CASE REPORT

Partial Hydatidiform Mole with Alive Pre-term Foetus: Case report.

Short title: Partial Hydatidiform Mole with Alive Pre-term Foetus.

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Abstract

**Background.** Partial hydatiform mole (PHM) with an alive foetus is exceptional (0.005% to 0.01% of all pregnancies).

**Case presentation.** Here we report a case of a 33-year-old multiparous woman. The diagnosis of PHM was suspected late, at 28 weeks gestational age. After a spontaneous initiation of the labour, at 34th weeks gestational age, she gave birth to a normal living baby. Histopathology of the placenta confirmed the PHM while the karyotype of the new-born was 46XX. The level of beta chorionic gonadotropin (βHCG) was negative after three weeks post-delivery. Currently, the child is two years old with normal psycho-motor development.

**Conclusions.** Despite the multiple and serious complications that may arise in patients with PHM, a favourable outcome is possible.

**Keywords:** alive foetus; diploid karyotype; management, partial hydatidiform mole; ultrasound.
Introduction

Gestational trophoblastic disease (GTD) is a heterogeneous group of pregnancy related disorders, characterized by abnormal trophoblastic proliferation. GTD encompasses hydatidiform mole (HM), which is considered to be a preneoplastic condition and gestational trophoblastic neoplasia (GTN) or gestational trophoblastic tumor (GTT) namely: invasive mole, choriocarcinoma (CC), placental site trophoblastic tumor (PSTT), epithelioid trophoblastic tumor (ETT) and mixed trophoblastic tumor. Among tumor like conditions, exaggerated placental site reaction (EPSR) and placental site nodule (PSN) are included (Figure1) [1, 2,3].

PHM is more common than the complete hydatidiform mole (CHM) with an incidence of 3 per 1000 pregnancies [4, 5]. The development of persistent gestational trophoblastic disease is observed in 0.5 to 3 % of cases [6] while the risk for CHM is 15 to 20% [2]; The risk of developing a trophoblastic tumor after PHM is <0.5% and 2% - 3% after CHM [1]. Much rarer, the PHM with coexisting foetus has an incidence of 0.005%–0.01% [7, 8]. According to our research, this was the 49th case of partial molar pregnancy with diploid foetus as of 2021 [9].

PHM is classically triploid and contains an additional haploid set of paternal chromosomes, giving a total of 69 chromosomes. In up to 90% of cases, the paternal triploidy is derived from dispermic fertilisation of a haploid egg with unreduced diploid sperm (diandric triploidy is the case in more than 80% of triploidy). Also, digyny is responsible for more cases of triploidy than previously thought. Digynic triploidy may be the result of fertilisation of a diploid ovum by a single sperm, with the diploid ovum being the result of an error in either the first (MI) or second (MII) meiotic division [10]. Furthermore, tetraploidy and mosaicism are reported in very rare cases in literature with coexistence of triploidy-diploidy or triploidy-diploidy-euploidy. Those cases explain why some extremely rare singleton foetus survive in the first trimester [11].

It is difficult to explain the events leading to different cell lines and therefore to placental mosaicism. Some authors assume that mitotic anomalies are bound to occur in the post-fertilization period, even at the first post-zygotic division [12]. Amniocentesis and placental sampling are used to identify the foetal karyotype. However, fluorescence in situ hybridization (FISH) is the most used method. Currently, the value of immunohistochemical analysis of p57 expression and molecular genotyping is demonstrated in a number of studies. These techniques exploit the unique genetic features of molar and non-molar specimens to improve diagnostic accuracy. It is also a potential marker that may help to distinguish PHM from CHM [13, 14].

PMHs share the same risk factors as other trophoblastic diseases, however several studies demonstrated that age does not significantly affect the incidence of PHM contrary to CHM [15]. Because of triploidy, the foetus is often the carrier of congenital malformations incompatible with life and growth restriction related to a poorly performing placenta resulting in intrauterine foetal demise. In addition, the woman is exposed to several life-threatening complications.

The coexistence of a PHM and alive diploid foetus is a real dilemma in pregnancy management, the woman must be counselled regarding the maternal and foetal complications. In this article, an unusual case of PHM with alive normal foetus is reported.

