Gestational trophoblastic disease (GTD) encompasses an intriguing group of interrelated diseases derived from placental trophoblasts. Variants differ in propensity for spontaneous resolution, local invasion, and metastasis [1]. The most serious form, choriocarcinoma, is usually preceded by a hydatidiform mole (HM), but can occur following any type of gestational event. As the name implies, all GTD variants arise following an antecedent pregnancy, although recent studies have shown that related pregnancy is sometimes not the one most temporally related [2].

Since pregnancy is an obligatory precursor, ideally, incidence ratios should be described using the total number of pregnancies, including unrecognized pregnancies. Because the total number of pregnancies is difficult to estimate, most epidemiologic studies of GTD have used surrogate denominators - usually, the number of deliveries and live births within a given hospital or institution. Over the past three or four decades, in many regions of the world, population-based registries dedicated to the study of GTD incidence rates have been established, and newer epidemiologic studies from these registries have begun to report GTD rates using population based denominators.

In recent years, it has also been shown that the determination of the absolute number of incident cases, or the true numerator for GTD, is almost as elusive as the absolute denominator. Newer approaches to clinical and laboratory diagnosis, including DNA flow cytometry, cDNA microarray, in situ hybridization, polymerase chain reaction (PCR), and recognition of particularly rare variants (placental site tumors, epithelioid trophoblastic tumor, placental site nodule) have improved the accuracy of estimations of the absolute number of GTD cases in some centers; however, these technological advances are not yet universally applied.

Dramatic differences in incidence rates for GTD have been reported from hospitals and regions throughout the world. These findings have led to speculation that there are environmental and perhaps, genetic differences in risk for GTD among different ethnic and racial groups. In this chapter, the epidemiology of GTD, including the difficulties encountered in determining incidence rates, are addressed. Despite the limitations of earlier investigative efforts, newer population-based data have enhanced our understanding of trends in GTD incidence rates. These studies, which suggest that GTD incidence rates are declining throughout the world, are presented, and possible etiologic risk factors are discussed. This edition will conserve, but not review the prior epidemiology studies. We will focus the new changed incidence of GTD and try to analyze how the improvement of medicine and society has caused
3.1 DEFINITIONS OF GESTATIONAL TROPHOBLASTIC DISEASE

For all GTD variants, the involved trophoblastic tissue is genetically distinct from the mother. That is, gestational trophoblastic diseases are allografts. Several different classification systems continue to be used for staging, including the World Health Organization (WHO) Scoring Index, the FIGO system, an NIH classification, and combination classification, although implementation of recent revisions should help to consolidate reporting [3-5]. WHO divides GTD variants histologically into distinct groups, including HM, choriocarcinoma, placental site trophoblastic tumor (PSTT), miscellaneous trophoblastic tumor (exaggerated placental site, placental site nodule or plaque), and unclassified trophoblastic lesions. Hydatidiform molar pregnancies (complete, partial, invasive) are thought to represent abnormally formed placentas with specific genetic abnormalities in the villous trophoblasts, whereas choriocarcinomas and PSTTs are considered true neoplasms, the former of previllous and the latter, of extravillous origin, and characterized by intermediate trophoblasts [6].

In 1977, Kajii and colleagues demonstrated the androgenetic origin of complete, or classic hydatidiform mole [7]. In complete moles, the nuclear DNA is exclusively of paternal origin. The majority are 46XX, and arise from fertilization of an empty pronucleus of ovum by a haploid sperm that undergoes duplication [8]. This is usually referred to as diandric diploidy. The remainder, 46XY, arise from the fertilization of an empty egg by two sperm, termed diandric dispermy [9-11]. Typically, the karyotype of partial moles is triploidy (69 chromosomes), and usually results from the fertilization of an oocyte by two spermatozoa, or diandric triploidy. These are cytogenetically distinguished from triploid conceptuses with a diploid set of maternal DNA and a haploid set of paternal DNA, or digenic triploidy [6, 12-13].

In studies that include both, enormous differences in ratios of complete versus partial mole variants have been reported. Ratios of 1 to 3 and 3 to 1 have been reported, although more recent studies tend to include more partial mole cases [14-18]. The difficulties in distinguishing complete from partial mole by microscopic morphology alone are underscored by a study conducted by pathologists with special interest in trophoblastic diseases. In this study, the diagnosis was agreed upon by all in only 35 of 50 cases (70%) [19]. While complete mole does not usually present a diagnostic dilemma, it is difficult and sometimes impossible to distinguish a partial mole from a hydropic abortus using light microscopy alone [6, 14-24].

P57kip2 is the protein product of a paternally imprinted or maternal gene that inhibits cyclin-dependent kinases (CDK), thus serving to inhibit cell proliferation and to suppress tumor growth. Its lack of expression in trophoblastic disease plays a role in its abnormal proliferation and differentiation. P57kip2 immunohistochemical staining was absent in the trophoblastic layers of complete HM and as effect on it.
positive in the trophoblastic layer of non-molar villi and mesenchymal dysplasia [25].

The possible role of genetic and environmental factors in the onset of GTD has been investigated. A cDNA microarray analysis consisting of 10,305 human genes revealed significant changes, with 91 genes being upregulated and 122 being down regulated. Significance analysis of microarray revealed significant changes in gene expression, including those associated with signal transduction, cell culture, transcription and apoptosis. Further RT-PCR analysis of altered gene expression in molar tissues supported the microanalysis results. This study confirmed the upregulation of TLE4, CAPZA1, PRSS25, RNF13, and USP1 in complete HM tissues. Moreover, this study provides the first evidence that ELK3, LAMA3, LNK, STAT2, and TNFR SF25 are downregulated in complete HM compared to normal early placenta tissues. This approach allowed us to identify genes that are differentially expressed in complete HM tissues as compared to early normal placenta tissues [26].

3.2 LIMITATIONS OF MOST EPIDEMIOLOGIC STUDIES

Despite extensive epidemiologic data spanning at least 50 years, considerable difficulty exists in determining racial and geographic differences in incidence rates for GTD, including HM and choriocarcinoma, throughout the world. The major limitations of data published between the 1960s and early 1980s include imprecise definitions of included cases, extensive variability in the methods used to detect cases, and differences in the denominators used [27].

3.2.1 PROBLEMS WITH CASE DEFINITION

For rates of GTD to be compared, reproducible definitions of the conditions encompassed by the term “GTD” had to be developed. Before the recommendations of the WHO Scientific Group meeting were accepted most reports lacked clear, precise, and reproducible case definitions [28-29]. Earlier epidemiologic studies also predate the discovery by Szulman and Surti of two genetically distinct and specific types of HM - partial hydatiform mole (PHM) and complete hydatidiform mole (CHM) [12]. Other terms were routinely applied before these discrete entities were recognized, and included “destructive mole”, “invasive mole”, “transitional mole”, and “hydropic degeneration”. At best, this terminology was confusing, and at its worst, comparisons of all GTD cases across studies were not possible [28]. As has been discussed, using light microscopy hydropic degeneration can be easily confused with PHM, and destructive and transitional mole with invasive mole [6, 15-24].

