

# Partial mole with coexistent live fetus: A systematic review of case reports

✉ Mishu Mangla<sup>1</sup>, ✉ Harpreet Kaur<sup>2</sup>, ✉ Kavita Khoiwal<sup>3</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Hyderabad, India

<sup>2</sup>Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Bilaspur India

<sup>3</sup>Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, Rishikesk, India

## Abstract

**Objective:** Molar pregnancy coexistent with a live fetus can be a diagnostic and therapeutic challenge. With increasing incidence of multiple pregnancies, there has also been an increase in twin pregnancy with one mole in the recent years. The authors discuss the epidemiology, clinical presentation, and prenatal diagnosis and attempt to design a possible management strategy, to help guide the treating physician, in the management of partial mole with live pregnancy, thereby improving maternal and fetal prognosis.

**Material and Methods:** Numerous case reports have been published in various journals regarding management of individual cases of partial molar pregnancy coexistent with live fetus (PMCF). Therefore, we conducted a systematic review of all the case reports and short case series in English concerning partial mole with live pregnancy from 1999 to 2019, that is in the last 20 years.

**Results:** In total, 44 case reports of PMCF were analyzed. The mean gestational age at diagnosis was 20+6 (range: 10-40) weeks. Less than half (19/44; 43.2%) were asymptomatic at the time of detection and PMCF was detected on routine scan done for fetal well-being or 11-13-week scan. The majority (56.8%) resulted in the birth of a healthy live fetus. Gestational trophoblastic neoplasia developed in 3/44 (6.8%).

**Conclusion:** PMCF involves a high risk of bleeding, preterm labour, intrauterine growth restriction and stillbirth. Successful management of such cases needs prenatal diagnosis, antepartum surveillance and post-natal follow-up. An obstetrician, maternal fetal medicine specialist, gynecology oncologist and neonatal intensivist should be involved in the care of such pregnancies. (J Turk Ger Gynecol Assoc 2022; 23: 83-94)

**Keywords:** Partial hydatidiform mole and coexistent live fetus, GTN, partial molar pregnancy, sad fetus syndrome

**Received:** 02 November, 2021 **Accepted:** 20 March, 2022

## Introduction

A molar pregnancy coexistent with a live fetus, also known as sad fetus syndrome is a rare phenomenon with an incidence reported to be approximately 0.005-0.01% of all pregnancies (1). Molar pregnancy results from genetically aberrant conceptus. Usually, the complete mole has 46 chromosomes but all are of paternal origin, as an empty egg is fertilized by a sperm with duplicate genetic material. A partial mole usually results from dispermic fertilization of a haploid normal ovum resulting in a triploid zygote or monospermic fertilization with duplication of the paternal haploid chromosome, whereas

the complete mole is result of fertilization of an empty ovum by a sperm (2). Though much rarer, there can be cases of mitotic abnormalities in the early post fertilization period, a form of placental mosaicism (3,4). USG in early pregnancy is the diagnostic tool to detect the majority of molar pregnancies. Though molar pregnancy can have varied presentation, most molar pregnancies present either as missed miscarriage or anembryonic pregnancy. Suction evacuation of products of conception followed by histopathology is confirmatory for diagnosis of a molar pregnancy (5). Women carrying a female fetus are more likely to have partial mole than mothers carrying a male fetus, with a ratio of 3.5:1 (1).



**Address for Correspondence:** Harpreet Kaur

e.mail: drharpreetsidhu7@gmail.com ORCID: orcid.org/0000-0001-7800-0076

©Copyright 2022 by the Turkish-German Gynecological Education and Research Foundation - Available online at [www.jtgga.org](http://www.jtgga.org)

Journal of the Turkish-German Gynecological Association published by Galenos Publishing House.

DOI: 10.4274/jtgga.galenos.2022.2021-9-11

There is evidence in cases of twin pregnancy when one fetus dies in utero, the effect on the other fetus may be the immediate demise of the other twin, an effect on cognitive development of the surviving twin and/or effects on the maternal coagulation system. With the increasing incidence of multiple pregnancies, mainly as a result of assisted reproductive technologies, there has been an increase in the twin pregnancy rate with one fetus presenting as partial mole in the recent years. These pregnancies are considered high risk pregnancies and need thorough counselling (6). Though termination of pregnancy remains an option taking into account the high incidence of complications in these pregnancies, many women, especially those who conceive after years of infertility treatment, may choose not to go for termination. There should be informed decision making after providing adequate information about the chances of a live birth (about 50%) and risk of maternal and fetal complications (7). One of the major concerns in these women is the risk of gestational trophoblastic neoplasia (GTN), and whether this risk will increase further with continuation of pregnancy needs to be discussed with individual patients. GTN in general can have a varied clinical presentation and can present at variable interval of time after index pregnancy (8).

From the clinical perspective, pregnancy with partial mole can be of the following two types. The most common type is a dichorionic twin pregnancy with one sac containing a normal euploid fetus and placenta and the other sac containing the molar pregnancy, which can be either complete or partial mole. The other possibility is a singleton pregnancy with focal areas of degeneration affecting small to large placental areas (9).

It is very important but difficult to differentiate a singleton pregnancy with focal molar changes in the placenta from a twin pregnancy with one normal fetus and the other complete mole. A method which has been suggested to differentiate the two conditions is to follow the placental insertion site of the umbilical cord and, if it attaches to the molar placenta, it suggests singleton pregnancy with focal mole whereas if it attaches to a normal placenta it is more suggestive of twin gestation (10). Other important differential diagnosis of partial mole in case of twin pregnancy includes placental mesenchymal dysplasia (confirmed on histopathology) (11,12). Differential diagnosis also includes placental tumor, such as chorioangioma. However, this is usually a well circumscribed lesion with a different echogenicity from the rest of placenta, protrudes into the amniotic cavity, shows increased vascularity along with a feeding vessel with flow synchronous with the umbilical artery on Doppler (13).

Cases of partial mole with a coexistent live fetus (PMCF) present a diagnostic and management challenge to the treating obstetrician. Most of the literature available is in the

form of case reports with varied presentation. Therefore, we performed a systematic review of cases of PMCF published in the last 20 years to examine the epidemiology, clinical presentation, prenatal diagnosis and to attempt to define a possible management strategy, to help guide the treating physician, thereby improving maternal and fetal outcome.

## Material and Methods

This being a systematic review of case reports ethics committee approval was not sought as systematic reviews are exempted from ethics review.

