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# Trends in incidence for gestational trophoblastic disease over the last 20 years in a population-based study

Y.K. Eysbouts [a,*], J. Bulten [b], P.B. Ottevanger [c], C.M.G. Thomas [d], M.J. ten Kate-Booij [e], A.E. van Herwaarden [d], A.G. Siebers [b], F.C.G.J. Sweep [d], L.F.A.G. Massuger [a]

[a] Department of Obstetrics and Gynecology, Radboud University Medical Centre, Nijmegen, The Netherlands
[b] Department of Pathology, Radboud University Medical Centre, Nijmegen, The Netherlands
[c] Department of Medical oncology, Radboud University Medical Centre, Nijmegen, The Netherlands
[d] Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands
[e] Department of Obstetrics and Gynecology, Erasmus University Medical Centre, Rotterdam, The Netherlands

## HIGHLIGHTS

- An overall incidence rate of 1.67 per 1000 deliveries per year was seen.
- After an initial rise, incidence rate stabilized from 2004 to 2013.
- Complete and partial HM reached comparable incidence rates from 2009 onwards.
- Unspecified HM diagnosis declined significantly, suggesting improved diagnostics.
- Therefore a true steady incidence rates may have been reached.

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## ABSTRACT

*Background.* Gestational trophoblastic disease (GTD) represents a heterogeneous group of disorders. Wide variations in incidence rates are reported worldwide, probably explained by a lack of centralized databases and heterogeneity in case definition. The aim of the present study was to determine the trends in incidence of GTD in the last 20 years with the use of population-based data.

*Patients and methods.* Data on patients with pathologically confirmed diagnosis of GTD between 1994 and 2013 were obtained from PALGA, a nationwide archive containing all pathology reports in the Netherlands.

*Results.* In the 20-year period 6343 cases were registered with GTD, representing an overall incidence rate of 1.67 per 1000 deliveries per year. An initial rise in incidence rate was seen over the first 10 years (0.075 per year, 95% CI 0.040–0.109), followed by a stabilization from 2004 to 2013 (increase per year 0.011, 95% CI −0.017–0.040). Although partial hydatidiform mole (HM) was more common in earlier years, complete and partial HM reached comparable incidence rates of 0.68 and 0.64 per 1000 deliveries respectively from 2009 onwards. In the last decade, unspecified HM diagnosis declined significantly from 0.14 per 1000 deliveries in 2003 to 0.03 per 1000 deliveries (per year −0.011, CI −0.016–0.06), suggesting improved diagnostic analyses.

*Conclusion.* After an initial rise in GTD incidence in the Netherlands rates remained steady from 2004 onwards. As pathological confirmation is currently the norm and advanced pathological techniques are now widely available, true steady incidence rates may have been reached.



## 1. Introduction

Gestational trophoblastic disease (GTD) represents a heterogeneous group of disorders with abnormal proliferation of placental trophoblastic tissue. It encompasses complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid, trophoblastic tumor, exaggerated placental-site reaction and placental-site nodule.

Our group has previously reported a GTD incidence rate of 1.56 per 1000 deliveries in the Netherlands in the period of 1995 to 2008, with an incidence of HM of 1.34 per 1000 deliveries per year. The overall incidence of GTD was low but showed a significant increase during the aforementioned time span [1]. The incidence rate of HM was broadly comparable with recent findings of population-based studies in

* Corresponding author at: Department of Obstetrics and Gynecology, Radboud University Medical Centre, Nijmegen, P.O. 9101, 6500 HB, The Netherlands.
*E-mail address:* yalck.eysbouts@radboudumc.nl (Y.K. Eysbouts).

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Sweden (1.2 per 1000 deliveries), Turkey (1.22 per 1000 deliveries) and the United States (1.19 per 1000 pregnancies) [2–4]. Reported frequencies from Asian countries are highly heterogeneous with rates ranging from 1 to 3 per 1000 pregnancies in Japan, China and Korea to over 10 per 1000 pregnancies in Indonesia and India [2,3,5–8]. The lack of a centralized databases, the inability to adequately describe the population at risk and the heterogeneity in case definition have probably contributed to the wide variations in incidence rates worldwide. Furthermore, incidence rates may be based on total number of pregnancies, deliveries or live births [9–12].

Although of great clinical relevance, comparing incidence rates with respect to choriocarcinoma and PSTT is even more difficult as these conditions are very rare and pathological confirmation is not always available [8,9,13].

In the Netherlands a national pathology database named PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief) with nationwide coverage since 1991 holds all records of histo-pathologic and cytopathologic diagnoses to facilitate research and quality control. This unique nationwide network provides a complete insight in incidence rates in the Netherlands [14].

The present study evaluates trends in incidence for GTD in the Netherlands between 1994 and 2013 using the population-based pathology database PALGA.

## 2. Material and methods

### 2.1. Database

The PALGA database is a nationwide archive containing all pathology reports in the Netherlands.

Present study identified all cases of GTD recorded in the PALGA database between 1994 and 2013.