Studies that included all GTD variants invariably also included cases that would be reclassified as first trimester abortions, if flow cytometry and/or cytogenetic analyses available today were applied [6, 15-24]. By design, studies in which the scope of investigation was
restricted to CHM and/or choriocarcinoma invariably reported lower incidence ratios, because partial moles were excluded [15-24, 28]. However, older studies that attempted to include all PHM cases, including clinically ambiguous ones, probably had falsely elevated numerators, because triploid conceptuses have many histological features similar to partial mole. The diagnosis of invasive mole requires histologic evidence of myometrial invasion. While this diagnosis can easily be made from microscopic evaluation of the uterus, hysterectomy is usually unnecessary and not routinely performed [27, 30]. The rare variants, including PSTT [31-33], epithelioid trophoblastic tumor [32, 34], and exaggerated placental site/placental site nodule [35], have only recently become recognized. PSTTs were initially thought to be clinically benign [31] and may not have been included in registry data until case reports of metastasis and even death despite conventional therapy began to appear [32-33]. While some early reports may have included metastatic PSTT as GTD or choriocarcinoma cases, prior to 1977 benign forms probably went unrecognized [31]. This is exemplified by an analysis of choriocarcinoma using data collected by the Surveillance, Epidemiology, and End Results (SEER) database. In the first 10 years of data entry (1973-1982), no PSTT tumors were listed [36].

Unlike most malignant tumors, GTD is unique in that surveillance and therapy is based less upon histopathologic diagnosis, and more upon the biologic behavior of the disease. Regardless of histology, and even in the absence of histologic confirmation, therapy has been based upon persistently elevated or rising human chorionic gonadotropin (hCG) levels, the most recent antecedent pregnancy, and presence or absence of one or more radiographically detectable metastatic lesions [3-5, 37]. The pitfalls of treatment based upon serum hCG levels alone have been addressed [37]. However, biopsy, especially when the vagina or distant sites are involved, is not feasible because of the highly vascular nature of these lesions [38]. Many excellent epidemiologic studies are limited by inclusion or exclusion of cases that lack pathologic confirmation [36, 39]. Excluding cases that lack pathologic confirmation from population-based studies is also problematic, as clinically relevant cases are missed [39]. In the study of choriocarcinoma using the SEER database, previously mentioned, histologic confirmation was obtained in 89.7% of cases, and the others the remainder were diagnosed on radiographic, clinical grounds, or observation at surgery [36].

Fortunately, other radiographic diagnostic tools including ultrasound, color Doppler ultrasonography, magnetic resonance imaging (MRI), computerized tomographic imaging (CT) and PET-CT are aiding in anatomic diagnosis. These studies have begun to be used in the clinical setting when a tissue diagnosis is not feasible [40-42]. When modern techniques that determine the cytogenetics of HM are applied with greater consistency in the clinical setting, more accurate classification, and comparison of other epidemiologic considerations including racial, regional, and cultural differences in risk, will be more feasible. Because the biologic behavior of molar pregnancies (especially PHM) detected using newer methods is less well
understood, hopefully, investigators having access to these newer tools will be able to determine those cases needing surveillance from those of little or no clinical significance. However, until the clinical significance of disputed cases is better understood, it would helpful to consider these separately from other GTD cases. Without staging and classification criteria that can be applied across all continents and registries, global differences in incidence rates will continue to remain an enigma.

3.2.2 PROBLEMS WITH CASE DETECTION

When GTD and choriocarcinoma cases are managed by regional referral centers and incidence rates are reported per live births and deliveries within a given institution or hospital, the number of cases relative to the regional population is invariably overestimated. It is now clear that many of the differences in incidence rates reported for different populations were the result of over-reporting of GTD cases. Hospital-based studies invariably tend to have falsely elevated incidence rates, particularly those from regions of the world where uncomplicated live births and pregnancies do not receive hospital-based care. Data derived from communities where medical attention is suboptimal are also likely to underreport GTD cases. For example, in regions of the world where spontaneous abortions and D&C specimens are not routinely subjected to histopathologic review, GTD cases that resolve spontaneously are probably not counted. Even in developed countries, under-registration of GTD has been reported. In Sweden, which maintains a national registry, 25% of HM cases diagnosed between 1971 and 1986, and 66% of treated cases, were not included within their cancer registry. The most common reason given for omission was absence of histopathological confirmation.

3.2.3 DIFFERENT DENOMINATORS FOR THE POPULATION AT RISK

GTD occurs as a result of an abnormal fertilization process, and can therefore occur following any type of conception. Thus, the total number of pregnancies is the preferable denominator to use when calculating GTD incidence ratios. Ideally, the pregnancy denominator should include all live births, stillbirths, spontaneous abortions, induced abortions, ectopic pregnancies, as well as clinically unrecognized pregnancies, if accurate estimates can be made. However, population-based data regarding unrecognized pregnancy loss is virtually nonexistent. In one study, the rate of early pregnancy loss in one year identified by a rise in urine hCG was found to 31%, and 22% of pregnancy losses occurred before the pregnancy was detected clinically [43]. Most of the earlier epidemiologic studies reported GTD ratios using deliveries or live births as denominator, which overestimated the reported incidence ratios. In a more recent population-based study, it was shown that calculations of
choriocarcinoma incidence rates using live births and deliveries falsely elevated incidence rates by approximately 20% [36]. While this study constitutes the best available published estimate of choriocarcinoma incidence rates in the United States, since the number of pregnancy terminations before 20 weeks of gestation and the number of ectopic pregnancies was unknown, it is likely that even their best estimates of the number of clinically recognized pregnancies over-estimated the ratio, because these data were not adjusted for unrecognized pregnancy losses.

Recent reports have attempted to record the best available numerator information including all GTD variants, as well as reasonably accurate denominator information (live births, clinically recognized pregnancies, and adult female population at risk). Age-adjusted standardization, which has proved to be a reproducible means of comparing malignancy rates over calendar time and across registries, may be an alternative means of estimating GTD incidence rates, especially if ratios are calculated including cases and women of reproductive age, who represent the fertile population [36, 44-45]. There are potential pitfalls with this denominator as well, because of differences in sterilization and hysterectomy practices in fertile women. However, because most countries maintain fairly accurate population-based age-specific census data for their adult populations, and many apply age-adjusted standardization to cancer statistics, this may prove to be a valuable means of comparing GTD incidence rates.

