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Differentiating complete hydatidiform mole and coexistent fetus and placental mesenchymal dysplasia: A series of 9 cases and review of the literature

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ABSTRACT

To identify the differentiating features in clinical presentation, management, and maternal/fetal outcome in complete hydatidiform mole and coexistent fetus compared with placental mesenchymal dysplasia.

Between 1997 and 2015, five women with complete hydatidiform mole and coexistent fetus and four women with placental mesenchymal dysplasia were managed at the University of California San Francisco. Clinical features were analyzed and compared with previously published data.

Of the five cases of complete hydatidiform mole and coexistent fetus, two had live births. β-hCG levels were > 200,000 IU/L in all cases. On imaging, a clear plane between the cystic component and the placenta favored a diagnosis of complete hydatidiform mole and coexistent fetus. None of the patients went on to develop gestational trophoblastic neoplasia (GTN), with a range of follow-up from 2 to 38 months. Combining this data with previously published work, the live birth rate in these cases was 38.8%, the rate of persistent GTN was 36.2%, and the rate of persistent GTN in patients with reported live births was 27%. Of the four cases of placental mesenchymal dysplasia, all four had live births. One patient developed HELLP syndrome and intrauterine growth restriction; the remaining three were asymptomatic.

Maternal symptoms, fetal anomalies, β-hCG level, and placental growth pattern on imaging may help differentiate between complete hydatidiform mole and coexistent fetus and placental mesenchymal dysplasia. There was not an increased risk of gestational trophoblastic neoplasia in patients with complete hydatidiform mole and coexistent fetus who opted to continue with pregnancy.

1. Introduction

Complete hydatidiform mole and coexistent fetus (twin mole) occurs in 1/20,000–100,000 pregnancies. These patients are at risk for many of the same complications as singleton complete molar pregnancy: hyperemesis, hyperthyroidism, pre-eclampsia, vaginal bleeding and persistent gestational trophoblastic neoplasia (GTN). There is debate in the literature as to whether the risk of persistent GTN is higher in women with twin mole than with singleton molar pregnancy (Sebire et al., 2002).

Placental mesenchymal dysplasia (PMD) was first described in the 1990 s and because of this relatively recent recognition, the exact incidence is not known, although it is estimated to be around 1/5000 pregnancies (Arizawa and Nakayama, 2002). It is a benign condition characterized by placentomegaly and cystic placental changes. It is this latter feature that gives it the appearance on antenatal imaging that can be difficult to distinguish from twin mole. In cases of PMD, maternal symptoms are rare, but there are associated fetal complications. Up to 23% of PMD cases are found in conjunction with infants with Beckwith-Wiedemann syndrome (BWS), which is characterized by omphalocele,

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macroglossia, placentomegaly, and macrosomia (Cohen et al., 2005). Indeed, some consider PMD and BWS to be a spectrum of disorders with varying degrees of placental and fetal anomalies. There appear to be more female than male fetuses affected with a ratio of 3.6:1. Intrauterine growth restriction (IUGR) and intrauterine fetal demise have also been reported. It is hypothesized that these two complications may arise from the vascular malformations found in PMD that shunt blood away from the fetus or from the multiple thromboses found in the villi that may disrupt blood flow (Kuwabara et al., 2001).

Thus although these two diagnoses appear similar on imaging, they have vastly different maternal and fetal implications. This makes differentiating them in the antenatal period critical for appropriate patient counseling and management.

2. Materials and methods

The pathology and radiology clinical databases at the University of California San Francisco (UCSF) were searched from 1990 to 2015 using the diagnoses of "twin pregnancy and complete mole" and "placental mesenchymal dysplasia." Both databases returned nine patients who had at least one imaging study and then went on to deliver at UCSF. The clinical charts of these patients were reviewed and data including maternal age, maternal symptoms, gestational age at delivery, mode of delivery, fetal complications, and maternal outcomes were extracted. All relevant radiologic images were reviewed and included ultrasound in all cases and MRI in three cases. Glass slides were re-reviewed by a gynecologic pathologist (JTR) to confirm the original pathologic diagnoses. Routine hematoxylin and eosin stained slides were sufficient to establish the diagnosis of all cases of placental mesenchymal dysplasia and 2/5 cases of twin gestation with complete mole. For the remaining 3 cases of complete mole, p57 immunohistochemistry was performed to demonstrate the diagnostic finding of loss of immunoexpression by the villous cytotrophoblast and mesenchyme. (Ronnett et al., 2011). IRB approval was obtained in order to perform this study through the UCSF Committee on Human Research, IRB # 15–16359.

To further evaluate whether twin mole was associated with a higher risk of persistent GTN than singleton complete mole, we compared our data to previously published work. References were identified through searches of PubMed with the search terms "twin mole," "complete molar pregnancy with coexistent fetus," and "persistent gestational trophoblastic neoplasia" from January 1, 1970 until October 31, 2020. Additional publications were identified via systematic review of all reference lists within publications retrieved from the MEDLINE search. Only papers published in English were used.

