The hydatidiform mole

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ABSTRACT

The hydatidiform mole (HM) is a placental pathology of androgenetic origin. Placental villi have an abnormal hyperproliferation event and hydropic degeneration. Three situations can be envisaged at its origin: 1. The destruction/expulsion of the female pronucleus at the time of fertilization by 1 or 2 spermatozoa with the former being followed by an endoreplication of the male pronucleus leading to a complete hydatidiform mole (CHM) 2. A triploid zygote (fertilization by 2 spermatozoa) leading to a partial hydatidiform mole (PHM) but can also lead to haploid and diploid clones. The diploid clone may produce a normal fetus while the haploid clone after endoreplication generates a CHM 3. A nutritional defect during the differentiation of the oocytes or the deterioration of the limited oxygen pressure during the first trimester of gestation may lead to the formation of a HM.

Introduction

In humans, 5–6 d post conception, the zygote gradually becomes a blastocyst. The peripheral cells of this blastocyst differentiate into 2 layers: a cellular trophoblast called the cytotrophoblast (CTB) and an expanding peripheral syncytial layer, the syncytiotrophoblast (STB), which then invades the endometrium and uterine vasculature (Fig. 1). These two tissues associated with the extra-embryonic mesoderm are at the origin of the placenta. When the proliferation/invasion phenomena are not well controlled, the trophoblast cells can give rise to a rare complication of pregnancy known as a hydatidiform mole (complete or partial). These hydatidiform moles belong to the gestational trophoblastic diseases of which represent the most common pathologies. These are the only pathologies of the group that can be recurrent in the same patient. The recurrent moles are a rarer occurrence and indicate a genetic predisposition. These tumors are also the only ones of androgenetic origin. In other words, the tumors do not have the alleles of the ovule which has been fertilized, contrary to all the other cells of the woman carrying this anomaly. Parthenogenesis but not androgenesis was observed in primates1 and partial moles (and not complete mole) was observed in chimpanzee, but the invasive forms were only found to exist in humans.2

Anatomy and histology

Description

The moles were first described by Hippocrates (470–410 BC) who explained their formation through the consumption of dirty water by the pregnant women, where the water originates from the marshes. However, the terms mole and hydatidiform were later employed by William Smelie (1752). This author describes this pathology as a bunch of grapes consisting of different sizes.3,4 The moles exhibit diffuse trophoblastic hyperplasia where the structures of villosities are particularly aberrant and hydropic (Fig. 1). Such disorganization of the trophoblast, results in the limited recognition of the presence of vascular structures.5 The problem of vascular maturation in the moles could be due to the increased level of apoptosis in the precursor components of the blood-vessels6 or to the defective recruitment of pericytes around the villous stromal vessels.7 Despite the presence of these vessels, it is not certain that they contain various haematopoietic components. This persistent vascular immaturity of the villous stroma could lead to hydropic villi mainly in CHM. In the case of PHM, these trophoblastic anomalies are less present and usually contain identifiable embryonic or fetal tissues, which is very infrequent in the case of the CHM.8 Surprisingly, this trophoblastic hyperplasia can continue to form to such an extent whereby it invades and subsequently exceeds the uterine cavity.
This observation suggests that these moles are not rejected by the uterus. Some authors could regard it as a missed abortion. In the Middle Ages one imagined that each focal swelling corresponded to an egg. Hertig and his colleagues in 1956 proposed a logical progression between the various types of moles, from PHM to CHM then to an invasive mole, followed by a very aggressive tumor, the choriocarcinoma. Today, it is known that it is not plausible, in particular because a woman can develop a choriocarcinoma after a HM but also after a normal pregnancy. It is more pertinent to speak of preneoplasia (premalignant) for the HM and of gestational trophoblastic neoplasia (malignant diseases) for the invasive moles and the choriocarcinomas.