An electronic search of Scopus, PubMed, Embase and other databases was conducted for case reports and case series of PMCF, published in English from 2000 to 2019. The electronic search strategy was done using keywords, such as “partial mole with live fetus” and “mole with live fetus”, “twin pregnancy with partial mole” and “hydatiform mole”, and “coexistent fetus” and “sad fetus syndrome” and “case reports”. We analyzed the title and abstracts of all case reports identified by the initial search. The reference lists of relevant reports were also explored. The data was double checked by two reviewers to avoid duplication.

The systematic review was planned and reported according to the preferred reporting items for systematic review and meta-analyses guidelines.

Published case reports and case series of partial mole coexistent with a live intra-uterine pregnancy at all gestational age were included in this systematic review. Case reports with complete hydatidiform mole coexistent with live fetus and case reports of partial molar pregnancy without live fetus were excluded. Review articles, original articles, clinical trials, conference abstracts, editorials, poorly described cases, articles in language other than English language or commentary were also excluded.

We extracted information, such as geographical distribution or country of occurrence of the case, year of publication, age of the patient at the time of presentation, gestational age at diagnosis, the time of delivery and the final outcome of the case in the form of live birth or abortion or induced termination and summarized it in a master chart. The various obstetric and medical complications that developed during the course of pregnancy were documented, such as miscarriage and gestational age at the time of miscarriage, pre-eclampsia and gestational age at which it developed, gestational diabetes, intra-uterine growth restriction, stillbirth, and preterm labor before 37 completed weeks of gestation. A note was also made of whether or not the patient developed GTN after termination of pregnancy and, if they did, the type of GTN and how long after termination of pregnancy GTN developed. Descriptive statistics was used to

calculate simple frequency, percentage, and proportion out of the total case reports.

## Results

A brief overview of the article screening process is shown in Figure 1. A total of 260 articles were identified on initial electronic database search, of which 41 articles, with a total of 44 cases of PMCF were included in the final analysis.

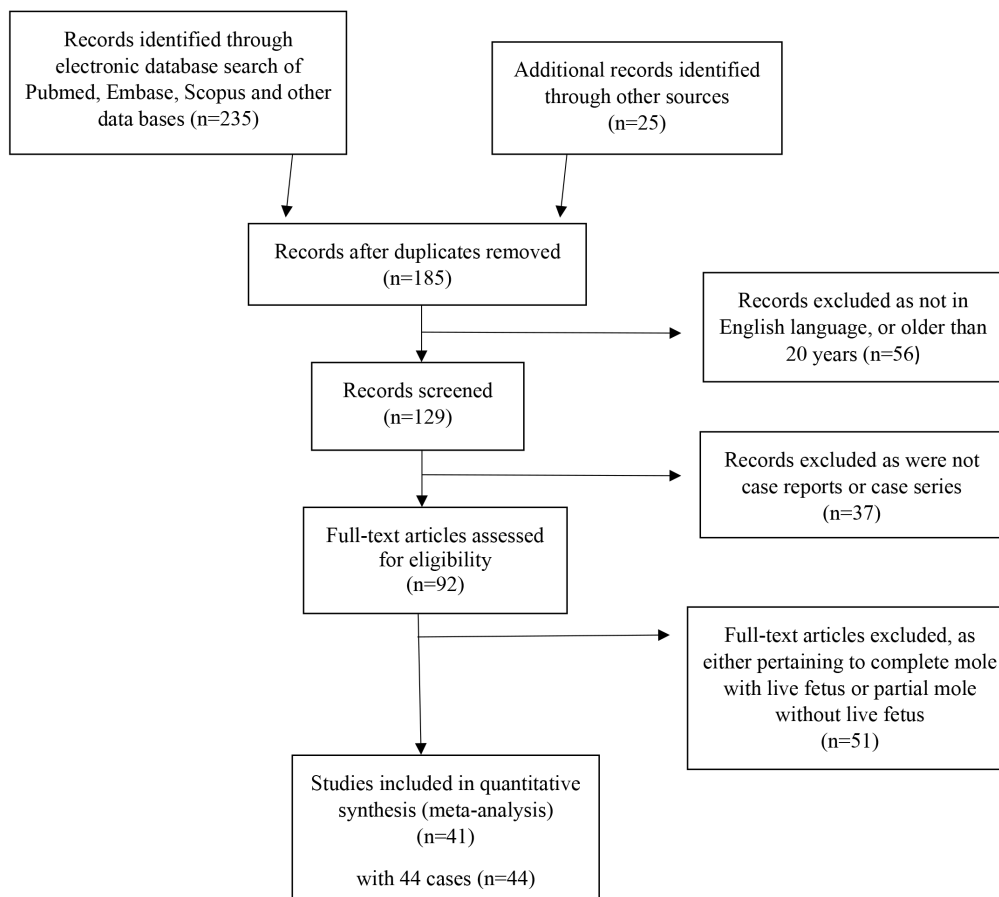
### Demographic characteristics

The geographic distribution of cases is shown in Figure 2 with the age distribution shown in Figure 3. The majority of the cases reported were aged between 26 and 30 years. This also represents the age when most pregnancies happen. The mean gestational age at diagnosis was 20+6 weeks ranging from 10-40 weeks.

### Clinical manifestations

Less than half of the cases (19/44, 43.2%) were asymptomatic at the time of diagnosis and were detected incidentally

during routine ultrasonography (USG) scan done for fetal well-being or at 11-13<sup>th</sup> week combined screening test. The diagnosis was made as early as 10 weeks of gestation in two patients because of the appearance of multiple cystic spaces in the placenta. Interestingly, both these patients were women with Turner syndrome mosaicism and pregnancy was a result of intracytoplasmic sperm transfer in both. False positive first trimester screen for Down syndrome and cystic hygroma at 11-14<sup>th</sup> week scan and hydrops raised suspicion in two cases. The most common clinical manifestation (13/44; 29.5%) that caused suspicion and eventual diagnosis was vaginal bleeding. Nine (69%) had bleeding in the first trimester and presented with threatened miscarriage. Two (15.4%) had vaginal bleeding in the second trimester and two further patients presented with ante-partum hemorrhage in the third trimester. Preeclampsia and eclampsia (5/44; 11.4%), hyperemesis (3/44; 6.8%) and hyperthyroidism (2/44; 4.5%) were other common manifestations. One patient was diagnosed due to progressive anemia as a result of fetomaternal hemorrhage. Preterm labor, intrauterine fetal demise and vanishing twin were the presenting clinical



**Figure 1. PRISMA flow chart**

*PRISMA: Preferred reporting items for systematic review and meta-analyses*

manifestations in one case each, which raised suspicion leading to diagnosis of partial mole (Figure 4).