3.3 GEOGRAPHICAL VARIATIONS IN THE INCIDENCE OF GTD

3.3.1 HYDATIDIFORM MOLE

For a long time, epidemiologists, genetics, and gynecologists have noted significant variability in GTD incidence rates between different regions of the world (Table 3.1). Differences by geographic region within the same continent or country have also been reported. The previously cited differences in study methodology clearly account for some of the reported differences. In China, a nationwide study conducted by the National Co-ordination Research Group of Chorioma (NCRG) [46] found an incidence of 0.78 (0.81) per 1000 live births (pregnancies), and Song and Wu [47] a rate of 0.67 per 1,000 deliveries, similar to that reported from Western countries [48]. However, significantly higher rates of GTD, especially from southern and coastal regions compared with other parts of China, have also been reported [46]. The incidence of molar pregnancy in Japan (2.0 per 1,000 pregnancies) is approximately three times higher than the reported incidence in Europe or North America (0.6 to 1.1 per 1,000 pregnancies) [49]. Another well-controlled study involving 20 different prefectures indicated that the incidence of HM in Japan (16,829 cases between 1974 and 1982) ranged from 2.83 to 3.05 per 1000 live births [50]. In South Korea, the nationwide incidence of HM ranged from 1.9 to 2.1 per 1000 deliveries comparable to that in Japan [51-52].
## Table 3.1 Selected incidences of hydatidiform mole reported by various authors

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## Table 3.2 Selected incidences of choriocarcinoma reported by various authors

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Indonesia has one of the highest reported incidence rates, 1 in 77 pregnancies (1 in 57 deliveries) [53]. It is generally accepted that GTD incidence rates are higher among non-White Hispanics [54-58], American Indians and Eskimos [45, 59], and Asian [46-47, 49-52, 60-72] populations. Alaskan natives appear to have rates 3 to 4 times greater than Caucasian Americans [59]. In Hawaii, Japanese and Philippine women have rates higher than Caucasians native to that state, but Hawaiian Japanese have lower rates than those native to Japan [60-63].

There is considerable variability in the rates of GTD found in women of Hispanic descent. Reports from Latin America include rates from 0.23 per 1000 pregnancies in Paraguay [57] to 4.62 per 1,000 pregnancies in Mexico [54]. Studies from Los Angeles [73], as well as from New Mexico (USA) [44] found no increased risk for GTD among Hispanic (1 in 759 live births, 1 in 877 pregnancies) relative to non-Hispanic whites (1 in 747 live births and 1 in 961 pregnancies) using conception-based denominators. In this study, there was a difference observed using the denominator of women-years (age-adjusted incidence rates per 100,000 women-years for Hispanic and non-Hispanic whites 5.32 vs. 3.57, respectively, p < 0.001). Higher fertility rates in Hispanic relative to non-Hispanic whites appeared to account for the observed differences [44]. Rates reported by these two USA studies are considerably lower than those reported in hospital-based studies from Mexico and Central America [54-59]. In more recent report in USA, Hispanic women had a higher incidence compared to blacks (2.38 vs. 1.34; P < 0.001), but not Whites (2.00; P = 0.17) [58].

There is also considerable variability in incidence rates in blacks, although available data is limited. In Rhode Island (USA) during a 10-year period between 1956 and 1965, the incidence of HM among blacks was found to be higher than for whites, but the difference was not statistically significant. However, only 15 of the 329 cases were in blacks [74]. Similarly, a case-control study that compared rates of molar pregnancy among Black, Caucasian, and Latin American women in Los Angeles, found no racial differences, but again, the sample size was small. Among all ethnic groups studied there were only 145 molar pregnancies and 1 choriocarcinoma in 74,548 deliveries [73]. Hayashi et al. estimated that the ratio of incidence cases per 100,000 pregnancies for blacks (58.2) was approximately half that of whites (119) and others (117.9) [48]. However, USA rates are substantially lower than those of older hospital-based studies from Africa, where ratios per delivery of 1:184 (Lagos, Africa) [75-76], 1:203 (Ibadan, Nigeria) [77]; 1:329 (University College Hospital, Ibadan, Nigeria) [78]; 1:401 (University of Lagos, Nigeria) [79]; and 1:375 (Ogbomoso, Nigeria) [80] have been reported. More recently, Osamor et al. [81], Leighton [82], and Egwuatu and colleagues [83] have reported lower rates (1:655 deliveries, 1:971 deliveries, and 1:1219 pregnancies, respectively). For choriocarcinomas specifically, Brinton and colleagues reported that blacks and other races, respectively, had 2.1- and 1.8-fold higher incidence rates compared with US whites [36]. A
more recent update of SEER registry data, using all choriocarcinoma and PSTTs registered between 1973 and 1997 has been conducted, and results are similar to the earlier SEER report. The relative risk (common odds ratio, COR) for blacks (COR 2.19, 95% CI 1.71-2.79) and other non-whites (COR 2.14, 95% CI 1.61-2.84) was significantly higher than that for whites. However, blacks alone (COR 2.60, 95% CI 1.28-5.27) were found to have significantly higher mortality rates [45]. The higher incidence and mortality among blacks for choriocarcinoma in the USA is similar to data with respect to other malignancies that are amenable to screening and early detection, and may be a reflection of reduced access to medical care [84]. A recent analysis of postmolar surveillance reported that postmolar surveillance among indigent women, particularly those belonging to minority groups, is substantially poorer [85].

For the most part, data from the United States [44, 48, 62-63, 73-74, 86-87], other parts of North America [88-89], Western Europe [87-95], and Australia [96-98] reveal fairly consistent incidence rates, although regional differences have been reported (Table 3.1). Hayashi et al. reported a rate of 1.08 per 2,000 pregnancies in American women [48] and Bagshawe and colleagues, 1.54 per 1,000 live births in England and Wales [92]. Sweden also maintains a population-based registry of all GTD cases, and reported incidence rates of 1 in 686 deliveries and 1 in 1103 pregnancies; no trends in incidence rates over the 14-year period were found [94]. Australian [96-98] and Greenland [90] studies estimate rates fairly consistent with those from the United States and Western Europe, although rates are higher from southern Europe [96-100], the Middle East [101-112], and higher still in Asian women [61-63, 70, 72, 113-119].

Within the USA, using data derived from the Hospital Discharge Survey obtained over the 1970s, the incidence ratio of hydatidiform mole was 1.1 per 1,000 (1 in 923) pregnancies, and rates in New England, Middle Atlantic, and East South Central states were higher than rates reported from the Mountain, West, and South Central regions. The highest rate (1.89) in the Rocky Mountains was 2.7-fold higher than the lowest rate (0.70) from New England [48]. Taken within the context of other studies, these observed regional differences probably reflect the cultural and racial distribution of women living in these areas, rather than equatorial differences.

The geographical differences in current incidence rates should be interpreted within the context of obstacles to accurate estimations of incidence ratios, previously discussed. Nevertheless, the preponderance of data overwhelmingly supports that the incidence of GTD is substantially higher in Oriental women, particularly those in Southeast Asia. Improved epidemiologic studies are needed that address temporal trends, genetic, and environmental factors within the context of accurate case detection.