Differentiation

The cells of the CTB actively proliferate immediately after implantation and invade the endometrium and the spiral arteries in a regulated manner, allowing the plugging of these vessels (Fig. 2). On the surface of villi the CTB cells generate, by asymmetrical cell division, the multinucleated syncytiotrophoblasts (STB) (Fig. 2). This STB loses any pre-existing mitotic activity and it is very sensitive to the presence of oxygen. The STB secretes numerous hormones, such as human chorionic gonadotrophin (hCG). The CTB cell proliferation is responsible of the production of 2 types of mature villi which are; floating and anchoring villi (Fig. 3). The proliferation is faster in the center of the placenta when compared to the periphery. The plugging of the trophoblastic cells avoids the teratogenic effect of too high oxygen pressure (pO2) in the embryo. During the 10–12 first weeks of the gestation, the STB does not secrete antioxidant enzymes. Conversely, this hypoxia supports placenta angiogenesis and the proliferation of the CTB cells. Around 10 weeks of gestation, the trophoblastic plugs are dissolved and the progressive maternal spiral arteries remodel into large diameter vessels (utero-placental arteries), which are responsible for the increased level of blood flow (Fig. 3). The maternal blood can now circulate easily between the villi, supply required nutrients from the mother to the fetus and eliminate the toxic elements from the fetus. These modifications occur in parallel to the significant growth of the fetus. During gestation, the CTB decreases in thickness at term, the STB is in close contact with placental vessels allowing efficient nutrient uptake by the fetus.

Regulators

The utero-placental regulators are organized at an early stage of pregnancy and correspond to a dialog between maternal cells (decidual cells, NK cells, macrophages) and trophoblastic cells. This effective dialog limits, in space and in time, the proliferation and invasion of extravillous CTB, respectively, to one third of the internal myometrium and until the 16th week of gestation. The hypoxic environment of the first trimester of...
Figure 2. Placenta during the first trimester and its histological description.

Figure 3. Placental development and its regulations according to pO2 variations. During the first trimester the plugging ("plug") of the arteries, generates weak pO2. The variations of pO2 induce a modification of different molecule synthesis, which supports the transition, spatially and temporally, from the proliferation phase to the differentiation phase of the trophoblast at the end of the first trimester and the remodeling of the arteries.
pregnancy promotes the cellular proliferation of trophoblast and avoids oxidative stress, the alteration of the villi and inhibits the differentiation of extravillous trophoblast to the invasive phenotype. This hypoxic environment is maintained for approximately 10 weeks of gestation. After this stage, the pO2 increases and the placenta phenotype becomes invasive, allowing the remodeling of the spiral arteries; leading to increased blood perfusion of the placenta (Fig. 3). Any deviations in these regulators (pO2 or/and trophoblast response), results in the placenta developing a proliferative phenotype; a situation that could be the cause of one of the histological aspects of molar pregnancies.

