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The involvement of the trans-generational effect in the high incidence of the hydatidiform mole in Africa

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ABSTRACT

Introduction: While the incidence of various chromosomal anomalies observed, including triploid partial moles is independent of the socio-economic level, higher incidences of complete hydatidiform mole "CHM" is generally associated with under developed areas. Moreover, studies have shown that some nutritional deficiencies are related to the abnormal development of oocytes and placenta. In Senegal and Morocco, the annual seasonal cycle contains one period with food shortages and the incidence of complete moles is significant. Accordingly, accurate statistical analyses have been performed in these two countries.
Methods: Each month during a one year period, we investigated the occurrence of normal conceptions, molar conceptions and the conception of the future patients in Senegal and Morocco. The comparisons of the conception dates for these three types of conception were analyzed using the Chi-squared test.
Results: 94% of the patients were conceived just prior to the period in the year with food shortages. Consequently, the development of the female embryos occurred under nutritional constraints, which negatively affect the recruitment of the vital factors required for the normal synthesis of DNA, proteins and placental differentiation.
Discussions: A nutritional deficiency in the mother at conception of their daughter (future patient) is implicated in the higher incidence of CHM in their daughters' filiation. These nutritional deficiencies during the first weeks of pregnancy will have repercussions on the normal development of the oocytes. Accordingly, these developmental impairments take place during the embryonic life of the future mothers of complete moles and not during the conception of the moles themselves.

1. Introduction

The hydatidiform mole belongs to the pathologies of gestation in which the trophoblast proliferates in an anarchistic manner and where the chorionic villi become hydropic (Fig. 1). It can be associated with embryonic tissues (partial hydatidiform mole: PHM) or with a complete lack of these tissues (complete hydatidiform mole: CHM). This abnormal proliferation of the trophoblastic cells could be a result of nutritional deficiency, particularly vitamin A [1–3] and the folates [4,5], an expression disorder of the variant hyperglycosylated hCG [6], or a defect in the methylation of imprinted genes [7]. These hypotheses can be modulated by the age and ethnic origin of the patient [8,9]. From a genetic viewpoint, hydatidiform moles are the only pathologies that can be of androgenetic origin. However, their genotype is variable according to the karyotype of the oocyte and the mode of zygote formation during the fertilization. This zygote can be diploid biparental, diploid androgenetic monospermic, diploid androgenetic dispermic, triploid diandric dispermic, triploid digynic, tétraploid triandric, aneuploid or mosaic. The situation can be further complicated as we cannot assign the specific mole type to a corresponding genotype. But, the

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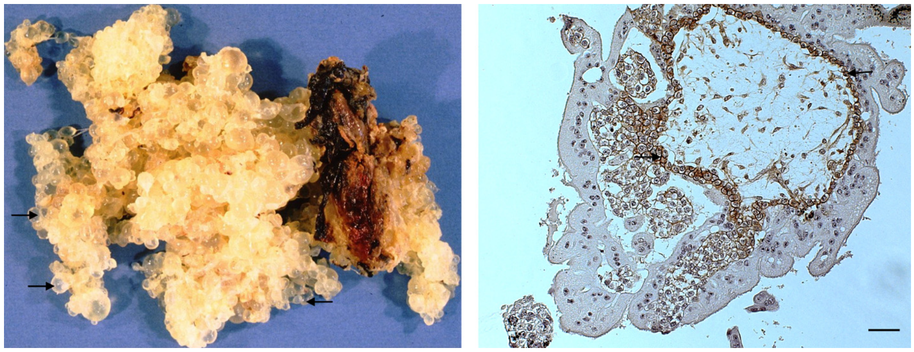

Fig. 1. Second trimester CHM after blood removal. (1) Macroscopic observation: note the absence of embryo and the grape-like appearance of the chorionic villi (arrows). (2) Histology with β-catenin staining of hydropic villi. Arrows show the cytotrophoblast (scale 50 μm).

great majority of CHM are diploid androgenetic, the other genotypes reported here are a minority of cases [10].

When the mole is formed, in particular if it is a CHM can become invasive or give rise to a gestational choriocarcinoma [11,12]. The frequency of these molar pathologies can vary from less than 1/1000 pregnancies in western countries to over 1/400 in developing and undeveloped countries [13–15]. The risk of developing a choriocarcinoma after a complete mole is approximately 1000 times more likely than after any pregnancy event [16]. The development of these molar pathologies remains difficult to understand. Their progression is difficult to evaluate, even after the evacuation of molar tissue [3,17].