3. Results

The clinical characteristics for these patients are summarized in Table 1. The mean maternal age at diagnosis was 34 in patients with twin mole and 30 in patients with PMD. The mean gestational age at time of delivery was 20 weeks in patients with twin mole and 34 weeks in patients with PMD. All five of the patients with twin mole developed symptoms during pregnancy: the most common being vaginal bleeding, followed by hyperthyroidism. In contrast, three of the four patients with PMD were asymptomatic.

Three of the patients with twin mole and three of the patients with PMD met criteria for postpartum hemorrhage. Three of the twin mole patients required a blood transfusion - one of which was administered pre-operatively for anemia in the setting of HELLP, while none of the PMD patients required a blood transfusion. Two of the patients with twin mole had live births; while all four of the patients with PMD had lives births.

Looking at the fetal side, two of the twin mole patients had amniocentesis: one because of the placental anomaly seen on ultrasound and

Table 1
Patient characteristics.

Case# /Dx	Patient Age	G/P*	GA (weeks)	Maternal symptoms	Highest Measured β-hCG (IU/L)	Delivery Indication	MOD	EBL (cc's)	Fetal Gender/Anomalies	Time to β-hCG Normalization
1. Twin Mole	37	G4 P2	12 + 0	Hyperemesis, Hyperthyroidism, Tachycardia, Vaginal Bleeding	>200,000	Patient decision	D&C	200	Male/None	Not recorded: decreased to 305 18 days after delivery
2. Twin Mole	37	G3 P3	34 + 2	Vaginal Bleeding	2,824,443	Planned given concern for invasive mole on imaging	RC/S and TAH	1700	Female/None	2 months
3. Twin Mole	30	G1 P1	25 + 3	HELLP Syndrome, Hyperthyroidism	1,046,000	Delivery for Pre-eclampsia with severe features	C/S	1200	Male/Clubbed Feet	5 months
4. Twin Mole	31	G2 P1	12 + 3	Vaginal Bleeding	>200,000	Patient decision	D&C	500	Unknown/None	3 months
5. Twin Mole	36	G1 P0	18	Vaginal Bleeding	582,240	Spontaneous Abortion	SVD	1700	Female/None	Unknown: decreased to 27 two months after delivery
6. PMD	32	G3 P3	39 + 1	None	22,866	Induction for delivery planning	SVD	800	Female/None	N/A
7. PMD	18	G1 P1	36 + 4	None	Not measured	Pre-term Labor	SVD	Not noted	Male/None	N/A
8. PMD	38	G2 P1	32 + 3	None	Not measured	PPROM followed by pre-term labor	C/S	1200	Male/Multiple: fetal hydrops, omphalocele, cardiac hypertrophy, hyper-extended neck, cystic kidneys, cystic liver	N/A
9. PMD	34	G3 P3	29 + 6	HELLP Syndrome	72,786	Induction of Labor for HELLP	SVD	1000	Female/IUGR	N/A

Dx is diagnosis; G/P is gravida/parity; MOD is mode of delivery; EBL is estimated blood loss; D&C is dilation and curettage; RC/S is repeat Cesarean section; TAH is total abdominal hysterectomy; SVD is spontaneous vaginal delivery; PPROM is pre-term, premature rupture of membranes.

* Parity includes outcome of case pregnancy.

one for advanced maternal age. Both showed normal karyotypes and normal AFP levels. Two of the patients with PMD had amniocentesis: one of which was normal and one of which was abnormal secondary to an elevated AFP. On prenatal imaging, one patient with twin mole had a fetus with bilateral clubbed feet; one patient with PMD had a fetus with multiple anomalies that resulted in neonatal death shortly after delivery; and one patient with PMD had a fetus with IUGR.

Measured β-hCG values were > 200,000 IU/L in all five patients with twin mole (maximum recorded value 2,824,443 IU/L). β-hCG levels were only measured in two of the patients with PMD, of which the highest recorded level was 72,786 IU/L.

The range of follow-up for patients with twin mole was 2–38 months. Four of the patients were followed at UCSF until their β-hCG levels normalized. None of them developed persistent GTN. The fifth patient was only followed for 2 months, during which time her β-hCG decreased from 582,240 IU/L to 27 IU/L. None of the patients received chemotherapy. Two of these patients went on to have subsequent pregnancies.

On literature review, twelve studies were identified that reported maternal and fetal outcomes of twin mole (Table 2). Pooling these results with the five patients in this study gave a total of 229 patients. The pregnancy outcomes were as follows: 36% of patients had a therapeutic abortion, 24.8% of patients had a spontaneous abortion or intrauterine fetal demise, and 38.8% of patients had a live birth. The overall risk of persistent GTN was 36.2% and the risk of persistent GTN in patients who had had a live birth was 27.5%.