3.3.2 CHORIOCARCINOMA (CC)

As has been shown for molar pregnancy, internationally, the incidence
rates of gestational CC also widely differ [36, 48, 86-87, 109, 111, 120-131] although some of these differences are attributable to the same methodological problems associated with epidemiologic studies of molar pregnancies. In Europe and North America, one in 30,000 – 40,000 pregnancies, and 1 in 40 molar pregnancies are affected [127-128] whereas in Southeast Asia, rates as high as one CC in every 500–3,000 pregnancies have been reported [129]. Estimations of the incidence of CC have been limited by some of the same problems as with HM. As indicated in Table 3.2, rates derived from Latin American (0.2 cases per 10,000 pregnancies) and Europe (0.2—1.5 cases per 10,000 births and pregnancies) are similar, whereas reports from Japan have indicated higher rates (0.83 cases per 10,000 pregnancies and births). Hospital-based studies have reported rates ranging from 0.2 to 20.2 per 10,000 pregnancies and deliveries. Problems with definitions and methodological design have an even greater impact upon epidemiologic studies of CC, because this variant relative to all GTD cases is relatively rare.

3.4 TIME TRENDS IN INCIDENCE OF GTD

While much of the literature regarding trends in GTD gives conflicting results, newer data population-based from the United States, and Asia demonstrate a decline in incidence rates for HM and CC. This section explores both older and more recent available information regarding temporal trends for GTD.

3.4.1 HYDATIDIFORM MOLE

In the United States, two hospital-based studies spanning the time period between 1940 and 1964, reported that the incidence of HM declined during World War II, and then increased, and eventually surpassed pre-war incidence rates [74]. Incidence rates also steadily increased in Jewish women living in Israel from 1950 to 1965 [102]. Similarly, among indigenous Greenlandic women from 1950 to 1974, incidence rates increased significantly after 1965 [90]. A Japanese study summarizing registered cases of GTD, and including 16,829 incidence cases of HM from 1974 to 1982, found that the rates per 100,000 women had decreased yearly from 10.2 in 1974, to 7.9 in 1982. While significant trends per 100,000 women were found, when live birth denominators were used, the incidence rates were virtually unchanged (mean ratio and range per 1,000 births 2.92 and 2.83-3.05, respectively) [118].

In Asian populations, extensive data suggests that GTD incidence rates are declining [46, 64-69, 117-118]. In Korea, between 1971 through 1995, and using live births as the denominator, a 17.5-fold decline in incidence rates [from 40.2 (1971-1975) to 2.3 (1991-1995)] and to 1.9 (2001-2005) was reported. This study, which appears to be the largest hospital-based study of GTD to date, included HM (5393 cases), invasive mole (2466 cases), GTN (1600 cases), and PSTT (38
In Okinawa, the average GTD incidence ratios per 100,000 populations and per 1,000 live births were 3.41 and 2.29, based upon a study of 417 cases (1986 - 1995). Although incidence rates in Okinawa were higher than those of mainland Japan, GTD rates from both have similarly declined, and the higher rates in Okinawa are proportional to higher crude birth rates [68]. Although Malaysia lacks a centralized registry, the ratio per live births for the 1991-1995 time periods was 2.8 per 1000 deliveries, much less than for earlier years [119].

The incidence of HM is well-known that it is the highest in South-East Asia. It ranges from 1/1000 pregnancies (Japan), 2/1000 pregnancies (China) to 12/1000 pregnancies (Indonesia, India and Turkey). However, the incidence in North America, Europe, and Oceania is about 0.5-1/1000 pregnancies. The data from South America and Africa is limited and sparse. The accurate explanation on these geographical differences is difficult. Researchers point out maternal age, diet, ethnicity, gravidity, poor social-economic conditions, and infection as different factors.

Recent data show the significant reduction of GTD incidence with the increase of GNP. This is prominent in South Korea from 4.4/1000 deliveries in the 1960s, 1.9/1000 deliveries in the 1990s, to 1.8/1000 deliveries in the 2000's [64]. Similar results are obtained from Japan from 4.9/100,000 population in 1974 to 1.9/10000 in 1993. This trend is also noted in Taiwan [70].

3.4.2 CHORIOCARCINOMA (CC)

As HM greatly influences GTN as a precursor pregnancy, GTN trend may be transposed into HM trend. India and Indonesia are the highest with 19.1/1000 [124] and 17.7/1000 [71] pregnancies respectively. It is lower in South-East Asia. Korea shows 4.4/10,000 births in 1960s to 1.9/10,000 births in 1990s [64]. The incidence of CC has decreased to a third in Israel from 1950-1954 to 1960-65 [102]. While many countries show a constant decrease, some are continuously increasing.

Until recently, data on temporal trends in CC were exceedingly sparse. In Israel, the incidence ratios for CC significantly decreased between 1950 and 1965, so that by 1960 to 1965, the rate was less than one-third of that for 1950 to 1954 [102]. In the study of registration systems for CC in Japan the incidence of CC per 100,000 women decreased yearly from 0.31 in 1974 to 0.19 in 1982 or by about two-thirds over this time period. It is also of note that the incidence per 10,000 births decreased slightly, from 0.86 in 1974 to 0.74 in 1982, with an average of 0.83 [118]. Although overwhelming evidence suggests that incidence rates for GTD in Asia are higher than in other regions, the specific factors that account for higher rates may be one or more of the following: race, maternal age, environmental, dietary, and lifestyle factors. To date, no study has specifically addressed all of these factors within a poly-ethnic community.

A recent analysis of CC and PSTT data (1973-1997) obtained from the SEER database, which has annually recorded population-based cancer statistics for approximately 10% of the US population, was
performed. The 25-year annualized age-adjusted incidence rate per 100,000 women was found to be 0.136; 5-year average annualized rates declined by 45.6% [from 0.180 (1973-77) to 0.098 (1993-97)]. The decline in incidence rates was seen for all races, although blacks and others consistently had approximately twice the rates of non-Hispanic whites [45]. While this study showed no statistically significant reduction in mortality rates over 25 years, in China between 1959 and 1985, mortality rates for CC have declined drastically, from more than 90%, to less than 20% [130]. Wang and colleagues noted a 90.6% survival rate in women treated at the National Yang-Ming University, Taipei, Taiwan [132].

3.5 RISK FACTORS FOR GTD

Many factors, including viral infection [133-134], poor nutrition [46], defective germ cells [8], as well as the effects of prior pregnancies, maternal age, consanguinity, genetics, and environmental factors have all been considered as risk factors for the development of GTD. Although a variety these, and potentially other factors have been considered, the etiology of GTD, and the role of each of these factors, is poorly understood.

3.5.1 AGE FACTORS

Maternal age has consistently been identified as an important risk factor. Age-specific incidence reports usually reveal a ‘J curve’. HM is increased in the extremes of reproductive age. That is, teenagers have higher incidence rates, and reproductive-aged women 40 years of age or older have incidence rates that are substantially higher [48, 57, 74, 87, 90, 102, 114, 135-136]. With respect to age-specific rates, the risk is slightly higher for women 15-20 years old, and about 20-fold higher in teenagers under 15 years of age. There is a progressive (above 10-fold) increase in risk in women over 40 years of age [92, 102], such that for women over 50 years old, the risk that a pregnancy will result in HM is about 200 times greater than for women 20 to 35 years of age [137]. These age-specific trends affecting younger and older women suggests that defects in ovoid function (ova that are premature or post-mature) is one etiologic factor contributing to the risk for GTD. Reinforcing this hypothesis are findings that this pattern is consistent throughout all regions and races [48, 62, 64, 90, 115-116, 138].