### 2.2. Patient selection

A selection of the database was performed for patients diagnosed with GTD on the following search criteria: complete mole (CHM), partial mole (PHM), mole, invasive mole, choriocarcinoma, metastasis choriocarcinoma, intratubular choriocarcinoma, persistent trophoblastic disease (PTD), trophoblastic proliferation, placental site trophoblastic tumor (PSTT), trophoblastic pseudotumor and epithelioid trophoblastic tumor (ETT), placental site nodule and exaggerated placental site reaction, identifying 7530 records. Reports were subsequently reviewed and categorized according to the WHO classification of GTD: complete and partial hydatidiform mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor, exaggerated placental-site reaction and placental-site nodule. Multiple abstracts per patient involving revisions of one specimen were combined, multiple gestational trophoblastic events per patient were however maintained.

Two categories were added: patients with clear diagnoses of HM not otherwise specified and patients where molar pregnancy could not be distinguished from abortion. Inconclusive reports were analyzed and classified by an experienced pathologist, specialized in gynecology.

Revisions from abroad ($N = 8$) and patients eventually not classified as GTD ($N = 326$) were excluded from further analysis. A total of 6341 cases were included in the present study.

### 2.3. Statistical analyses

Incidence rates were calculated per 1000 deliveries for HM, GTD, exaggerated placental site reaction and placental site nodule and per 100,000 deliveries for choriocarcinoma and PSTT annually. Data on the number of deliveries nationwide were obtained from Statistics Netherlands (CBS) [15]. All analyses were carried out using Microsoft Office Excel 2007 and SPSS for Windows (version 20).

## 3. Results

### 3.1. Gestational trophoblastic disease

In the 20-year period between 1994 and 2013, a total of 6341 cases were registered with gestational trophoblastic disease in the Netherlands, representing an overall incidence rate of 1.66 per 1000 deliveries per year. Their median age was 31 years (minimum 13, maximum 79). To evaluate potential trends in the annual incidence rates, Fig. 1 shows the annual incidence rates in the Netherlands between 1994 and 2013. An initial significant increase is seen over the first 8 years (0.075 per 1000 deliveries per year, 95% CI 0.040–0.109), followed by a stabilized incidence rate from 2002 to 2013 (increase per 1000 deliveries per year 0.011, 95% CI −0.017–0.040). An overview of the average frequency and incidence of individual entities of GTD is shown in Table 1 with moles comprising the majority of cases.

### 3.2. Benign trophoblastic lesions

Since 1994 a total of 578 cases with a benign trophoblastic lesion originating from the intermediate trophoblast were recorded in the Netherlands, involving 306 (52.9%) patients with placental site nodule (PSN) and 272 (47.1%) patients with exaggerated placental site (EPS). As shown in Fig. 2, a significant rise in incidence for placental site nodules is apparent from 2004 onwards (increase per 1000 deliveries per year 0.012, CI 0.03–0.20), whereas the incidence rise in exaggerated placental site lesions showed a small increase over the years (increase per 1000 deliveries per year 0.003, CI 0.002–0.004). Median age was 33 (minimum 19, maximum 79) and 32 years (minimum 16, maximum 58) for placental site nodule and exaggerated placental site respectively, with 89.0% of patients under 40 years of age. To evaluate whether knowledge of these conditions may be associated with changes in incidence, the number of PubMed hits for each entity per year was calculated. A very modest number of hits varying from 0 to 7 hits per year however was seen over the years without an apparent increase.

### 3.3. Hydatidiform mole

In Fig. 3 the trends in annual incidence rates for HM over the years are shown. Between 1994 and 2013 a total of 5153 cases with HM were registered in the Netherlands resulting in a total incidence of 1.36 mole (complete, partial, unspecified) per 1000 deliveries per year. This comprises 81.0% of all GTD. Comparable with the incidence pattern in total GTD, a significant increase in molar pregnancies per 1000 deliveries per year was apparent between 1994 and 2001 (increase per year 0.068, CI 0.051–0.085) followed by an unchanged level since 2002 (increase per year 0.002, CI −0.023–0.027).

CHM and PHM represented 31.4% (incidence 0.52 per 1000 deliveries) and 40.2% (incidence 0.67 per 1000 deliveries) of all GTD cases, respectively. A gradual increase in CHM was seen in recent years with incidence rates increasing from 0.46 per 1000 deliveries in 2005 to 0.74 per 1000 deliveries in 2013 (per year 0.036, CI 0.014–0.059). PHM showed a significant increase in incidence from 1994 to 2002 (increase per year 0.058, CI 0.047–0.069), followed by a significant decline from 2003 onwards (per year −0.021, CI −0.037–0.05). The incidence rates for both CHM and PHM have become more comparable in recent years, resulting in a change of CHM to PHM ratio from 0.67 to 1.1. in 2000–2008 and 2009–2013 respectively. The mean maternal age for CHM and PHM was 31.1 and 30.4 years respectively. The distribution of CHM and PHM per age group is shown in Fig. 4 with a significant over presentation of CHM in the extreme age groups ($P < 0.001$).

### 3.4. Unspecified diagnosis

Patients with a clear diagnosis of HM not otherwise specified and patients with uncertainty concerning discrimination between molar