Case Presentation

A 33-year-old patient; G2P2 (1 caesarean section – tween pregnancy), 0Rh+, no consanguinity, with no relevant past. During the first trimester, the clinical exam, the initial scan, and the prenatal check were apparently normal; the 8HCG measurement was not carried out. She did not suffer from vaginal bleeding or abdominal pain but reported excessive nausea and vomiting.
At the 20th week of amenorrhea; the patient’s second ultrasound (US) showed a Swiss-cheese appearance in a portion of the placenta, raising suspicion of PHM, without other alarming signs concerning the insertion and the size of the rest of the placenta. The patient was referred to a maternity ward of the public hospital of Bologhine Ibn Ziri in Algiers. She was admitted at 28 weeks gestational age, hemodynamically stable (blood pressure: 110/60 mmHg); weighting 75 kg; without oedema, abdominal or pelvic pain. The uterine size was consistent with gestational age. Blood tests indicated haemoglobin level of 11g/cl; platelet count, liver and renal function test, 24 urinary proteins and thyroid function were normal while the βHCG level was at 50.773 mIU/ml. The US showed a singleton foetus with heart rate of 140 times/min, with normal morphology, biometry, and amniotic index fluid. The placenta implanted in the fundus of the uterus was abnormally thickened with focal area including multiple cystic like snowstorm (Figure 2) and no boundary between the normal placental tissue and the cystic one. The diagnosis of PHM with normal foetus was suspected.

The multiple risks were clearly explained to the patient by the medical staff and the decision to continue the pregnancy under strict observation was discussed with the couple who rejected the idea of termination of the pregnancy and refused performing genetic amniocentesis. A second dosage of βHCG was at 47.215 mlU/ml at 30 weeks of amenorrhea, in addition the follow up did not detect any abnormalities.

At 33 weeks of gestation, the patient was admitted to the emergency room due to beginning of the labour. She presented in good general condition. A caesarean section was performed for a foetus with breech presentation and a scarred uterus, under spinal anaesthesia and after antibiotic prophylaxis. Alive female foetus was delivered; Apgar score 7 / 9 (1st minute / 5th minute); weighting 2200 g. The new-born physical examination was strictly normal (Figure 3). A complete single placenta was removed, with molar changes reaching up to one third of the total placental volume (Figure 4). The uterine cavity was cleaned, and uterine wall was closed in a double layer. Blood loss was estimated at 400 ml. The diagnosis of PHM was confirmed by histopathology.

The patient was discharged in a good general condition after two days and a hormonal contraception was prescribed. A βHCG monitoring was done once a week until negative. After the caesarean section, the βHCG level decreased to 300miu/ml, then to 82miu/ml and was negative after the third week post-delivery. It was stopped after three negative results. The karyotype of the new-born was 46XX.

Discussion

PHM coexisting with a normal alive foetus as seen in our case is very rare [16]. Histology remains the gold standard for diagnosing PHM [17]. In the majority of cases early diagnosis of PHM leads to termination of the pregnancy due to either the frequency of triploidy [18] or maternal risks and the possibility of the progression to trophoblastic disease. The common maternal symptoms are: vaginal bleeding (27%) in the first trimester, an early preeclampsia before 20 weeks of gestation (18%) raised in case of fetal triploidy (41%) [9] especially, an hyperemesis gravidarum, an hyperthyroidism, an anaemia, a preterm delivery, and a disproportionate increase in the size of the uterus with high βHCG levels, often greater than 100,000miu/ml [19].

In some extreme situations, the woman is exposed to the risk of severe bleeding requiring a hysterectomy and a trophoblastic pulmonary embolism. Foetal complications include abortion, congenital abnormalities, foetal anaemia, intrauterine foetal demise, preterm birth and intrauterine growth restriction (IUGR) which is observed in 70% of the fetuses in the case of triploidy [20]. For this reason, the placenta should be examined with histological diagnosis in the face of any foetal or maternal complication.
The only clinical sign our patient presented with was hyperemesis gravidarum. Her first clinical check and US did not suspect any abnormality. A misdiagnosis is not uncommon [21], because not all ultrasonographers pay attention to the placenta appearance or the size of ovaries, mostly when there is a foetal heartbeat, which is reassuring in the first trimester [22]. Recent studies [21] have shown that ultrasonography is much more accurate in diagnosing CHM than PHM. Detection rates of CHM have been reported at 58% to 95%, and at 17% to 29% for PHM. Jackie A. Ross [21] suggested that there has been an increase in both the predictive value and the sensitivity of US over time in the diagnosis of molar pregnancy particularly for PHM. In PHM, there is a cavity, sometimes larger than it should be, including a ratio of the transverse to anteroposterior diameter of the gestational sac (GS) of more than 1.5 [22], with a thick echogenic placenta associated with small anechogenic cystic spaces (honey comb, Swiss cheese or snow storm-like), an amniotic cavity can be found; either empty or containing a yolk sac, with or without an embryo. Also, US scan reveals multiple thin septa within the GS [22]. The power Doppler US shows marked focal hyper vascularity of the placenta [22], in addition less often, lutein ovarian cysts can be visualised.