Paternal age has also reported as a significant risk factor in some studies, although data are inconsistent [62, 139]. In at least one Japanese study, paternal age did not appear to play a significant role. [140].

3.5.2 REPRODUCTIVE AND OBSTETRIC HISTORY

The importance of including all conceptions in the denominator, and not just live births, has previously been discussed. Unfortunately, very
few existing reports make the distinction between gravidity and parity. Epidemiologic studies that adjust for potentially important overlapping effects, including maternal age, age at first pregnancy, induced abortions, miscarriages, spacing between pregnancies, and infertility, spacing between pregnancies and history of infertility are few and far between. No studies have included all of them.

A history of a previous HM appears to be a strong and well-established risk factor predisposing to another molar pregnancy [62, 102, 138, 141-142]. The risk of HM increases with prior history of HM. The relative risk for recurrent mole is anywhere from 20 to 40 times that for the general population [74, 102].

After the first HM, a second molar pregnancy occurs in 0.6-2.60% of pregnancies [142-146]. Women who have given birth to twins also appear to be at increased risk. In one study, the incidence of HM following twin pregnancies was substantially higher than that for the general population [147].

In both Rhode Island (USA) [74] and in Italy [148], parity was not found to be associated with an increased risk for HM, after adjustment for maternal age. However, another Italian study found an elevated risk of HM in nulliparous women with a history of miscarriage [142]. In the same study, difficulties in conception were significantly more common in women who subsequently developed HM pregnancies [142], but in a similar study conducted in Baltimore, no relationship between a history of infertility and menstrual problems and subsequent HM was found [139].

A higher rate of HM after artificial insemination by donor compared with normally conceived pregnancies was found in one report from Australia [98]. Also, repetitive molar pregnancies with different male partners have been reported. Six patients experienced a total of 34 pregnancies with 20 different partners. These pregnancies resulted in 15 HMs, 8 term live births, 7 therapeutic abortions, 3 spontaneous abortions, and 1 preterm delivery. The rate of persistent GTD was 3 (20%). Interestingly, 3 of the males reported normal pregnancies with other partners [149]. A significantly high incidence of triploidy in a woman with recurrent GTD following normal conception has been reported after two cycles of in vitro fertilization [150]. Thus, it appears that previous history of conceptions that occur and proceed normally reduces a woman’s likelihood of developing GTD. Whether this reduction in risk merely reflects the absence of adverse genetic or environmental factors that are known to induce abnormal fertilization, and thereby increase the risk for GTD, is unknown.

3.5.3 ETHNICITY

Several studies have been undertaken in polyclonal societies, and give insight into possible racial and ethnic factors in the risk for GTD. As previously discussed, in the United States from 1970 to 1977, black women had about half the rate of HM compared with non-black women [48]. Matsuura et al. reported that the rate of HM was 8.0 per
1,000 pregnancies in Caucasians, 17.5 in Filipinos, 16.5 in Japanese and 7.7 in Hawaiians [62]. There were also significant differences in incidence rates among Oriental women native to Hawaii compared with those born in Japan [62]. A study of Alaskan natives shows that the incidence is 3-5 times higher than the whites [59].

A Singapore study including cases and women between 1953 and 1965 found that the incidence of HM was 1 in 811 viable Chinese pregnancies, and occurred more commonly in Indian and Eurasian populations; in fact, no GTD cases occurred in Caucasians within the region during the entire 11-year study period [114]. HM was almost twice as likely to occur among Eurasians in Singapore compared with Chinese and Malaysian women [114]. Considerable differences by ethnicity within different provinces of China have also been reported [46, 47].

The differences in risk between white and Chinese populations may be genetic, environmental, or both. A comparison of differences in human leukocyte antigen (HLA) sharing in Taiwanese was compared with Pittsburgh (USA) couples. Taiwanese couples alone were found to share HLA B (p < 0.04), HLA DQ (p < 0.007) and also shared 3 or more HLA A, B, DR, and DQ (P < 0.02) compared with USA couples. These results support the hypothesis that GTD development occurs on a sporadic basis in whites and on a genetic basis in Chinese. [151]. Indians and Pakistani women have also found to be at increased risk for recurrent molar pregnancy, compared with Caucasians [152]. In this study, those who presented with a partial mole tended to have a partial mole as the second event, but those with a history of CHM were at increased risk for PHM, CHM, or CC [152].

There is much evidence to show the correlation of ethnic difference with molar pregnancy rates. However, it still remains a problem to study the exact mechanism behind ethnicity.

3.5.4 GENETIC FACTORS

The importance of genetic factors in the etiology of HM is exemplified by several observations [153-154]. It is speculated that some of the wide variability in incidence rates observed among different populations may be due to genetic differences. The high incidence of HM and other trophoblastic tumors in certain populations, including women in Indonesia, Taiwan, the Philippines, and the Far-East has been attributed to inbreeding [150-151]. Among these groups, the risk of recurrent HM in a subsequent pregnancy is high: 0.6-3% [102, 146, 155], and similar to certain polygenic conditions. A case report of three families has described recurrent HM in female siblings, and suggests that the proposed defect in the ovum could be due to a mutant gene [156].

In some studies, the ABO blood groups of patients and their husbands have not been found to be different from normal populations [157], but a significantly higher incidence of blood group B has been identified in women with recurrent molar pregnancies [149]. In one investigation, women with molar pregnancy in Japan had
a lower frequency of Rhesus (Rh) negative blood type compared with the general population [158].

Cytogenetic studies in two series [8, 159] have reported a frequency of balanced translocations of 4.6% in women with CHM, compared with 0.6% for unaffected populations. It is possible that women with a balanced translocation have a greater chance of abnormal events during meiosis, increasing the probability of inducing empty or inactivated eggs.

Karyotypic studies using molar tissues have found that in most cases, PHM cases demonstrate triploidy or trisomy [13, 160]. However, CHM cases are exclusively or predominantly 46 XX female karyotype by Q polymorphism [7-8]. Some CHM cases do result from doubling of a haploid sperm, and in such cases, they are genetically homozygous. Less commonly, CHM may be genetically heterozygous, resulting from the fertilization of an anucleate ovum (empty egg) by two sperms [9-10, 161-163]. This basic classification appears to explain the vast majority of all CHM cases, although other cytogenetic types including tetraploidy variants exist [164]. Current technology permits the accurate classification of HM into PHM and CHM, also allows CHM cases to be subclassified genetically into monospermic or dispermic variants, using the PCR with primers for a variable number of tandem repeat sequences and the Y chromosome-specific sequences [165].