These regulators are controlled by a number of factors present in the trophoblast, such as hypoxia-inducible factor 1α (HIF1α), and in the decidua, such as transforming growth factor β (TGFβ) and Decorin. The expression of transcription factor HIF1α is high during the early stages of pregnancy and decreases after 9 weeks of gestation, when pO2 begins to increase. Under reduced pO2, the trophoblast cells activate HIF1α, which in turn upregulates TGFβ expression. The TGFβ and Decorin subsequently inhibit the growth, migration and invasion of extravillous trophoblast. However, the neoplastic placenta resists the negative regulations of TGFβ. This resistance may be related to the decreased expression of tissue inhibitors of metalloproteinases (TIMPs). Other factors such as Leukemia Inhibitory Factor (LIF), signal transducer and activator of transcription 3(STAT3) and specific integrins are expressed with increasing pO2 and promote invasion. STAT3 activation is necessary for the invasive phenotype of trophoblastic cells and can be controlled via LIF. LIF provides a soluble extracellular signal that stimulates trophoblast invasion. Thus, CTB cells present a dynamic expression of certain adhesion molecules (integrins, E-cadherin) depending on the oxygen pressure. Authors show that, when the placenta transforms from the proliferative phase to the differentiation phase, the trophoblastic cells switch their expression of specific integrins (α6/β4 to α1/β1 and α5/β1), which is also associated with a decreased expression of the E-cadherin (Fig. 3). If the CTB cells do not adopt the required cell adhesions, cell proliferation is favored over invasion. This transition to the invasive phenotype of trophoblast is also very dependent on the expression of the canonical Wnt pathway associated with the expression of transcription factor 4(TCF-4) and with the recruitment of β-catenin. The hyperactivation of the Wnt pathway and nuclear expression of β-catenin are involved in the formation of hydatidiform moles. At the time of the trophoblastic transition, a differential expression of growth factor receptors is also observed. Epidermal growth factor receptor (EGFR) and erythroblastic leukemia viral oncogene homolog 4 (ERBB4) are expressed in the proliferative phenotype while ERBB2 and 3 are expressed in the invasive phenotype (Fig. 3). These receptors are activated by EGF and heparin binding EGF (HB-EGF) solely throughout the proliferative phase. In the case of CHM, there is an increase in the expression of the EGFR, which may explain the hyperplasia of the trophoblast. The invasive trophoblast also produces proteases (specifically MMP2 and MMP9) that degrade the proteins of the extracellular matrix in the decidua, which in turn would facilitate the invasion. We can also observe the expression of inhibitors of these proteases as TIMPs and plasminogen activator inhibitors (PAIs ) in the trophoblast and decidua, which would impede the invasion of the trophoblast cells. Finally, the different forms of hCG present unique kinetics during gestation. The hyperglycosylated hCG (HhCG) is strongly synthesized by the cells of the extravillous CTB in early pregnancy, which promotes the implantation of the embryo (hCG is normally produced by the STB and its concentration rapidly decreases to less than 2% after the first trimester). Deregulation of the production of hCG is associated with hydatidiform moles, particularly the HhCG rate is increased by 5% in complete moles and approximately 4% for the partial mole. The transition to an invasive tumor is also associated with a significant increase of HhCG, reaching 30/35% of the total hCG in invasive moles and up 100% for choriocarcinomas. Overall, these different factors involved in regulated manner, are associated to the change in pO2. The factors act together or in succession during the end of the first trimester of pregnancy and are responsible for transition of the proliferation phase to the invasion phase of the placenta and its well development (Fig. 3).

**Epidemiology**

In developed countries, the incidence of CHM is approximately 1–3 per 1000 pregnancies and those of the PHM about 3 per 1000 pregnancies. These moles are sporadic and not recurrent except for rare cases known as singleton cases (when a single family member has recurrent HM) and familial recurrent HMs (when at least 2 women have one or several HMs); where the genetic origin has been shown and correspond to an autosomal recessive disease with mutations in 2 genes, NLRP7 and more rarely, KHDC3L. The frequency of common moles varies considerably in developing countries, where cases are 10 times more likely in some Asian or African countries. These situations tend to have decreased with time due to the advances in medical monitoring.
and better sources of food. After one molar pregnancy, the chance of a second complete or partial mole is 1–2%. The risk of a third molar pregnancy increases substantially to 15–20% and is not decreased by changing partners and may be related to familial or sporadic biparental molar disease. More generally, it is considered that the risk of an additional mole in the next pregnancy is approximately 5–10 fold higher than the baseline risk for the “normal” population. However, the spontaneous rejection of mole formation has also been observed. Conversely, it is impossible to know whether it is more frequent with PHM. The difficulty, even today, is to obtain a correct diagnosis between partial and complete moles when these pathological entities are poorly developed during the first trimester of pregnancy. The term, partial mole was accepted in 1977 and coincides with the improved technology of ultrasounds. During the first trimester, the villi are not yet substantially hydropic and still present vessels. The classification of these tumors during this period of development presents many uncertainties. Higher frequencies of molar pregnancies are seen in the upper and lower extremes of maternal age; younger than 13–18 y or older than 45–50 y. The ratio of complete to partial moles changes significantly with age. It is higher in the upper extremes of maternal age, 63% for those aged 13–18 y and 55% to 93% for those aged 41–50 y respectively. The study by Savage and Williams provides detailed data regarding the risk of partial and complete molar pregnancies with increasing maternal age and confirms that the risk of partial molar pregnancy varies relatively little with age, while complete molar pregnancies contributing to the main component of the overall increase with age. This work shows that the PHM likely corresponds to fertilization anomalies observed in the general population unlike CHM (PHM are biparental but 2 spermatozoa are fertilizing).