### Diagnosis

Of 44 cases, the diagnosis was made on USG examination in 36 (81.8%). In approximately 43% of cases (19/44), it was an incidental finding on routine USG examination, while others were detected on a detailed examination done due to vaginal bleeding or cystic hygroma, hydrops, placentomegaly or unusual elevation in the levels of beta-human chorionic gonadotropin ( $\beta$ -hCG). Four cases were detected only on the pathological examination of the placenta after delivery. The presence of grape-like vesicles or cystic areas in the placenta on gross examination, fetal growth restriction or unexplained fetal anemia due to fetomaternal hemorrhage raised suspicion, thereby prompting histopathology. On gross examination, the partial mole was focal in 11 cases and did not involve the entire placenta.

Out of 44 cases, the karyotype of the fetus was normal in 29 (65.9%). Among those with abnormal fetal karyotype, one

fetus had trisomy 21, one had monosomy X, two had triploidy and in three patients, although the placenta was triploid, fetal karyotype was diploid. One case of Dandy-Walker malformation was also reported with diploid fetus. Karyotype was not done or not mentioned in 11 patients.

The structural congenital anomalies associated were cystic hygroma, omphalocele, hydrocephalus, meningomyelocele, spina bifida, congenital talipes equinovarus and hypospadias.

### Fetal and maternal outcome

Figure 4 illustrates the major maternal and fetal complications seen in cases of partial mole with one live fetus. Twenty-five (56.8%) resulted in live birth, although there was one case of early neonatal death. Two babies were born with severe anemia and required multiple transfusions after birth, but survived. One baby died after 65 days of life due to respiratory failure because of hyaline membrane disease and severe hypothermia. Intra uterine death of fetus was reported in six cases, and pregnancy was terminated in 12 cases mainly due to excessive bleeding complications.

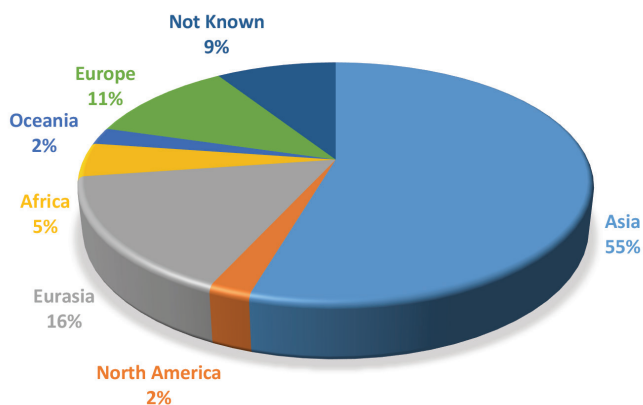
Thirteen patients delivered vaginally, nine out of these after 34 weeks of gestation. Four were preterm deliveries: two patients went into spontaneous preterm labour at 28 weeks, one at 30 weeks of gestation and one woman delivered at 24 weeks due to vaginal bleeding followed by preterm labor. Twelve patients were delivered by Caesarean section (CS), the most common indication for CS being excessive vaginal bleeding or antepartum hemorrhage. Ten out of these 12 CSs were done preterm, from 26 to 32 weeks of gestation. Other common indications for CS were severe growth restriction, compromised Doppler and prematurity. In 11/12 (91.7%), the birth weight was less than 10<sup>th</sup> centile with four out of these having birth weight less than 3<sup>rd</sup> centile.

One patient underwent emergency hysterectomy and internal iliac artery ligation as a consequence of excessive haemorrhage associated with placenta accreta in a woman with PMCF. Theca lutein cysts were found in 4/44 (9.1%). Two out of 44 (4.5%) developed hyperthyroidism that was managed medically with propylthiouracil in both.

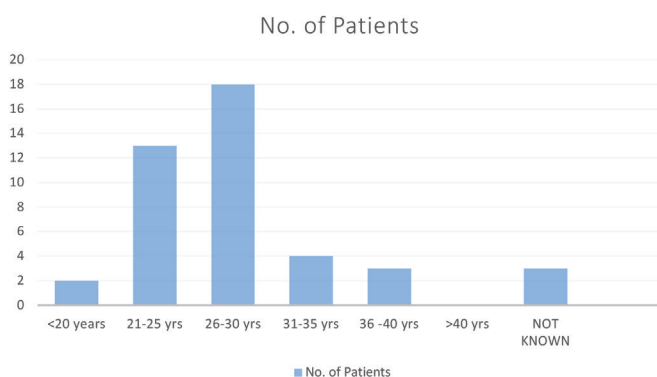
### Follow-up

Complete  $\beta$ -hCG follow-up was not mentioned in all cases. The duration from pregnancy termination until undetectable  $\beta$ -hCG values was available for 21/44 cases. GTN was reported in 6.81% (3/44). All three patients developed choriocarcinoma which responded completely to chemotherapy. Persistently raised  $\beta$ -hCG on follow-up, associated with vaginal spotting, was the main presentation, which led to the diagnosis of GTN. The time duration between termination of pregnancy and development of GTN was one month in two cases and two

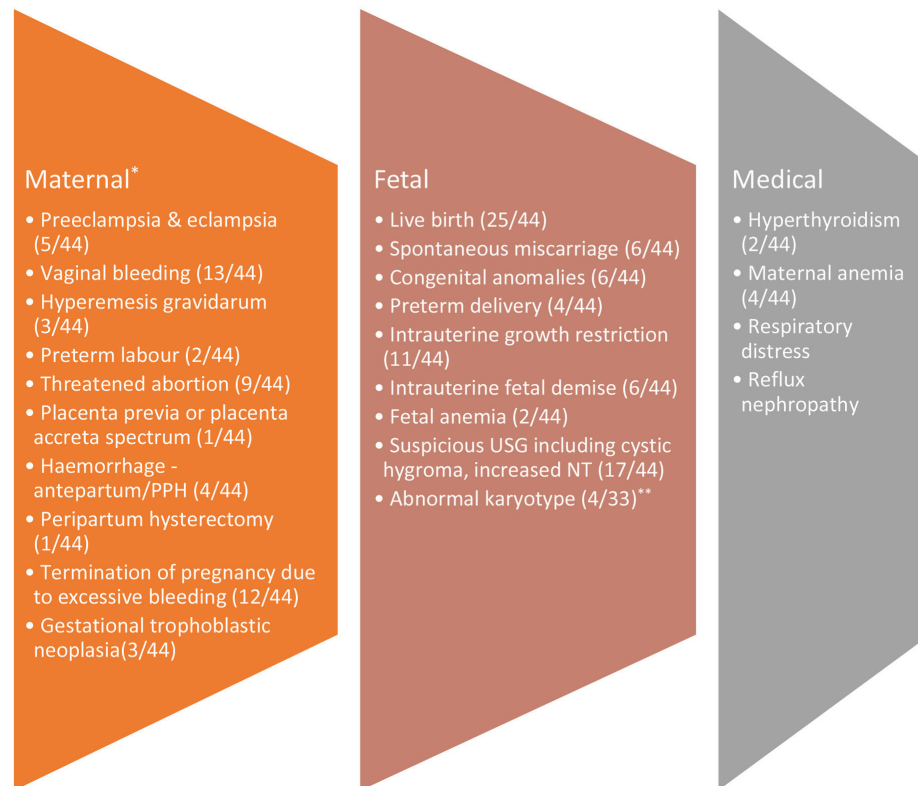
### DISTRIBUTION OF CASES REPORTED IN LAST 20 YEARS