In the group of GTN, invasive mole can be identified during the US by the presence of heterogeneous myometrial nodules or masses with hypervascularity on color Doppler. The rarity of PSTT and ETT makes diagnosis challenging. US features are similar to other forms of GTN with the presence of heterogeneous myometrial nodules or masses; ETT expands with sharp borders and PSTT penetrates between myometrium muscle fibers [23]. Choriocarcinoma has variable sonographic features but always with hypervascularity on color Doppler [24].

At the second trimester of pregnancy the diagnosis is easier, the cystic changes of the placenta are more obvious, the foetus may be alive but with many bony, cerebral, cardiac, renal, or digestive malformations or with intrauterine growth restriction. Only in rare cases, the foetus can be morphologically normal. It is simpler to identify the changes of molar pregnancy when gestation is more advanced [22, 25], the villi are more hydropic, and the tissue mass is more important. In the case described, a PHM was suspected at 28 weeks of amenorrhea when the US check revealed a focal aspect of honeycomb-like echo in the placenta without any further foetal abnormalities.

All the possibilities had to be considered since it is known that molar pregnancy coexisting with a normal alive foetus is not necessarily a PHM. Three types of molar pregnancy concomitant with a normal foetus have been identified so far [26]: the first type and the most common is twin pregnancy with a normal foetus, a normal placenta and another CHM, the second type is twin pregnancy with a normal foetus, normal placenta and another PHM. The third and most uncommon is a singleton normal foetus with PHM pregnancy. In the case of twin pregnancy, usually there is a clear line between normal and molar placenta. There is also an effective way that could exclude the twin pregnancy, by following the foetus umbilical cord. If it links with the molar placenta, we conclude that it is a singleton foetus with PHM, but if it links with normal placental site, differentiation of two structures is not possible by ultrasonography [7]. In this case, the umbilical cord linked with the molar placenta and the boundary between the normal placental tissue and the cystic one was not clear, no signs of placental separation could be found, hence a twin pregnancy was eliminated. We had to consider other differential diagnosis as the chorioangioma, generally characterized sonographically by an intraplacental structure of different echogenicity, well-circumscribed which may protrude into the amniotic cavity. Its US diagnosis is based on increased vascularity or a large nourishing vessel with the same pulse frequency as in the umbilical cord. This characteristic is generally absent during the US scan in molar placentas as it was in the case at hand [7]. Furthermore, we thought about the placental mesenchymal dysplasia (PMD) which shows at the US examination a thickened placenta (placentomegaly) with hypoechoic areas, absent or low venous signals inside. Dilated chorionic vessels can be associated with foetal growth restriction (IUGR) in the majority of cases, with a Beckwith–Wiedemann syndrome (BWS) or intrauterine foetal demise (IUFD) but can also be associated with
normal appearing foetus [27]. PMD is more likely to be associated with elevated AFP levels, although it may present with an increased HCG level (38%) but less than a molar pregnancy [28]. In the reported case, similar sonographic findings were noticed between the two entities. The AFP level wasn’t done, the serum βHCG was at 50773mIU/ml. The diagnosis of PMD was eliminated after birth by histological examination of the placenta. Lastly, a normal pregnancy with myoma in necrobiosis can take the aspect of PHM with typical hyperechoic, iso echoic intra myometrial structures and anechogenic foci, that is misleading [29], but the absence of the peripheral vascularization aspect as found in the myoma makes the difference.