More recent technological advances that may further elucidate GTD variants include gene amplification [166], identification of specific tumor suppressor genes (or their receptors) such as DOC-2/hDAb2 [167], TNF-α [168], and paternally derived H19 [169]. The imprinting of IGF2 and H19 was maintained in all normal placenta tissues but relaxed in GTD. Promoter usage pattern of IGF2 changed with gestational stage of normal placenta and GTD. These results suggest that LOI, deregulation of IGF2 promoter, and altered expression levels of IGF2 and H19 genes might be associated with progression of GTD [170].

The oncoproteins p53, p21, Rb, and mdm2 have been investigated, but the overlap in differences in expression among GTD variants appears to be too great for clinical utility [171]. There is an increase in circulating soluble interleukin-2 receptor (SIL-2R) coincident with reduced serum IL-2 levels in women with GTD compared with normal controls; SIL-2R levels were 3.9-fold higher in complete and partial moles, and 6.1-fold higher in high risk CC cases [172]. PCR polymorphisms have also been found to identify very specific genetic origins of trophoblast tumors [173]. In addition to flow cytometry, previously discussed [15-24], in-situ hybridization [174] and deoxyribonucleic acid image and interphase cytogenetic analysis [175] are being investigated. GTD in a 42-year old with congenital trisomy 8 mosaicism has been described [176]. It is thought that there is an increased risk for cancer in tissues with constitutional genetic imbalance, including trisomies or translocations. Nonetheless, using data from the Danish National Register, no increased risk for other cancers, except subsequent CC was seen in a study of 1520 women and their male partners [177].
The relationship between genetics and GTD will be discussed in greater detail in a separate chapter devoted to this topic in this text.

3.5.5 FAMILIAL OCCURRENCE AND CLUSTERING

There are several reports of the influence of consanguinity, or family history, on the incidence of mole [85,154]. One study reported three families in India each having two or more sisters with HM in one or more pregnancies [156]. La Vecchia et al. reported that among patients with molar pregnancy in Italy, there was a history of HM in four of 100 relatives of the woman (three CHM, one CC), and in one of 100 relatives of the father (CHM), compared with no family history among 200 age-matched controls [142]. There have been numerous reports of recurrent moles in single individuals, but very few describe familial occurrence of molar pregnancies.

3.5.6 DIET AND NUTRITION

Information regarding the role of diet and nutrition is inconclusive, and inextricably linked to other potential factors including socioeconomic status and geographic location. Although there has been much speculation that one or more dietary factors predispose to the development of HM, there is very little evidence supporting this hypothesis. Early reports from the Philippines [113], Mexico [178] and Taiwan [179] all suggested that nutritional deficiencies play a role, especially in regions of the world where malnutrition is common.

In one study, which included 25 women with HM, the serum albumin and total protein were significantly lower compared with healthy controls [180]. However, two other reports, including a study from Hawaii [59] and another on native Alaskans, who have a diet high in animal protein [59] were unable to detect a similar association between HM and diet. Berkowitz et al. reported that dietary carotene above the median level of consumption in the control group appeared to reduce the risk of CHM (relative risk 0.6; \( p = 0.02 \)) [143]. In another study, Parazzini et al. identified an inverse relationship between HM and certain foods, such as carotene, and a significant trend toward lower GTD rates in women with higher rates of consumption of carotene and animal fat [181]. However, these results differ from others, including a case-control study from China that found no association with dietary intake of vitamin A, or any other specific food group [182].

3.5.7 ENVIRONMENTAL FACTORS

To date, no specific environmental factors have been identified that can be linked with certainty to an increased risk for GTD. However, because these are potentially correctable risk factors, preliminary data addressing the role of environmental agents are discussed.
Cigarette smoking

Despite extensive data regarding the effects of cigarette smoking, including second-hand smoke, on neonatal birth weight and preterm labor, there have been relatively few studies that have examined the effects of cigarette smoking on risk for GTD. Parazzini and colleagues found that cigarette smoking increased risk of HM [148]. In women who smoked more than 15 cigarettes per day, the relative risk for CHM was 2.6, compared with 2.2 for women who smoked less than 15 cigarettes a day. La Vecchia et al. noted that the duration of smoking was associated with an increased risk [142]. Assuming the relative risk in women who never smoked is 1, for women who smoked less than 5 years, the risk for HM was 1.3, compared with 2.3 in women who smoked 5 to 9 years, and 4.2 for a smoking history of 10 or more years. However, in several other studies, no association with smoking before or during pregnancy and subsequent HM development was found [74, 139, 143, 182].

Oral contraception and intrauterine contraceptive devices

There is conflicting evidence on the relationship between oral contraceptives (OCs) and intrauterine contraceptive devices (IUCDs) before pregnancy and risk of HM. In China, the past use of OCs was associated with an increased risk of HM; the relative risk for four or more years of use was 2.6, and there was a significant trend with increasing years of use [182]. These results are supported by those of Palmer, who found a six-fold increased risk of CC in women who had taken OCs for more than five years [183]. However, in the same study, no association with invasive mole and CHM was found. Because it was unclear if OCs are truly a risk factor, or a chance finding in women with underlying difficulties with conception, a large multicenter trial was performed to evaluate the effects of OCs and subsequent risk for GTD [184]. In this study, the relative risk for GTD for any prior use of OCs was 1.9 (95% confidence interval {CI} 1.2-3.0). The highest risk index was in women using OCs during the cycle in which they became pregnant (relative risk 4.0, 95% CI 1.0-10). Nevertheless, because the relative risk was small, the authors cautioned that a change in OCs use based upon this study was not recommended [184].

During postmolar surveillance, Stone et al. reported that women taking OCs resulted in a delay in decline of hCG levels in women who were not receiving chemotherapy for GTD [185]. However, Berkowitz et al. [186] and Curry et al. [187] found no adverse effect. The prospective randomized trial by the Gynecology Oncology Group found that the median range to spontaneous regression for women using OCs and barrier methods was 9 and 10 weeks, respectively, and the rate of conception during surveillance was reduced by 50% [187]. Use of OCs in women with a history of HM compared with other forms of contraception (barrier methods, IUCDs, no method) has been found to actually reduce the risk for post-molar GTD. Using a stepwise regression analysis, the type of contraception used compared with other risk factors including theca-lutein cysts, Asian descent,
interval from last menstrual period, and advanced maternal age, was the most important prognostic factor in postmolar GTD development [188].

Previous use of an IUCD has also been found to be significantly associated with HM in an Italian study [142], but Berkowitz et al. found a much weaker relationship [143], and the Baltimore study showed no correlation [139].

Diethylstilbestrol (DES) may also be a risk factor. In one study, 2 of 129 daughters of mothers who had used DES in pregnancy developed HM [189]. Although the incidence ratio (15.5 per 1000 pregnancies) is disconcerting, it is based upon only two exposed cases; however, the effect of DES exposure merits further study. Since daughters of mothers who took DES are aging, and risk increases with maternal age, the exposure may be only coincidentally related.