**Figure 2. Geographical distribution of cases of partial mole with live fetus in last 20 years**



**Figure 3. Age distribution of cases of partial mole with live fetus reported in literature in last 20 years**



**Figure 4. Maternal and fetal complications associated with live pregnancy with partial mole**

\*Majority less than half were diagnosed as incidental finding on USG (19/44), \*\*in 11 cases fetal karyotype was not done or documented

#### USG: Ultrasonography

months in the third case. There was no sign of residual disease or recurrence in any of these three patients after completion of chemotherapy (Table 1).

Sixteen case reports mentioned about follow-up after normalization of  $\beta$ -hCG values. Duration of follow-up was five years in one, two years in three, one year in seven and six months or less in the remaining five cases reports. Four case reports mention follow-up until time of publication, but this makes it difficult to estimate the actual follow-up duration as publication delay was unknown (Table 1).

## Discussion

We present here a comprehensive systematic review of published case reports of PMCF in the last 20 years. There were only 44 such cases worldwide published in English, over a period of 20 years, suggesting the rarity of this entity. Therefore, this systematic review will help to aid in understanding the epidemiology, clinical presentation, and prenatal diagnosis and may help to identify a possible management strategy.

Most cases (55%) were reported from Asia. This correlates with the geographical distribution of molar pregnancy. The incidence

of molar pregnancy is higher in Asia, compared to Europe and North America (9). This epidemiological distribution might be affected by the reporting system of each country.

The most common presenting complaint was vaginal bleeding, although it affected less than a third of cases. This correlates with the large placental size, cystic changes in the placenta and the non-viability of the molar tissue. The bleeding in these cases may present at any time during pregnancy. In our case series, the earliest presentation was in the first trimester as missed miscarriage associated with vaginal bleeding and patients presented in the late third trimester with antepartum haemorrhage. Bleeding in the first or second trimester of pregnancy is one of the most common complications in such cases. Bleeding at any time may prove life threatening for the mother, thereby necessitating urgent delivery (14). The large size of placenta also increases the chances of placenta previa (15) and other placental abnormalities, such as circumvallate placenta. Ante-partum and post-partum hemorrhage necessitating massive transfusions or even emergency hysterectomy has been reported.

Clinical presentation may be diverse. Less than half of the cases (43%) in the present systematic review were diagnosed

**Table 1. Summary of clinical parameters of included case reports**

Author, year	Maternal age (years)	Gestational age at delivery/termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL)	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Rahamni and Parviz (37), 2016	26	26	Normal	IUD, preterm delivery	64750	Undetectable at 1 month	6 months
Gupta et al. (38), 2015	30	13+3	-	Spontaneous abortion	180000	Undetectable at 8 weeks	NA
Hassan et al. (39), 2018	25	18+6	-	Spontaneous abortion	561771	24 hours- 210310 Undetectable at 6 weeks	NA
Rathod et al. (6), 2014	-	34	Normal	Preterm delivery	23500	UPT negative at 6 weeks	12 months
Chu et al. (40), 2004	29	24	Mole - XXY, Fetus XY	Preterm delivery	-	Normal at 1 month (7 mIU/L)	NA
Göksever Çelik et al. (41), 2017	27	12	-	Spontaneous abortion	606104	10 days - 7538, 18 days - 1373, and at 25 days - 364	On F/U at time of reporting-exact duration not mentioned
Rathod et al. (42), 2015	24	28	-	Preterm delivery	121993	Undetectable at 4 weeks	On F/U at time of reporting-exact duration not mentioned
Ara et al. (43), 2016	26	40	Normal	Term delivery	-	-	12 months
Tesemma (16), 2019	18	34	-	Preterm delivery	-	48 hours - 162, normal at 3 weeks, undetectable at 3 months	NA
Koregol et al. (44), 2009	22	31	-	Preterm delivery followed by early neonatal death	-	-	NA
Shobha et al. (45), 2010	21	37	-	IUD, term delivery	1600247	-	NA
Rao et al. (18), 2015	24	32	Normal	Preterm delivery	603360	-	NA
Rao et al. (18), 2015	27	27	Normal	IUD, preterm delivery	192640	Declined initially F/B rise after 15 days,  Was given 2 doses of methotrexate	12 months
Rai et al. (46), 2014	25	36	-	Preterm delivery	374747  declined in 2nd trimester with decrease in size of theca lutein cysts.	1 week - 111,  Normal - 3 weeks post-partum	On F/U at time of reporting-exact duration not mentioned

**Table 1. Continued**

Author, year	Maternal age (years)	Gestational age at delivery/termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL)	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Sun et al. (47), 2012	32	35	Mole 69XXY, Villi 46XY	Preterm delivery	-	Undetectable at 6 months	NA
Güven et al. (48), 2007	21	28	Normal	IUD, preterm delivery	499000	-	NA
Lembet et al. (15), 2000	28	21	Normal	Induced abortion	79.642	7 weeks	2 years
Atuk and Basuni (49), 2018	21	28	Normal	Preterm delivery followed by early neonatal death on day 12	NA	4 weeks	NA
Kawasaki et al. (22), 2016	27	25	Placenta 69XXX, Fetus 46 XX	Preterm delivery	468185	-	NA
Copeland and Stanek (50), 2010	29	28	Placenta triploid, Fetus diploid	Preterm delivery	NA	-	NA
Agarwal et al. (51), 2005	-	28	Normal	Preterm delivery	-	-	NA
Sak et al. (52), 2012	28	37	Normal	Term delivery	94753	2 weeks	NA
Hsieh et al. (53), 1999	30	32	Normal	Preterm delivery	167596	4 weeks	NA
Shiina et al. (54), 2002	23	20	Normal	Induced abortion	603.84	At 3 weeks - 6584 At 5 weeks - 8830  Developed GTN  Received chemotherapy Undetectable at 22 weeks	2 years
De Franciscis et al. (55), 2019	37	31	Normal	Preterm delivery	14898	-	12 months
Santos et al. (17), 2017	28	20	69XXX	Induced abortion	1891264	At one-month 520 mIU/mL	6 months
Singh et al. (56), 2017	24	21	Trisomy 21	Hysterotomy	424249	8 weeks	1 year
Fdil et al. (57), 2018	26	14	Placenta 69XXY, Fetus diploid	Spontaneous abortion	72000	5 weeks	6 months
Park et al. (20), 2018	37	12	45X Turner	Induced abortion	50,000	12 weeks	2 year
Sargin et al. (19), 2015	27	11	-	Induced abortion	550000	12 weeks	1 year
Abukaftah et al. (58), 2018	40	28	Normal	Preterm delivery	106000	-	NA

