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Hydatidiform mole incidence in Lombardy, northern Italy, 2009–2022: continued decline or plateau?

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ABSTRACT

Introduction: Hydatidiform mole (HM) incidence has shown contrasting temporal trends across different regions.

Methods: We analyzed HM incidence in Lombardy, Italy, from 2009 to 2022. HM cases were identified through regional registry data.

Results: A total of 1,131 HM cases occurred among 1,471,567 pregnancies, averaging 77 cases per 100,000 pregnancies. A significant decline was observed between 2009 and 2015 ($p=0.01$), but no consistent trend emerged over the full period ($p=0.76$). HM incidence was highest in women aged ≥ 46 (699.1/100,000) and < 20 (107.6/100,000), and among women of Asian origin (110.4/100,000).

Discussion: The study suggests that diagnostic practices and demographic shifts may have influenced HM trends, while also confirming persistent ethnic and age-related risk patterns.

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Introduction

Hydatidiform mole (HM) incidence has shown contrasting temporal trends across different regions [1,2]. Most available data on HM incidence are based on statistics before 2010, and more recent population-based data are lacking. In Lombardy, a northern Italian region of about 10 million inhabitants, maternal demographics have shifted in recent years, with higher maternal age and a slight increase in foreign-born mothers [3,4].

We analyzed recent regional healthcare administrative registry data to assess whether the previously observed decline in HM persisted into the 2010s. Between 1996 and 2008, Lombardy saw a modest but significant decrease in HM incidence, mainly due to fewer cases among women of Asian origin [2]; we now extend this analysis through 2022.

Methods

All HM cases (ICD-9-CM code 630) from 2009 to 2022 were identified through the hospital discharges registry. When handling repeated hospitalizations, cases of persistent disease were not classified as new episodes of HM. In contrast, recurrent HM diagnoses were considered new events. A 12-month window was applied to differentiate new episodes from follow-up or persistent disease. The denominator comprised the total number of pregnancies in the region during the same period, including both births and abortions (regardless of gestational age). These were identified using the same registry based on ICD-9-CM diagnosis and intervention codes and diagnosis-related group (DRG) codes associated with delivery or miscarriage. HM rates per 100,000 pregnancies were computed stratified by maternal age and geographic origin. To assess trends over time, we used jointpoint regression

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models [5], allowing up to two joinpoints. According to Italian regulations, analyses of anonymized administrative databases in retrospective studies do not require Ethics Committee approval.

Results

Table 1 gives the HM incidence rate in Lombardy, both crude and standardized for age and/or nationality. From 2009 to 2022, a total of 1,131 HM cases (including 13 recurrent cases) were recorded among 1,471,567 pregnancies, corresponding to an average incidence of 77 per 100,000 pregnancies. Annual HM rates fluctuated within the range of expected random variation. No significant trend was found over the entire 2009–2022 period with joinpoint regression ($p=0.77$). However, when analyzing the period from 1996 to 2022, we observed a significant decreasing trend from 1996 to 2014 ($p<0.01$), followed by a stable trend thereafter ($p=0.51$). A Poisson regression model including age and nationality terms yielded consistent results, showing no significant trend over the entire period ($p=0.76$). However, a decreasing trend was observed between 2009 and 2015 ($p=0.01$). When stratified by nationality, the analysis showed a significant decreasing trend for Asian women over the entire period ($p=0.02$).

The incidence of HM was highest at the extremes of reproductive age. Women aged ≥ 46 years showed the highest incidence (699.1 per 100,000 pregnancies), approximately nine-times the average. Teenagers (<20 years) also showed an elevated risk (107.6 per 100,000). Both age groups showed a reduced incidence compared to 1996–2008. The lowest HM incidence was observed among women aged 30–39 years (60.5 per 100,000).

Table 1. Hydatidiform mole (HM) cases and incidence in Lombardy by maternal age group and nationality.