Other environmental factors

Constable and Hatch have recently reviewed several studies from Southeast Asia that have addressed the role of herbicides (including agent orange) and an increased risk for HM [190]. Two studies from South Vietnam of women with HM and CC treated at the Gynaeco-Obstetrical Hospital of Ho Chi Minh City were reviewed [191-192]. Rates of HM and CC minimally increased from 8.61 per 1,000 pregnancies in 1952 to 8.7 in 1971, after which it rose abruptly to 45.4 in 1979, declining only slightly in the following two years. If herbicides were to influence directly the development of HM, one would expect the epidemic and the spraying to be more closely linked in time. Alternatively, herbicides enter the food chain and take several years to affect reproductive processes. The limitations of such studies are failure to control for maternal age, parity and other variables that are known risk factors.

A follow-up case-control study of agent-orange and risk for GTD in this same population has been conducted. Cases were found to eat less meat, own fewer consumer goods, and an increased risk was associated with the breeding of pigs. When a cumulative agent orange exposure index was constructed, using complete residence histories, no statistical differences between cases and controls for other agricultural pesticides, or agent orange (OR 0.7, 95% CI 0.2-1.8) was found [190]. In another review, the use of herbal medicine during the first trimester was associated with an increased relative risk for hydatidiform mole, major birth defects, and liver cancer [192]. An ecological investigation of exposure to ionizing radiation from 1974 to 1976 in Japan, and its association with a higher incidence of GTD, supports the hypothesis that ionizing radiation may have a causal role [193]. Although these studies have some methodological problems that limit their value, nevertheless, environmental factors appear to be implicated. Potentially, temporal exposure to these factors at the time of, or near fertilization, could result in abnormal gametogenesis, thereby inducing a complete or partial mole.
3.6 RELATIVE RISK (ODDS RATIO) FOR CHM AND PHM

According to several reports, complete and partial mole share several epidemiological features. In studies where complete mole and partial mole are analyzed separately, many social and demographic risk factors were common to both [194-196]. For example, nulliparous women, those with low parity, and those with a personal history of infertility problems, spontaneous miscarriages, previous GTD or a family history of GTD are at increased risk for both PHM and CHM [197]. Other risk factors including smoking and higher levels of education are more commonly seen with PHM, and maternal AB or A blood groups with CHM [193]. Neither has been linked to induced abortions, age at first pregnancy or alcohol consumption (Table 3.3).

In one study within a poly-ethnic community, Filipino, but not Japanese women, were found to be at increased risk for CHM but not PHM [194]. The increased rate of PHM seen in better educated and presumably, more health-care conscious women may be a reflection of better access to pathologic assessment of abortion specimens and to follow-up in specialist centres. Several identified risk factors, including the relationship with maternal age and ethnicity are similar for both variants, although the data available is insufficient for formal statistical evaluation or inference. In a case-controlled study of PHM vs. CHM, using multivariate analysis, irregular cycles, pregnancy histories including only male infants among prior live births, and oral contraceptive use for over 4 years independently and significantly increased the risk for PHM, and dietary factors had no effect [196]. Of note, while maternal age is a well-recognized risk factor for CHM, maternal age has not been found to increase the risk for PHM [194-196].

As previously discussed, the use of flow cytometry and other cytogenetic studies increases the detection of PHM [15-24]. However, the clinical ramifications of identification of these cases are uncertain. While the risk of GTN following a CHM is approximately 20%, in one review, the risk following PHM was found to be only 2.9% [199]. Berkowitz reported that the risk for gestational trophoblastic neoplasia (GTN) following PHM was 9.9%, but in this series, all had non-metastatic disease [200]. CC following partial mole is a rare event; as of July 1, 2000, only 21 cases have been reported [201-203]. Using data derived from a large trophoblastic disease referral system, Seckl and colleagues reported that 15 of 3000 partial mole pregnancies eventually required chemotherapy for GTN and 3 (0.1%) developed CC [204]. Although the risk is rare, the importance of appropriate surveillance, and inclusion of PHM in registry data, is emphasized by these studies.
Table 3.3 Corresponding relative risks of various factors reported to correlate with molar pregnancy occurrence.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Complete mole</th>
<th>Partial Mole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Reproductive history</td>
<td></td>
<td></td>
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<tr>
<td>Parity at conception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Spontaneous miscarriages &gt;2</td>
<td>1.5-3.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Problems with Infertility</td>
<td>2.4-3.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Contraception</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of oral contraceptives</td>
<td>1.1-2.6</td>
<td>1.3</td>
</tr>
<tr>
<td>IUCD user</td>
<td>1.7-3.7</td>
<td></td>
</tr>
<tr>
<td>Age of 1st pregnancy &lt; 25</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Previous molar pregnancy</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous abortion (yes)</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Socioeconomic and lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>0.9-2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Marital status</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Never married</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>&gt; 15 cigarettes per day</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 drinks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABO blood types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>2.1</td>
<td>1.2</td>
</tr>
<tr>
<td>A</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>Maternal A, husband O</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin A in diet above control median</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>

Source: Grimes [28], Matsuura et al. [62], Bracken [87], Olesnicky and Quinn [98], Messerli et al. [139], La Vecchia et al [142], Berkowitz et al. [143], Brinton et al. [182], Steigrad [197], Altieri et al [198].
3.7 RISK FACTORS FOR CHORIOCARCINOMA

In the vast majority of cases, CC arises following an antecedent molar pregnancy. However, CC may follow any antecedent pregnancy, including a delivery, stillbirth or spontaneous abortion. Cytogenetic studies have shown that there can also be intervening pregnancies that are unrelated. Studies have shown that CC is approximately 1,000 times more likely to develop following a CHM than after a normal pregnancy, and the risk for CC following CHM is much greater than for PHM. Clinically, it would be invaluable to determine factors responsible for malignant transformation following a gestational event. Potentially, if these factors could be reliably ascertained, selective surveillance for high-risk pregnancies (including term births) could be offered, instead of the protocols for currently following all molar pregnancies.

3.7.1 AGE

The median age for women with CC is generally somewhat higher than that for normal pregnancy. Some reports [102] described slightly higher rates of CC for teenagers than for women aged 20-40 years, while others noted lower rates. As with HM, older women account for a minority of cases of CC due to their low fertility. The potential effect of the age of the father is unknown.

3.7.2 ETHNICITY

Little information is available on ethnic variability. In the Singapore study [114], the incidence was highest in Malaysians compared with other ethnic groups, but the data were rather inadequate, so that no definite conclusions could be drawn.

3.7.3 REPRODUCTIVE AND OBSTETRIC HISTORY

The data concerning the effect of gravidity, independent of age, are inadequate and no firm conclusions can be drawn. Poor obstetric histories associated with increased fetal wastage may increase the risk of GTN [205-206]. It was found that the risk of GTN was 21, 31 and 34 times higher for women with one, two and three or more fetal losses, respectively, than those whose known pregnancies all ended in live births [206].