The CHM are more frequently invasive than PHM. This malignant change in molar pregnancies seems to be associated with the male origin of the DNA. The possibility that heterozygous moles (see above) arising from 2 sperm fertilising the “empty egg” may have a higher risk of malignant change is another observation. Approximately 80% of the HM is self-limiting i.e., prevents itself from becoming invasive. The proportion of HM which change into invasive moles ranges from 7–17% or in rare cases 2–5% to a choriocarcinoma; a malignant, rapidly growing and metastatic cancer. 60% of all the choriocarcinoma are not preceded by a clinically recognized HM. The CHM carry approximately a 15% risk of malignant change, while the PHM have a much lower risk of malignant change; approximately 0.5–1%. The fact that these HM can be repetitive with different male partners rather suggests an underlying oocyte problem. Therefore, an important question to address would be; what is the karyotype of these moles?

Genetic background

Since the 1980s, several theoretical models have been proposed to explain the occurrence of these moles. In the case of complete moles, the oocyte would lose its nucleus just after sperm penetration followed by a duplication of the paternal chromosomes (Fig. 4A), unless 2 sperm are fertilizing (Fig. 4B). The oocytes may present a level of immaturity which could be responsible for a delay in the division of the female pronucleus when compared to the male pronucleus. Thus, during the first cell divisions of the zygote, this dysynchrony would promote the destruction / rejection of the maternal chromosomes. It may be observed, in rare cases of CHM, the presence of one maternal chromosome among the duplicated paternal chromosomes, which provides an additional argument for advocates of this hypothesis. Among the CHM, 80% to 90% have a diploid genome and are androgenetic. Among them, the majority are monospermic and 10%-20% are dispermic. The remaining 10% to 20% have a 2-parent genomic contribution to their genome.

In other rarer cases (1% CHM) (Fig. 4D), fertilization takes place between a healthy sperm and a haploid egg carrying a mutated copy of the gene NLRP7 (47 different mutations have been described) or KHDC3L gene (minor gene), which are probably involved in maintaining the integrity and organization of the oocyte cortical region and the orientation of cells in the pre-implantary embryo toward the formation of the trophoblast or embryo. This results in biparental diploid CHM that are recurrent in the same woman, which is not the case for androgenetic moles (the most common moles) that are generally sporadic and non-recurrent. Once again, we find that with these recurrent moles, the expression of the mutated genes responsible for the abnormal differentiation of oocytes, which corroborates our earlier hypothesis regarding the oocyte immaturity. For partial moles, fertilization takes place between the oocyte and 2 sperm (or more rarely with a diploid sperm). The zygote is thus triploid (Fig. 4C). In rare cases the PHM have also been reported with other karyotypes (diploid biparental, triploid dyginic, tetraploid triandric). These explanations were reconsidered in 2003 by Golubovsky. He points out that (1) it would need a regular “stock” of anuclear oocytes in order to ensure the frequency of the CHM, (2) the empty oocytes can be obtained “in vitro” but question their viability “in vivo” and/or whether they can be fertilized (3) in the case of
twins, of which one is a CHM and the other a fetus, it has been observed that the prevalence of CHM diploids is androgenetic 46XX, which can be explained by diploidization concept and the monozygotic origin of such associations (Fig. 4C). With regards to the first remark, the fast disappearance of the maternal chromosomes in the zygote is presented and not in the oocytes, which avoids the problem of the stock of empty oocytes. To explain the appearance of a complete mole, Golubovsky suggests a haploid oocyte fertilized by 2 spermatozoa. During the first divisions, the triploid zygote would be at the origin of a cellular clone with 2n chromosomes and of another with 1n paternal chromosomes. The 2n clone will form a normal fetus and the clone with 1n after endoreplication of the chromosomes will give rise to a CHM (twin fetus) (to refer to Fig. 4C). From the epide-
miologic point of view, the frequency of these triploidies (1% of all the conceptuses) logically could include all the types of HM, in particular the partial moles as they are of triploid origin. It should be noted that the frequency of the triploidies obtained by digyny increases with the age of the patient, contrary to the triploidies obtained by diandry that are more frequent in the younger patients. Thus, the number of PHM of dispermic origin are reduced with the age of the patient. This new explanatory framework proposes that the oocyte presents an abnormal cortical reaction which would support the entry of 2 spermatozoa (normally, the release of the cortical granules enzymatic contents prohibits the access to the oocyte to more than one sperm). These various hypotheses assume that the differentiation of the oocyte was inadequate, which reinforces the hypothesis of an immature oocyte. Other observations show that the nutritional environment of the woman during her pregnancy can also be responsible.

