another benefit of the registry approach for this condition, is that there is minimal loss to follow up due to dedicated personnel performing this task.

Limitations of this study include its retrospective nature and reliance on historical data, which in some instances was incomplete or difficult to interpret. Over the study period, there have been changes in practice that contribute to heterogeneity within the group. This population lacks a comparison group, due to the strong preference for methotrexate as first line treatment for the condition. Our group of patients with WHO risk scores of 5-6 is limited by small numbers, representing only eleven patients in a twenty-year period. There is a need for international collaboration between several registries to study these patients in detail.

*Table 1. Gestational Trophoblastic Disease in Victoria (2000-2019)*

| | |
|---|---|
| **Complete molar pregnancies** | 1216 (41.86%) |
| **Partial molar pregnancies** | 1626 (55.97%) |
| **Unspecified hydatidiform mole** | 19 (0.65%) |
| **Invasive mole** | 11 (0.38%) |
| **Choriocarcinoma** | 26 (0.90%) |
| **Placental site trophoblastic tumour** | 5 (0.17%) |
| **Epithelioid trophoblastic tumour** | 2 (0.07%) |

*Table 2. Baseline characteristics and WHO Risk Score Elements of low-risk GTN patients 2000 - 2019*

| | **Registry cases with Low-risk disease (n = 115)** |
|---|---|
| **Age at diagnosis (years)** Mean (range) | *33 (18 –53)* |
| **Antecedent pregnancy** | |
| Molar pregnancy | 110 |
| CHM | 103 |
| PHM | 7 |
| Abortion or term pregnancy | 0 |
| Other | 5 (CHM associated with non-molar twin pregnancy) |
| **Ethnicity** | |
| Caucasian | 68 (59.1%) |
| Asian | 37 (32.2%) |
| African | 5 (4.3%) |
| Aboriginal or Torres Strait Islander | 0 |
| Pacific Islander | 1 (0.9%) |
| Unknown | 4 (3.4%) |
| **Pre-treatment serum hCG** | |
| < 1000 mIU/ml | 25 (21.7%) |
| 1,001– 10,000 mIU/ml | 42 (36.5%) |
| 10,001 – 100,000 mIU/ml | 44 (38.3%) |
| >100,000 mIU/ml | 4 (3.5%) |
| **Largest tumour size** | |
| < 3 cm | 58 (50.4%) |
| 3 – 5 cm | 34 (29.5%) |
| > 5 cm | 23 (20.0%) |
| **Site of metastasis** | |
| None | 102 (88.7%) |
| Lung | 13 (11.3%) |
| Spleen, kidney, GI, liver, brain | |

| | |
|---|---|
| **Number of lung metastases** | |
| 0 | 102 (88.7%) |
| 1 – 4 | 9 (7.8%) |
| 5 – 8 | 2 (1.7%) |
| > 8 | 2 (1.7%) |
| **FIGO Staging** | |
| 1 | 102 (88.7%) |
| 2 | 0 |
| 3 | 13 (11.3%) |
| 4 | 0 |
| **WHO risk score** | |
| 0 | 10 (8.7%) |
| 1 | 30 (26.1%) |
| 2 | 28 (24.3%) |
| 3 | 21 (18.3%) |
| 4 | 15 (13.0%) |
| 5 | 9 (7.8%) |
| 6 | 2 (1.7%) |