**Table 1. Continued**

Author, year	Maternal age (years)	Gestational age at delivery/termination (weeks)	Cytogenetical analysis	Pregnancy outcome	Beta HCG at presentation (mIU/mL) CGHCG	Follow-up beta HCG (time following pregnancy termination)	Total duration of follow-up (after normalization of beta HCG)
Parveen et al. (59), 2004	23	39	Normal	Term delivery	Not performed	UPT negative at 6 weeks	4 months
Dhingra et al. (60), 2009	28	38	Normal	Term delivery	NA	NA	NA
Dhingra et al. (60), 2009	22	34	Normal	Preterm delivery	NA	NA	NA
Rato et al. (61), 2014	30	37	Normal	Twin 1- IUD at 18 weeks Twin 2-Term delivery	-	-	NA
Shiozaki et al. (23), 2012	30	20	Normal	Induced abortion	-	-	NA
Tamrakar and Chawla (62), 2011	26	32	Normal	Preterm delivery	Not performed	UPT negative at 3 weeks	5 years
Papoutsis et al. (21), 2011	31	30	Normal	IUD, preterm delivery	34554	4 weeks	Normal ever since as per the authors
Allgayer et al. (63), 2010	-	40	Normal	Term delivery	449503	-	NA
Allgayer et al. (63), 2010	-	27	Normal	Preterm delivery	-	-	NA
Unsal et al. (14), 2010	32	13	-	Spontaneous abortion Acute hemorrhage during evacuation due to placenta accreta, hysterectomy was performed	-	-	NA
Sánchez-Ferrer et al. (64), 2009	25	21	Normal	Spontaneous abortion	365,745	After an initial decline to 3000, beta HCG increased to 9000. Developed GTN Required 7 cycle of chemotherapy	On F/U at time of reporting-exact duration not mentioned
van der Houwen et al. (65), 2009	33	38	Normal	Term delivery	423000	At 4 days -440	NA
Ingec et al. (66), 2006	17	11	-	Induced abortion	276079	At 2 weeks - 5457, Then lost to F/U At 2 months - 6690 Developed GTN Received 2 courses of chemotherapy	1 year

USG: Ultrasound, HPE: Histopathology, IUD: Intrauterine death, F/U: Follow-up, NA: Not available, UPT: Urine pregnancy test, GTN: Gestational trophoblastic neoplasia



incidentally as a result of routine USG done in early weeks of gestation. Hyperemesis, early onset preeclampsia and eclampsia (16,17), hyperthyroidism (11), unexplained intrauterine fetal demise (18) or fetal growth restriction, preterm labor or premature rupture of membranes (6), and pain in the lower abdomen, were the other presenting complaints. Rarely, cases attracted clinical attention due to positive first trimester screen or detection of cystic hygroma or fetal hydrops on USG examination (19,20). Partial mole may be detected incidentally on gross or pathologic examination of the placenta. There should be a high index of suspicion in cases with fetal or neonatal anemia or unexplained intra uterine death of fetus (21). Rarely, PMCF was reported to be complicated by progressive anemia (22) or respiratory distress (23).

Cystic changes in the placenta or placentomegaly are one of the earliest USG findings that attract attention. A large sized placenta also predisposes to placenta previa and even cases of morbidly adherent placenta necessitating emergency peripartum hysterectomy have been reported (24). There was one case of one patient undergoing peripartum hysterectomy and internal iliac artery ligation for antepartum haemorrhage associated with placenta accreta.

Although USG is the initial modality of choice for the diagnosis of molar pregnancy, the sensitivity is only 40-60% (25). Detection rate on USG is higher for complete moles than for partial moles, as most partial moles may be mistaken sonographically as missed or incomplete abortions in early pregnancy, as the appearance is quite similar (26,27). However, the following features on USG have been said to be suggestive of partial mole:

- a. thickened placenta with hypoechoic areas (11);
- b. absent or low venous flow inside the placental lesion, especially during the first two trimesters, helps to differentiate it from chorioangioma or complete mole (28);
- c. increased echogenicity at the maternal fetal interface;
- d. altered gestational sac diameter ratios, cystic changes in the placenta or snow storm appearance (28).

The definitive diagnosis of partial mole can be established only by a pathological examination of the placenta (29). Immunohistochemical analysis for p57 protein, which is expressed only from the maternally derived antigens, may be helpful to differentiate partial from complete mole, especially in cases that are difficult to diagnose by USG alone. This is becoming increasingly important as with earlier diagnosis and therapeutic termination, the differentiation of molar from non-molar pregnancy has become difficult. As complete mole lacks a maternal genome, p57<sup>KIP2</sup> immunostaining will be absent, whereas hydropic abortuses and partial mole show positive staining. Positive p57 staining has high sensitivity and specificity to exclude the diagnosis of complete mole (30,31). So, p57

staining complements the ploidy studies to refine the diagnosis of early molar pregnancies.

The diagnosis of PMCF can also be suspected on the basis of abnormal prenatal screening testing results. Single nucleotide polymorphism-based, non-invasive prenatal testing has the potential to detect uniparental disomy, which is the hallmark of complete molar pregnancy (32), and can also detect cases of both diandric or digynic triploidy, characteristic of partial mole (33,34).

Preeclampsia is thought to be mediated by circulating factors of placental origin, mainly sFlt-1 and S-endoglin. The sFlt-1: placental growth factor ratio are also usually extremely high and are one of the factors implicated in early onset preeclampsia before 20 weeks of gestation (17).

Live birth rate was 56.8%, whereas intrauterine death was reported in 20% of cases. Pregnancy was terminated in 27% due to excessive vaginal bleeding. Mode of delivery depends upon the maternal and fetal condition. In published cases, CS was performed mainly for antepartum hemorrhage. One patient required emergency hysterectomy and internal iliac artery ligation due to associated bleeding with placenta accreta.

Cases of PMCF are at high risk for developing GTN, which occurred in 7% of the cases reviewed. All three patients developed choriocarcinoma which completely responded to chemotherapy. Histopathological examination of placenta and strict follow-up with  $\beta$ -hCG monitoring is necessary for timely identification of the development of GTN and the success of treatment.