The higher proportion of CC following HM could be attributable either to the high incidence of HM in some countries or to a higher percentage of HM patients in those countries developing CC. The percentage of cases of CC preceded by HM ranges from 39% [193] to 83% [194] in reports published since 1960. Since HM is an uncommon pregnancy outcome, the high percentage of cases of CC which follow HM indicates that HM is a powerful risk factor for CC. Brinton and colleagues reported that the overall incidence of CC in the United States
was 1 in 19,920 live births and 1 in 24,096 pregnancies [36]. The risk for HM developing into CC is probably less than 5% [131].

3.7.4 OTHER FACTORS

Palmer found a six-fold increased risk of CC in women who had taken OCs for more than five years, but no such association with HM in the same study [184]. Based on the result of their case control study, Buckley et al. [207] suggested that below-normal estrogen levels may predispose to CC. Two different mechanisms were proposed that may explain these results: hormonal changes may effect oocyte development, and low estrogen levels may be the result of an ovarian abnormality. Pregnancies occurring within one year of diagnosis of HM do not appear to be at higher risk for adverse effects [208-210].

3.7.5 GENETIC FACTORS

As HM has been separated into two clinical and genetic entities (CHM and PHM), the incidence of developing GTN following the two separate pathological entities is also different. The incidence of GTN following a CHM is 2-20% [101, 199, 201], while GTN and CC following PHM is probably of 0.5% and 0.1%, respectively [201]. The variable genetic constitution of HM does make it possible to identify HM and distinguish between a PHM, a monospermic CHM and a dispermic CHM by using genetic analysis techniques such as cytogenetic polymorphism, enzyme polymorphism and restriction fragment length polymorphisms of DNA, and more recently PCR. The relative risk of a dispermic or a monospermic CHM progressing to a GTN has yet to be established, although it has been suggested that the dispermic CHM may have a higher malignancy potential [11, 211]. CC developing in older women, and certainly women over 50 years of age, is associated with a poorer prognosis [212-213]. Women who experience repeated abortion are also at increased risk for CHM [214].

3.7.6 MATERNAL AND PATERNAL BLOOD GROUP

Maternal blood groups of the mother and her consort have been studied but the data are inconclusive.

ABO group

Blood group A women with incompatible blood group consorts appear to have a higher risk of CC. Data from the USA [215] and the UK [154] for patients with CC showed a slight excess in group A above group O. The UK data suggested that the risk of a woman getting CC is also influenced by the blood group of her husband, and the effect was most marked in cases where CC was preceded by term delivery [157].
In a UK series of 115 patients with CC following term pregnancy or non-molar abortions at Charing Cross Hospital, for whom mating types were available, the ratio of incompatible/compatible matings was 2.19, indicating a predisposition to CC in the incompatible matings [137]. It is important that more large studies on blood group data should be done worldwide.

HLA types

Data are available on patients and husbands in a series treated for GTN. The overall frequencies of the HLA-A and HLA-B locus antigens in 225 Caucasian patients did not differ significantly from those of the normal control population [216]. However, the degree of incompatibility between husband and wife, as measured by the number of antigenic incompatibilities (0, 1 or 2), indicates that there is a trend for patients who are more compatible with their husbands for the B locus antigens to fall into the higher-risk treatment categories. Consanguinity as a risk factor will require evaluation in large-scale studies with modern cytogenetic techniques.

3.8 TIME TREND OF MORTALITY RATES OF THE GTD

3.8.1 HYDATIDIFORM MOLE

Inadequate management of HM may bring about acute complications, which results in severe morbidity and mortality. Late complication of progression to persistent GTN is noted in 57~36% of patients and this is higher in high risk complete mole. High risk CHM has base-line hCG over 100,000 milli IU/ml, uterine size greater than gestation age, ovarian theca lutein cyst over 6cm, associated medical factors (hyperthyroidism), and maternal age over 40 years or less than 18 years [217-219].

When postmolar evacuation follow-up is inadequate or when GTN diagnosis is inaccurate, optimal management may not be made in sufficient time. This results in increase in morbidity and mortality.

3.8.2 GESTATIONAL TROPHOBLASTIC NEOPLASIA (GTN)

Compared with many other human malignant tumors, the decrease in mortality with chemotherapy treatment is outstanding. This dramatic improvement in cure rate results from the specific biomarker β-hCG RIA and sensitive chemo-agents. Currently, low risk GTN has the cure rate of nearly 100%. However, in spite of tremendous improvement, the treatment of high risk HM and GTD is still not satisfactory in poorly developed countries. The mortality of ultra-high risk GTN is around 40~50% [220].

On the global trend, the incidence of GTD is on the decrease, yet the remission rate of high risk patients is not satisfactory.
The 5-year survival rate of CC in Japan was very low in the past. It increased from 23.1% in the 1960s to 52.6% in the 1970s. This has improved to 86.7% and 85.8% in the 1980s and 1990s [117].

In Korea, the survival rate of GTN patients improved from 73.2% in 1970s, to 92.9% in 1980s, to 96.1% in 1990s, to 96.6% in 2000s [51-52, 64]

3.8.3 OVERALL REMISSION OF GTN

Development of chemotherapy and improvement of general health services are directly responsible for improved survival. Better socioeconomic state and improved nutritional conditions are indirect causes. We hope that studies on genetic factors will shed new light on our understandings of the disease.

The 26th Annual report from FIGO on Gynecologic Cancer Treatment shows the total number of GTN has decreased since 1938 (1979-1981). Patients are mostly 25-29 years old and 82.7% of patients are under the age of 40, which indicates that this is a tumor of young females [221]. The 5-year survival rate of GTN is 92.7% in the 2000s. However, when analyzed in depth, the rate is 61.9% for stage IV compared with 97.3% of stage I, which clearly shows the problem of this disease [221].

Management of recurrent and drug-resistant GTN remains the biggest challenge in striving towards 100% survival even in the best centers in the world.

3.9 SUMMARY

Gestational trophoblastic disease is still an important reproductive health problem worldwide. The problem is that much information of GTD has come from less developed countries, where proper diagnostic tools and up-to-date treatment cannot be employed. Maternal age, previous HM, race and geographical region have been identified as clear risk factors for GTD. Etiological factors of GTD have long been studied but no definite causes have yet been found. However, it can be speculated that during gametogenesis and fertilization, the risk factors may act synergistically. Genetic sub-classification may be helpful in this context. Geographic variations of incidence exist but are inextricably linked with above-mentioned risk factors. Important prerequisites for accurate evaluation are common denominators, standard classification and definition of index cases, and same-study methodology. The development and improvements in suction curettage, termination of pregnancy, contraceptive techniques, diagnostic imaging and biochemical testing have been associated not only with a fall in the birth rate but also with a reduction in the incidence of trophoblastic disease. Further investigations on possible etiological factors based on case-control studies in different geographic settings are essential.
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