The survival of singleton normal foetus with PHM depends on several factors [30]. The foetal prognosis is better if the karyotype of the foetus is normal, the molar placenta is smaller than the normal one, the molar degeneration has a low speed, and there is no foetal anaemia. Regarding the maternal prognosis, it depends on the maternal complications such as pre-eclampsia. In the current case, even though the karyotype was not done (the parents refused performing genetic amniocentesis), the other factors were reassuring. Actually, no maternal complications were noticed, and the molar placenta occupied a third of the total placenta’s volume where a tendency towards a slow degeneration speed was observed and there were no signs of anaemia, so the cerebral Doppler has not been done. In most PHM, the foetus has a triploid karyotype and presents anatomical malformations. When the karyotype is diploid, a normal alive foetus can be expected [31, 32], although the placenta can have some variation, from diploidy of the amnios to triploidy of the chorionic villi. In our case, the karyotype of the new-born revealed a 46XX without any abnormality. In successful PHM outcomes with viable foetuses, the serum βHCG level usually starts to decline from the beginning of the second trimester. The βHCG level of the reported patient wasn’t so high and it’s common to the PHM if we compare to CHM. The molar placenta occupied the third. The follow up of the patient showed a tendency to a slow degeneration speed. The foetus grew normally without diagnosed malformations or signs of anaemia; this explains why a cerebral Doppler wasn’t done. The reported patient didn’t develop any complications. All this data were in favour of a conservative approach under a close monitoring.

In the 33rd weeks of amenorrhea, the patient did consult at the gynaecology emergency for a starting labour. She had a caesarean section for a breech foetal presentation and a scarred uterus. A live preterm female infant weighting 2200g with an Apgar score of 7 at 1minute and 9 at 5 minutes was delivered. Only one placenta was completely extracted. It confirmed the presence of focal molar aspect within the normal placenta, reaching up to one third of the total placenta’s volume. The microscopic findings confirmed a partial molar placenta. After the caesarean section, the βHCG following was stopped after three negative rates obtained after the third week post-delivery.

Generally, Follow-up of PHM is concluded once the βHCG has returned to normal on two samples, at least 4 weeks apart [33]. The probability of postpartum development into persistent trophoblastic disease varies between 0, 5% and 3% which is much lower than that for CHM. Therefore, chemotherapy is rarely needed and most often no metastasis occurs. Literature on obstetric outcomes following molar pregnancy is poor; A meta-analysis done on 2021 by Vito Andrea Capozzi et al showed that a live birth rate after complete mole was statistically higher compared to the live births after partial mole.

Besides, patients with partial molar pregnancy were more likely to develop a subsequent partial molar pregnancy. Patients with molar pregnancy should be reassured about subsequent pregnancies since adverse obstetric outcomes in terms of ectopic pregnancies, stillbirths, preterm birth, termination of pregnancy, and miscarriage were rare events with an incidence comparable to the general population [34]. Except in patients treated with Chemotherapy for GTN, ovarian function may be affected, especially when multiple agents are administered; therefore, ovarian tissue cryopreservation is advised [24].
PHM with a live foetus can have a good outcome with a delivery of a normal infant [18, 35]. We propose a management of PHM with an alive foetus which is outlined as an algorithm in (Figure 5). It is developed according to the review of literature and based on the available and cited evidences. [9, 19, 20, 26, 29, 30, 36-39].

Conclusions
This case is of particular interest because it demonstrates an atypical presentation of a PHM which went unnoticed in the first trimester hence the interest of being meticulous at this stage of pregnancies and knowing the evocative signs of PHM. At the second trimester of the pregnancy the diagnosis is easier, based on the clinic symptoms, evocative US signs and βHCG level. Nowadays, it is reasonable to offer expectant management to PHM with an alive foetus with close monitoring and delivery at term. This is however conditioned by having the couple’s agreement, no major foetal malformations, a normal foetal karyotype, and no severe maternal complications. The management of such a pregnancy remains a real challenge but it is worth it, however.

Compliance with Ethical Standards

Author’s contribution:
L.B provided the medical care to the patient including the monitoring and the surgery. L.B, Z.K, I.D, A.A and A.DD conceptualized the case report; collected data and wrote the manuscript draft; Bruno V and Djokovic D reviewed the manuscript; all authors approved the final manuscript.

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References


Figure 1. Group of GTD according to the WHO classification 2020.

Figure 2. Focal cystic aspect within the placenta.

Figure 3. New-born baby with normal physical appearance.
**Figure 4.** The molar part has been detached from the placenta and represented up to one third of the total placental volume.

**Figure 5.** Algorithm of the management of partial molar pregnancy with an alive foetus.