### Epigenetic factors

Numerous risk factors for molar pregnancies have been suggested, including paternal age, maternal genetic anomalies, blood group, oral contraceptives, maternal age and environmental factors; in particular vitamin A and the folates. However, the only clear data is related to maternal age and the previous occurrence of a prior molar pregnancy. The excess risk is rather associated with CHM and less with PHM. Despite this, findings from various studies in animals show that diet can reset the genetic imprint, which is important for the normal development of the human embryo. Moreover, a deficit of vitamin A or/and of folates during the period...
of 18 to 21 d of gestation is associated with an absence of vascularisation of the placental villosities,\textsuperscript{65} which is observed in the CHM. It is also noted that a reduction in vitamin A in the food of the patients at the time of their pregnancy could explain the geographical distribution of these moles.\textsuperscript{64}

Our recent study\textsuperscript{65} carried out in Morocco and Senegal, where the annual cycle of the seasons is defined with one period of severe diet (limited fresh products), showed a strong correlation between the nutritional deficit of the mothers at the time of the conception of their daughters and the development of a CHM during the pregnancy of the daughters as an adult. It is mainly a deficit in vitamin A and/or B9 (folates) during the first weeks of the development of the female fetus which could deteriorate the normal differentiation of their oocytes. Vitamin A plays a significant role in the progress of meiosis; its insufficiency is responsible for the development of an immature oocyte\textsuperscript{66,67} and prevents meiosis II from being carried out correctly.\textsuperscript{68} The folates are necessary for the synthesis of proteins and the DNA. Their effects were observed on the one hand, in the differentiation of the oocyte and the zygote, in particular to the integrity and organization of the cortical zone\textsuperscript{51} and on the other hand over the instability of the chromosomes of maternal origin.\textsuperscript{69} At the time of fertilization, the male pronucleus continues its mitotic division; the chromosomes of the female pronucleus would be destroyed or rejected quickly. Moreover, vitamin A and folates intervene in the mechanisms of the DNA methylation during the reprogramming of the parental imprinting. Contrary to other human genes, these genes (approximately 1% of the genome) are expressed only in a monoallelic way according to the paternal or maternal origin of the zygote chromosomes. It is the existence in the Human species of these imprinted genes that prevent the parthenogenesis\textsuperscript{70} and allows the successful development of the human embryo. Such deficits that occur during oogenesis are responsible for the qualitative and functional anomalies of the oocyte.\textsuperscript{61} Such methylation defects affect the imprinted genes in the oocyte. The maternal methylation disappears and is replaced with paternal methylation. Undoubtedly this is one of the reasons why the affected women may have HM with various sexual partners.\textsuperscript{71}

Other studies carried out in Hawaii where the risk of CHM is weak, show that the women whose migration toward Hawaii was recent; present a high rate of CHM. In fact, these women were born in the Philippines where this rate of CHM is high. The Japanese women who settled in Hawaii, but whose migration is much older, do not present any additional risk (Japan at the time was a high-risk country).\textsuperscript{72} Moreover, in Japan between the years 1974 and the 2000, the incidence of the HM significantly decreased by 2.79/1000 alive births in 1976 to 1.61/1000 in 1997. However, this regression is associated only with the fall of the CHM which decreased from 1.71/1000 alive births in 1985 to 0.49/1000 in 2000 and not to the PHM. Nonetheless, the first were shown to be androgenetic while the latter were shown to be triploid diandric. After the deprivations of the war (1937–1945), the economic conditions gradually improved and the gametogenesis among women gradually normalized, explaining the reduction of the CHM.\textsuperscript{73} The PHM which are mainly the result of the anomalies of the process gametogenesis/fertilization in the human species are not influenced by such variations in the nutritional environment.

In conclusion, the data suggests that it is the mother of the patient with the mole occurrence who is responsible for this pathology and not the patient themselves. This can be attributed to the transgenerational effect.\textsuperscript{65} Finally what is known about the history of the HM remains partly an enigma.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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