The decision to continue pregnancy is very much dependent on the karyotype of the fetus. The best method to determine the fetal karyotype still remains controversial. Although chorionic villus sampling has an advantage of diagnosis at an earlier gestational age, it may not be diagnostic of the fetal karyotype due to confined placental karyotype aberration. Amniocentesis remains the diagnostic test of choice. Therefore, USG guided placental biopsy, fetal karyotype by either amniocentesis or fetal blood sampling, combined with serum monitoring for  $\beta$ -hCG should be used to guide decision making (15).

### Management strategy

Sad fetus syndrome, or live pregnancy with coexistent mole is a rare entity, yet poses a great diagnostic and management challenge to the obstetrician. Here we propose a management plan on the basis of the available evidence obtained from this literature review.

A high index of suspicion should be kept in all cases at extremes of age, in mothers of Asian origin, women with multiple pregnancies, those who conceived by assisted reproductive methods or those presenting with bleeding in early pregnancy. A USG examination of both the fetus and placenta should be

performed. All cases presenting with cystic changes in the placenta should have a detailed examination to see whether the changes are focal or complete and whether a live fetus coexists with a molar pregnancy. Cord insertion should be looked for, if it inserts on the cystic placenta, a focal mole is more likely and if the cord inserts on a normal placenta, a twin pregnancy with coexistent mole is an option. Women should be counselled about all the complications that can develop during the course of continuing this pregnancy, including the risk of GTN, and need for chemotherapy if it occurs. The risk of triploidy and congenital anomalies in the fetus, preterm labor, fetal growth restriction, intra uterine fetal demise, ante-partum or post-partum hemorrhage any time necessitating urgent delivery or peripartum hysterectomy should also be discussed with the patient.

Factors that should be kept in mind when counselling patients regarding fetal prognosis include the karyotype of fetus (6), parity of the woman, coexistent obstetric and medical complications and the rate of degeneration of molar tissue.

If the patient decides to continue with the pregnancy, these patients might need multidisciplinary care throughout the pregnancy. An obstetrician, maternal fetal medicine specialist, gynecologic oncologist and neonatologist should be involved in the care of such a pregnancy.

An amniocentesis at around 16 weeks to determine fetal karyotype, detailed USG to rule out any congenital abnormalities in the fetus, including fetal echocardiography, should be offered. Serial scans for fetal growth may be needed every 2-3 weeks, as these fetuses are very high risk for fetal growth restriction and oligohydramnios. These fetuses should be under strict surveillance for impaired circulation due to abnormal development of villi; they are at very high risk for sudden death or still-birth. These women are at risk of torrential life-threatening hemorrhage at the time of delivery. Therefore, all necessary preparations should be made beforehand. If an elective CS is planned, especially in the setting of previous two or three Caesareans, pre-operative balloon catheters in the uterine or internal iliac arteries might be needed in order to minimize blood loss. Uterine artery embolization has a role in cases of excessive hemorrhage associated with molar pregnancy (35). An adequate amount of blood should be cross matched and be available at the time of delivery, should the need arise.

Even after delivery, the patient needs weekly  $\beta$ -hCG monitoring for early diagnosis and management of post molar GTN and single additional confirmatory normal  $\beta$ -hCG measurement one month after the first normalization of  $\beta$ -hCG after a partial mole and for at least six months after a complete mole (36).

### Study Limitations

The present systematic review provides the most recent and comprehensive overview of epidemiology, clinical manifestations, prenatal diagnosis and management in cases of PMCF. All globally published cases in English have been identified by extensive electronic database searches. However, the data was heterogeneous, and the analysis was descriptive, which are limitations of this systematic review. Case reports and case series published in other languages were not included, which might be another limiting factor.

### Conclusion

PMCF should be considered as a high-risk pregnancy. A high index of suspicion is required for timely diagnosis and successful management. Prenatal diagnosis and counselling, strict antepartum surveillance and adequate post-natal follow-up play a vital role in optimal maternal and fetal outcome. An obstetrician, maternal fetal medicine specialist, gynecologic oncologist and neonatologist should be involved in the care of such a pregnancy.

**Ethics Committee Approval:** *This being a systematic review of case reports ethics committee approval was not sought as systematic reviews are exempted from ethics review.*

**Informed Consent:** *It wasn't obtained.*

**Peer-review:** *Externally peer-reviewed.*

**Author Contributions:** *Surgical and Medical Practices: M.M., H.K., K.K.; Concept: M.M., H.K., K.K.; Design: M.M., H.K., K.K.; Data Collection or Processing M.M., H.K., K.K.; Analysis or Interpretation: M.M., H.K., K.K.; Literature Search: M.M., H.K., K.K.; Writing: M.M., H.K., K.K.*

**Conflict of Interest:** *No conflict of interest is declared by the authors.*

**Financial Disclosure:** *The authors declared that this study received no financial support.*

### References

1. Suzuki M, Matsunobu A, Vakita K, Osanai K. Hydatidiform mole with surviving co-existent fetus. *Obstet Gynecol* 1980; 56: 384-88.
2. Vaisbuch E, Ben-Arie A, Dgani R, Perlman S, Sokolovsky N, Hagay Z. Twin pregnancy consisting of a complete hydatidiform mole and co-existent fetus: report of two cases and review of literature. *Gynecol Oncol* 2005; 98: 19-23.
3. Yanik A, Yanik FF, Urman B. Partial hydatidiform mole in a triplet pregnancy following intracytoplasmic sperm injection: Case report and review of the literature. *J Turk Soc Obstet Gynecol* 2006; 3: 70-2.