Calendar year	No. HM	No. pregnancies	2009–2022		1996–2008 [§]					
			Rate/100,000 pregnancies	SE	Standardized* rate/100,000 pregnancies	SE	No. HM	No. pregnancies	Rate/100,000 pregnancies	SE
1996 [§]	143	112,329	127.3	10.6	127.3					
2000 [§]	127	123,613	102.7	9.1	101.6					
2005 [§]	136	132,042	103.0	8.8	102.4					
2009	118	130,578	90.4	8.3	90.4					
2010	107	126,236	84.8	8.2	88.2					
2011	81	121,959	66.4	7.4	69.5					
2012	73	118,551	61.6	7.2	66.9					
2013	92	114,370	80.4	8.4	82.2					
2014	66	111,399	59.2	7.3	59.6					
2015	70	107,081	65.4	7.8	67.2					
2016	96	103,351	92.9	9.5	95.4					
2017	81	99,221	81.6	9.1	87.0					
2018	56	94,864	59.0	7.9	60.8					
2019	81	91,821	88.2	9.8	90.0					
2020	72	84,635	85.1	10.0	84.4					
2021	73	84,160	86.7	10.1	89.6					
2022	65	83,341	78.0	9.7	79.5					
			2009–2022		1996–2008 [§]					
			Rate/100,000 pregnancies	SE	Standardized* rate/100,000 pregnancies	SE	No. HM	No. pregnancies	Rate/100,000 pregnancies	SE
Age										
<20	24	22,314	107.6	21.9	103.7		51	35,818	142.4	19.9
20–29	276	395,745	69.7	4.2	69.2		503	499,034	100.8	4.5
30–39	528	872,016	60.5	2.6	59.7		687	764,676	89.8	3.4
40–45	177	163,469	108.3	8.1	106.1		128	71,257	179.6	15.9
≥ 46	126	18,023	699.1	62.1	666.3		64	2004	2045.9	316.3
Nationality										
Italian	704	952,222	73.9	2.8	63.0		1143	1,145,026	99.8	3.0
European	129	200,384	64.3	5.7	62.3		85	75,797	112.1	12.2
South American	57	58,045	98.2	13.0	86.4		77	43,538	176.9	20.1
Asian	114	103,276	110.4	10.3	101.8		71	43,567	163.0	19.3
African	104	134,102	77.6	7.6	63.9		54	63,444	85.1	11.6
Other [§]	23	23,538	97.7	20.4	84.7					

SE, standard error. *Standardized for age and/or nationality, as appropriate. Standardized rate by age and nationality were computed by the direct method using the 2009 cases as standard. [§]Data from previous study [2]. [§]Including Central and North America, Oceania, and unspecified areas.

The incidence of HM also varied by maternal origin. Women of Asian origin experienced the highest rate (110.4 per 100,000) followed by those from South American (98.2 per 100,000). In contrast, women from European countries had the lowest incidence (64.3 per 100,000), while Italian natives and those from African countries had intermediate rates (~74–78 per 100,000). Except for women of African origin, all other nationalities reported a lower incidence rate than in 1996–2008.

Discussion

Our study is limited by the reliance on administrative hospital discharge data, as this did not allow us to access detailed pathological reports. We were unable to confirm whether diagnoses were based solely on hematoxylin and eosin morphological examinations or if ancillary tests, such as p57 immunohistochemistry, were also used. Consequently, it was not possible to distinguish between complete and partial hydatidiform moles.

The absence of data on individual risk factors (e.g. parity, nutritional status, environmental exposure) and clinical parameters that are routinely documented in patient charts (e.g. body mass index, gestational age at diagnosis, beta-hCG levels) limits the comprehensiveness of the study as this information is not available in hospital discharge records. Nevertheless, all diagnoses were pathologically confirmed, and the population-based design (nearly all deliveries in Lombardy occur in hospitals, captured by the regional health registry) ensures that our findings are representative.

Another limitation of our investigation was the exclusion of outpatient-managed cases of HM. Although it is reasonable to assume that these cases represent a minority, we acknowledge that cases managed exclusively in outpatient settings were not captured.

However, all these limitations should be present (and similar) also in the previous published analysis of considering the hospital discharges registry of Lombardy Region considering the period 1996–2008 [2], thus allowing for robust comparisons. In general, the diagnostic criteria for partial and complete mole improved over the considered period; thus, to allow a correct comparison of the frequency of the disease over a period of approximately 30 years, it is important to maintain diagnostic criteria that are as similar as possible.

The reasons for the observed temporal patterns are not fully understood. The higher risk among Asian women appears to persist even after migration to low-incidence settings, as observed in Northern England [6].

The diagnosis of hydatidiform mole directly affects incidence statistics, the pathological misdiagnosis rates of complete HMs and partial HMs can reach 30 and 71%, while p57 immunohistochemical staining is particularly useful for diagnosing complete HMs. However as already discussed this point should not be a major limitation in the analysis of temporal trends.

Otherwise, the increasing use of medical (non-surgical) management of early pregnancy failures has reduced the histological examinations that detect HM, thereby lowering reported incidence [7]. Additionally, improvements in nutrition, including widespread access to vitamin A and folate supplementation, may have contributed to a decline in HM incidence [1]. For example, the proportion of women taking folic acid in the preconceptional period in Italy was about 25% in a study conducted in 2012 [8] and 42% in a more recent analysis [9].

In summary, some decline in trend in HM incidence observed in Lombardy through the late twentieth century continued into the early 2010s but appears to have plateaued over recent years.

Author contributions

CRediT: **Vittorio Parodi**: Writing – original draft, Writing – review & editing; **Sonia Cipriani**: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing; **Anna Cantarutti**: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing; **Matteo Franchi**: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – review & editing; **Giovanni Corrao**: Supervision; **Carlo Lazzaro**: Supervision; **Carlo La Vecchia**: Supervision, Writing – review & editing; **Fabio Parazzini**: Conceptualization, Supervision, Writing – original draft; **Giovanna Esposito**: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

Disclosure statement

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Data availability statement

The data that support the findings of this study are available from Lombardy Region, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Lombardy Region.

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