***Table 3. Comparison of patient characteristics for those who had complete response to chemotherapy and those who developed treatment resistance***

| | Complete response to primary chemotherapy n = 87 | Treatment resistance n = 21 | OR | 95% CI | *p* value |
|---|---|---|---|---|---|
| **Age** | | | | | |
| Years (avg) | 33 | 35 | 1.03† | 0.97 – 1.09 | .363 |
| **Pre-treatment HCG** | | | | | |
| ≤ 10,000 mIU/ml | 58 (66.7%) | 7 (33.3%) | 4.00 | 1.46 – 10.99 | .007 |
| > 10,000 mIU/ml | 29 (33.3%) | 14 (66.7%) | | | |
| **Metastatic Disease** | | | | | |
| Metastasis present | 10 (11.5%) | 2 (9.5%) | 0.81 | 0.16 – 4.01 | .797 |
| No Metastasis | 77 (88.5%) | 19 (90.5%) | | | |
| **WHO Risk Score** | | | | | |
| 0 – 4 | 82 (94.3%) | 15 (71.4%) | | | |
| 5 – 6 | 5 (5.7%) | 6 (28.6%) | 6.56 | 1.73 – 24.27 | .005 |

† Odds ratio for age is interpreted as the odds of treatment resistant disease for each one-year increase in age

***Figure 1. Low-Risk GTN Treatment Pathways and Outcomes***

Legend: This flowchart shows the pathway of patients through treatment of low-risk GTN. The surgical treatments that patients received are described in the text.

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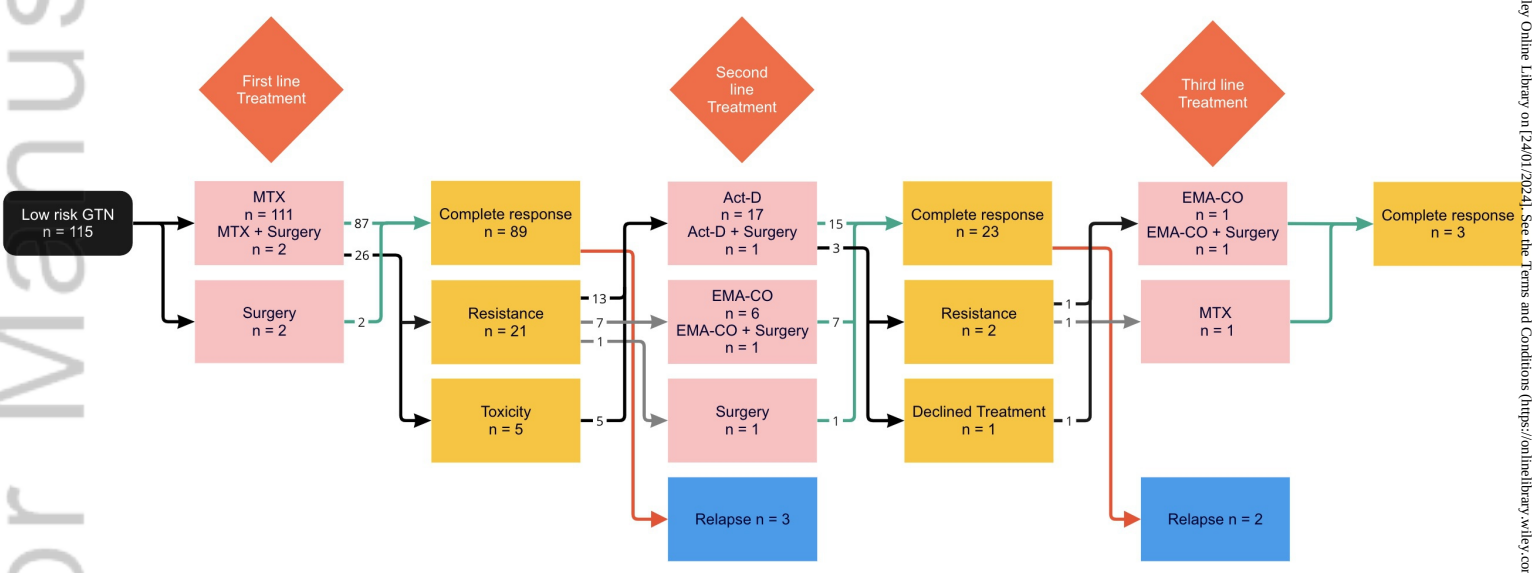


Low Risk GTN Figure 1.2.jpg