4. Dolapcioglu K, Gungoren A, Hakverdi S, Hakverdi AU, Egilmez E. Twin pregnancy with complete hydatidiform mole and co-existent live fetus: Two case reports and review of the literature. *Arch Gynecol Obstet* 2009; 279: 431-36.
5. Tidy J, Seckl M, Hancock VW. On behalf of Royal College of Obstetricians & Gynaecologists. Management of gestational trophoblastic disease. *BJOG* 2021; 128: e1-e27.
6. Rathod AD, Pajai SP, Gaddikeri A. Partial mole with a coexistent viable fetus—a clinical dilemma: a case report with review of literature. *J South Asian Feder Obstet Gynaecol* 2014; 6: 51-5.
7. Wee L, Jauniaux E. Prenatal diagnosis and management of twin pregnancies complicated by a co-existing molar pregnancy. *Prenat Diagn* 2005; 25: 772-76.
8. Mangla M, Singla D, Kaur H and Sharma S. Unusual clinical presentation of choriocarcinoma- A systematic review of case reports. *Taiwan J Obstet Gynaecol* 2017; 56: 1-8.
9. Sarno AP Jr, Moorman AJ, Kalousek DK. Partial molar pregnancy with fetal survival: an unusual example of confined placental mosaic. *Obstet Gynaecol* 1993; 82: 716-19.
10. Vejerslev LO. Clinical management and diagnostic possibilities in hydatidiform mole with coexistent fetus. *Obstet Gynecol* 1991; 46: 577-88.
11. Moscoso G, Jauniaux E, Hustin J. Placental vascular anomaly with diffuse mesenchymal stem villous hyperplasia. A new clinicopathological entity? *Pathol Res Pract* 1991; 187: 324-28.
12. Zalel Y, Gamzu R, Weiss Y, Schiff E, Shalmon B, Dolizky M, et al. Role of color Doppler imaging in diagnosing and managing pregnancies complicated by placental chorioangioma. *J Clin Ultrasound* 2002; 30: 264-69.
13. Tse KY, Chan KKL, Tam KF, Ngan HYS. An update on gestational trophoblastic disease. *Obstetrics, Gynaecology & Reproductive Medicine* 2012; 22: 7-15.
14. Unsal MA, Aran T, Dinc H, Cekic B. Internal iliac artery embolisation in the treatment of uncontrolled haemorrhage associated with placenta accreta and partial hydatidiform mole. *J Obstet Gynaecol* 2010; 30: 310-1.
15. Lembet A, Zorlu CG, Yalçın HR, Seçkin B, Ekici E. Partial hydatidiform mole with diploid karyotype in a live fetus. *Int J Gynaecol Obstet* 2000; 69: 149-52.
16. Tesemma MG. Singleton Partial Molar Pregnancy Delivered in Third Trimester: A Case Report. *J Pat Care* 2019; 5: 147.
17. Santos A, Trocado V, Gama AP, Pinheiro P, Nogueira R. Partial molar pregnancy with live foetus diagnosed on second trimester: a case report. *J Gynecol Neonatal Biol* 2017; 3: 1-4.
18. Rao AR, Daffe K, Padamshri G, Rao DR, Sivakumar NC. Pregnancy outcome with coexisting mole after intracytoplasmic sperm injection: A case series. *J Hum Reprod Sci* 2015; 8: 178-81.
19. Sargin MA, Tug N, Yassa M, Yavuz A. Prenatal screening tests may be a warning for the partial molar pregnancy? case report. *Pan Afr Med J* 2015; 20: 323.
20. Park JE, Park JK, Cho IA, Baek JC. Partial molar pregnancy and coexisting fetus with Turner syndrome: Case report and literature review. *J Genet Med* 2018; 15: 43-7.
21. Papoutsis D, Mesogitis S, Antonakou A, Goumalatsos N, Daskalakis G, Papantoniou N, et al. Partial molar pregnancy with chromosomically and phenotypically normal embryo: presentation of an extremely rare case and review of literature. *J Matern Fetal Neonatal Med* 2011; 24: 1289-93.
22. Kawasaki K, Kondoh E, Minamiguchi S, Matsuda F, Higasa K, Fujita K, et al. Live-born diploid fetus complicated with partial molar pregnancy presenting with pre-eclampsia, maternal anemia, and seemingly huge placenta: A rare case of confined placental mosaicism and literature review. *J Obstet Gynaecol Res* 2016; 42: 911-7.
23. Shiozaki A, Takemura K, Yonezawa R, Yoneda N, Fukuda K, To M, et al. A rare case of partial mole and co-existing normal fetus originated from one embryo shows preeclampsia-like symptoms at 19 weeks gestation: Angiogenic imbalances in molar placenta leading to hypertension, proteinuria and pleural effusion. *Placenta* 2012.
24. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet* 2010; 376: 717-29.
25. Kirk E, Papageorgiou AT, Condous G, Bottomley C, Bourne T. The accuracy of first trimester ultrasound in the diagnosis of hydatidiform mole. *Ultrasound Obstet Gynecol* 2007; 29: 70-5.
26. Sebire NJ, Rees J, Paradinas F, Seckl M, Newlands E. The diagnostic implications of routine ultrasound examination in histologically confirmed early molar pregnancies. *Ultrasound Obstet Gynecol* 2001; 18: 662-5.
27. Radhouane A, Imen BA, Khaled N. Twin pregnancy with both complete hydatiform mole and coexistent alive fetus: case report. *Asian Pac J Reprod* 2015; 4: 331-33.
28. John J, Greenwold N, Buckley E, Jauniaux E. A prospective study of ultrasound screening for molar pregnancies in missed miscarriages. *Ultrasound Obstet Gynecol* 2005; 25: 493-7.
29. Genest DR. Partial hydatidiform mole: clinicopathological features, differential diagnosis, ploidy and molecular studies, and gold standards for diagnosis. *Int J Gynecol Pathol* 2001; 20: 315-22.
30. Merchant SH, Amin MB, Viswanatha DS, Malhotra RK, Moehlenkamp C, Joste NE. p57KIP2 immunohistochemistry in early molar pregnancies: emphasis on its complementary role in the differential diagnosis of hydropic abortuses. *Hum Pathol* 2005; 36: 180-6.
31. Samadder A, Kar R. Utility of p57 immunohistochemistry in differentiating between complete mole, partial mole & non-molar or hydropic abortus. *Indian J Med Res* 2017; 145: 133-37.
32. Dar P, Curnow KJ, Gross SJ, Hall MP, Stosic M, Demko Z, et al. Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am J Obstet Gynecol* 2014; 211: 527.e1-17.
33. Nicolaidis KH, Syngelaki A, der Mar Gil M, Quezada MS, Zinevich Y. Prenatal detection of fetal triploidy from cell-free DNA testing in maternal blood. *Fetal Diagn Ther* 2014; 35: 212-17.
34. Pergament E, Cuckle H, Zimmermann B, Banjevic M, Sigurjonsson S, Ryan A, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstet Gynecol* 2014; 124: 210-18.
35. Sidhu HK, Prasad GRV, Jain V, Kalra J, Gupta V, Khandelwal N. Pelvic artery embolization in the management of obstetric hemorrhage. *Acta Obstet Gynecol* 2010; 89: 1096-9.
36. Coyle C, Short D, Jackson L, Sebire NJ, Kaur B, Harvey R, et al. What is the optimal duration of human chorionic gonadotrophin surveillance following evacuation of a molar pregnancy? A retrospective analysis on over 20,000 consecutive patients. *Gynecol Oncol* 2018; 148: 254-57.
37. Rahamni M, Parviz S. A case report of partial molar pregnancy associated with a normal appearing dizygotic fetus. *Asian Pacific J Reprod* 2016; 5:171-3.
38. Gupta K, Venkatesan B, Kumaresan M, Chandra T. Detection by Ultrasound of Partial Hydatidiform Mole With a Coexistent Live Fetus. *WMJ* 2015; 114: 208-11.
39. Hassan SA, Akhtar A, Ud Deen Z, Khan M, Jamal S, Sohail S, et al. Sad Fetus Syndrome: Partial Molar Pregnancy with a Live Fetus. *Cureus* 2018; 10: e3175.
40. Chu W, Chapman J, Persons DL, Fan F. Twin pregnancy with partial hydatidiform mole and co-existent fetus. *Arch Pathol Lab Med* 2004; 128: 1305-6.