These data and the fact that: (1) these CHM are sporadic and not recurrent, (2) in the literature some CHM contain small amounts of DNA of maternal origin [18], (3) some CHM arising from dispermic fertilization [9], strengthens our hypothesis leading us to consider that the starting point of these molar pathologies is not a genetic mutation but rather the inaptitude of the oocyte to undergo normal embryonic development.

We studied the monthly data from normal and molar conceptions as well as the dates of conception of women who will subsequently bear a complete mole (these women will be referred to here as the patient) in two areas, Senegal and Morocco. In these two countries we observed bioclimatic cycles with one period of transition during which food substances rich in certain vitamins were reduced and there was a high incidence of moles. Moreover, the women who will subsequently generate a CHM primarily developed their ovaries during this period of transition of the seasonal cycle (period of the year with significant food shortages), whereas the normal and molar conceptions date were not associated with the seasonal cycle.

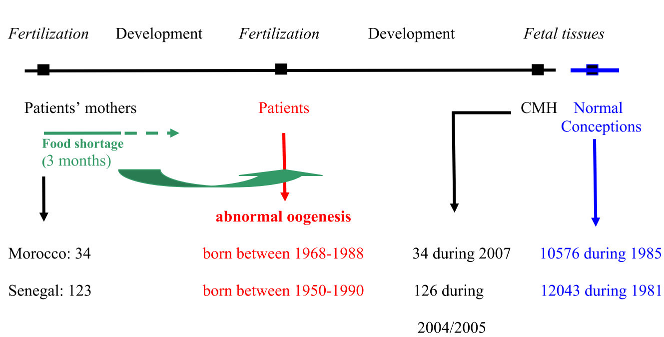

Fig. 2. Types and number of samples. Kinetics of the nutritional deficit related to oogenesis of the patients. In green, showing the food shortage effects on the embryonic development of the patients (girl) in the uterus of their mother, when these mothers undergo these nutritional difficulties during the first three months of their pregnancy.

2. Materials and methods

2.1. Study groups

The patients that had a CHM were recruited in the hospitals in Dakar in Senegal and Casablanca in Morocco. These two countries present agricultural cycles associated with seasonal cycles. In all cases, echographic, anatomical and histological interpretations of uterine pathological tissues were carried out. Biochemistry of the βHCG was also interpreted. The data was obtained from the registers of these hospital departments, particularly by analysing the dates of the last menstruations of the patients. The most frequent age of these moles was three months, because the women presented several clinical signs at these dates (pains, bleedings) causing them to consult. We cannot be certain in these cohorts which CHM case was a CHM of androgenic origin. However, the literature shows that the presence of a CHM of another origin, in particular diploid bi-parental, is lower than 10%. Accordingly Jacobs and Couillin in Hawaii and Senegal had respectively observed 1/19 in each case [19,20]. To perform the statistical studies we investigated the calendar distribution of:

- normal conceptions
- molar conceptions
- conception of the patients (their mothers pregnancy)

2.2. Data analysis (Fig. 2)

To compare the number of conceptions during the climatic and agricultural cycles it was necessary to collect the data of these conceptions each month over one year. Consequently, we were able to analyze the conceptions of patients between the years 1950–1990 for Senegal and the years 1968–1988 for Morocco. We studied 123 conception dates of the patients in Senegal and 34 in Morocco. These patients conceived 126 mol in 2004/2005 in Senegal and 34 mol were conceived in 2007 in Morocco. The normal reference (normal conception) corresponded to the two years where we obtained a large number of reliable data, the years 1981 for Senegal and 1985 for Morocco.

The comparison of the conception dates each month during one year for the normal fetuses, the hydatidiform moles and the patients were analyzed using the Chi-squared test and the confidence intervals were defined. As a control we studied the calendar distribution of the conception (between 2006 and 2008) of 219 patients (with future molar pregnancy) born in France between 1952 and 1989.

3. Results

The results are presented in Figs. 3 and 4. In Senegal (Fig. 3) we observed a significant reduction in normal conceptions (curve A) during the period preceding the harvest period (food shortage period). The number of molar conceptions progresses at the same time as that of the normal conceptions (curve B). On the other hand, the period of the year during which the patients were conceived oscillates around a peak, which is present just before the food shortage period (curve C, $\chi^2 = 20.66$; $p < 0.05$).

In Morocco (Fig. 4) the number of normal conceptions presents few variations during the year, except around May/June, which represents the beginning of the food shortage period, where a decrease was observed (curve A). The number of molar conceptions (curve B) does not present any differences during the year compared to the normal conceptions. Conversely 94% of the patients were conceived during the April–July period with a peak