41. Göksever Çelik H, Demirezen GM, Erdem B, Atiş Aydın A, Ülker V. Management of twin pregnancy with a hydatidiform mole and surviving healthy co-existent fetus. *Int J Reprod Contracept Obstet Gynecol* 2017; 6: 5636-7.
42. Rathod S, Rani R, John LB, Samal SK. Successful Outcome of twin gestation with partial mole and Co-Existing live fetus: A Case Report. *J Clin Diagn Res* 2015; 9: QD01-2.
43. Ara R, Begum J, Kasem SB, Hoque S, Nargis SF. Partial Hydatidiform Mole with Alive Term IUGR Foetus. *J Bangladesh Coll Phys Surg* 2016; 34:164-7.
44. Koregol M, Bellad M, Malapati C. Partial hydatidiform mole with a live fetus- a rare entity. *South Asian Fed Obstet Gynaecol* 2009; 1: 77-9.
45. Shobhau N, Dhananjaya B, Sunil K, Gopal N, Tejeswini KK, et al. A Term Pregnancy with Partial Molar Changes - A Case Report. *Int J Biol Med Res* 2011; 2: 1191-92.
46. Rai L, Shripad H, Guruvare S, Prashanth A, Mundkur A. Twin pregnancy with Hydatidiform Mole and Co-existent Live Fetus: Lessons Learnt. *Malays J Med Sci* 2014; 21: 61-4.
47. Sun CJ, Zhao YP, Yu S, Fan L, Wu QQ, Li GH, et al. Twin pregnancy and partial hydatidiform mole following in vitro fertilization and embryos transfer: a novel case of placental mosaicism. *Chin Med J (Engl)* 2012; 125: 4517-9.
48. Guven ES, Ozturk N, Deveci S, Hizli D, Kandemir O, Dilbaz S. Partial molar pregnancy and co-existing fetus with diploid karyotype. *J Matern Fetal Neonatal Med* 2007; 20: 175-81.
49. Atuk FA, Basuni JBM. Molar pregnancy with normal viable fetus presenting with severe pre-eclampsia: a case report. *J Med Case Rep* 2018; 12: 140.
50. Copeland JW, Stanek J. Dizygotic twin pregnancy with a normal fetus and a nodular embryo associated with a partial hydatidiform mole. *Pediatr Dev Pathol* 2010; 13: 476-80.
51. Agarwal R, Agarwal S, Roy KK, Kumar S. Diploid partial mole with neonatal survival-a case report. *Indian J Pathol Microbiol* 2005; 48: 225-7.
52. Sak ME, Soydinc HE, Evsen MS, Sak S, Firat U. Diploid karyotype partial mole co-existing with live term fetus--case report and review of the world literature. *Ginekol Pol* 2012; 83: 789-91.
53. Hsieh CC, Hsieh TT, Hsueh C, Kuo DM, Lo LM, Hung TH. Delivery of a severely anaemic fetus after partial molar pregnancy: clinical and ultrasonographic findings. *Hum Reprod* 1999; 14: 1122-6.
54. Shiina H, Oka K, Okane M, Tanno W, Kawasaki T, Nakayama M. Coexisting true hermaphroditism and partial hydatidiform mole developing metastatic gestational trophoblastic tumors. A case report. *Virchows Arch* 2002; 441: 514-8.
55. De Franciscis P, Schiattarella A, Labriola D, Tammaro C, Messalli EM, La Mantia E, et al. A partial molar pregnancy associated with a fetus with intrauterine growth restriction delivered at 31 weeks: a case report. *J Med Case Rep* 2019; 13: 204.
56. Singh S, Swain S, Das L, Das PC. Partial molar pregnancy associated with a normal appearing foetus: a case report and review of the literature. *Int J Reprod Contracept Obstet Gynecol* 2017; 6: 2681-3.
57. Fdii ME, Bzikha R, Rahioui F, Kamoune J, Grohs A, Filali A, et al. Twin Dizygotic Pregnancy Associating Partial Mole and a Normal Appearing Fetus: A Case Report and Review of Literature. *Sch. J. Med. Case Rep* 2018; 6: 585-9.
58. Abukaftah A, Jabeen S, Moawad A, Almetrek M. A Case Report of Partial Molar Pregnancy Associated with A Normal Dizygotic Twin. *Egypt J Hosp Med* 2018; 70: 1221-23.
59. Parveen Z, Bashir R, Jadoon T, Qayum I. Partial hydatidiform mole along with term gestation and alive baby. *J Ayub Med Coll Abbottabad* 2004; 16: 84-5.
60. Dhingra KK, Gupta P, Saroha V, Akhila L, Khurana N. Partial hydatidiform mole with a full-term infant. *Indian J Pathol Microbiol* 2009; 52: 590-91.
61. Rato I, Centeno M, Susana S, Pinto L, Graca L. Twin pregnancy with a partial hydatidiform mole and a coexistent viable fetus: a case report. *J Mat Fet Neonat Med* 2014; 27: 435-36.
62. Tamrakar SR, Chawla CD. Preterm gestation along with partial hydatiform mole and alive foetus. *Kathmandu Univ Med J* 2011; 35: 222-4.
63. Allgayer D, Latrlich C, Holschbach V, Ortmann O, Germer U. Case report: Two moles with living healthy fetuses. *Arch Gynecol Obstet* 2010; 282(Suppl 1): S159.
64. Sánchez-Ferrer ML, Ferri B, Almansa MT, Carbonel P, López-Expósito I, Minguela A, et al. Partial mole with a diploid fetus: case study and literature review. *Fetal Diagn Ther* 2009; 25: 354-8.
65. van der Houwen C, Schukken T, van Pampus M. Transient early pre-eclampsia in twin pregnancy with a triploid fetus: a case report. *J Med Case Reports* 2009; 3: 7311.
66. Ingec M, Borekci B, Altas S, Kadanali S. Twin pregnancy with partial hydatidiform mole and co-existent normal fetus. *J Obstet Gynaecol* 2006; 26: 379-80.