All nine patients in this study had a prenatal ultrasound that was re-reviewed by a radiologist. Eight of the patients had normal ovaries on ultrasound, while one of the twin mole patients had multiple, bilateral ovarian cysts. In four of the cases of twin mole, the cystic molar component and the normal placenta were clearly demarcated and in separate areas of the uterus. In contrast, in three of the cases of PMD the placenta was described as “cystic” and without a clear plane of demarcation between the cystic component and the normal placenta. Another feature found in one of the twin mole cases was exponential growth of the cystic component: something that was not seen in any of the PMD cases. Cases 3 and 6 caused the most diagnostic difficulty, with case 3 being favored as PMD until after delivery and case 6 being favored as twin mole until the third trimester of pregnancy. Looking back at case 3 on imaging, there is reported to be exponential growth in the multicystic mass over time, and on MRI the cystic component and the placenta are clearly separate (Fig. 1A, C). Looking back at case 6, on MRI there is no clear delineation between the placenta and the cystic mass (Fig. 1B, D). Additionally, twin mole is often associated with hemorrhage around or within the cystic mass, which is not the case with PMD. Presence of slow flow in the dilated vessels of PMD has also been helpful in our experience. This has been reported in the literature, in which it is noted that no flow is expected in the hydropic villi of partial or complete mole (Kuwata et al., 2014; Nayeri et al., 2013). These differences can also be seen histologically (see Fig. 2).

4. Discussion

Distinguishing twin mole from PMD in the antenatal period can be difficult. The rarity of these two pathologies makes it particularly important to summarize the known characteristics of each so that the correct diagnosis can be made antenatally. This is especially crucial given the widely different risks and outcomes associated with each.

Based on our nine cases, combined with previously published work, the best way to accurately diagnoses these two diseases appears to be a combination of maternal symptoms, fetal anomalies, β-hCG levels, and imaging findings.

All five of our patients with twin mole had some presenting symptom. Although pre-eclampsia is often associated with molar pregnancies, HELLP syndrome was only seen in one of our patients with twin mole. Notably, HELLP syndrome was also seen in one of the PMD patients, which suggests that the presence or absence of pre-eclampsia may not be a usual tool in differentiating these two entities. Indeed, there is debate in the PMD literature as to whether PMD is itself associated with pre-eclampsia, with some suggesting it is, and others suggesting that the perceived association is biased by the fact that pre-eclampsia is a relatively common diagnosis.

The β-hCG levels were markedly more elevated in our patients with twin mole compared to the patients with PMD. β-hCG levels were not checked in all of our patients with PMD. However, the fact that levels were > 200,000 IU/L in all of our twin mole patients suggests this is a useful tool. On imaging, one of the most helpful findings was the presence or absence of a clear demarcation between the cystic component and the normal placenta. Recent literature supports this concept of a clear demarcation between the fetal placenta and cystic component as a way to help differentiate the two entities (Himoto et al., 2014). In our patients, MRI had utility when ultrasound findings were non-diagnostic. As the technology expands, a potential future direction would be the use of cell-free DNA to distinguish between these etiologies (Gabra et al., 2020). However, this was not in use when this patient information was collected.

In our four patients with long-term follow-up, none of them went on to develop GTN. Published papers on this topic show a large range of persistent GTN rates, from 19.5 to 62.5%. Part of this is likely because twin mole is uncommon, making it hard to determine the true incidence. Analyzing the 229 available patients from the literature and our series,

Table 2
Risk of persistent GTN after twin mole pregnancy.

Authors	# of Cases	Pregnancy Outcome			Persistent GTN	Lives Births with Persistent GTN
		Therapeutic Abortion	Miscarriage or Intra-uterine Fetal Demise	Live Births		
Steller et al. (1994)	8	6	1	1	5 (62.5%)	0 (0%)
Fishman et al. (1998)	7	5	0	2	4 (57%)	2 (50%)
Matsui et al. (2000)	18	13	2	3	9 (50%)	1 (11.1%)
Bruchim et al. (2000)	15	0	0	15*	8 (53%)	6 (75%)*
Sebire et al. (2002)	77	26	31	20	15 (19.5%)	Not reported
Niemann et al. (2007)	8	5	2	1	2 (25%)	0 (0%)
Massardier et al. (2009)	14	8	3	3	7 (50%)	0 (0%)
Lin et al. (2017)	70	17	17	36	31 (44%)	8 (22%)
Case reports: Chhetry et al. (2019), Lipi et al. (2020), Johnson et al. (2019), de Marcillac et al. (2015)	7	1	0	6	2 (28%)	2 (28%)
Current study	5	2	1	2	0 (0%)	0 (0%)
Total	229	83 (36%)	57 (24.8%)	89 (38.8%)	83 (36.2%)	19 (27.5%)**

* Excluded 2 lives births that are already accounted for in the Fishman study.
** Excluded the 20 live births from Sebire study as they did not report GTN rates.

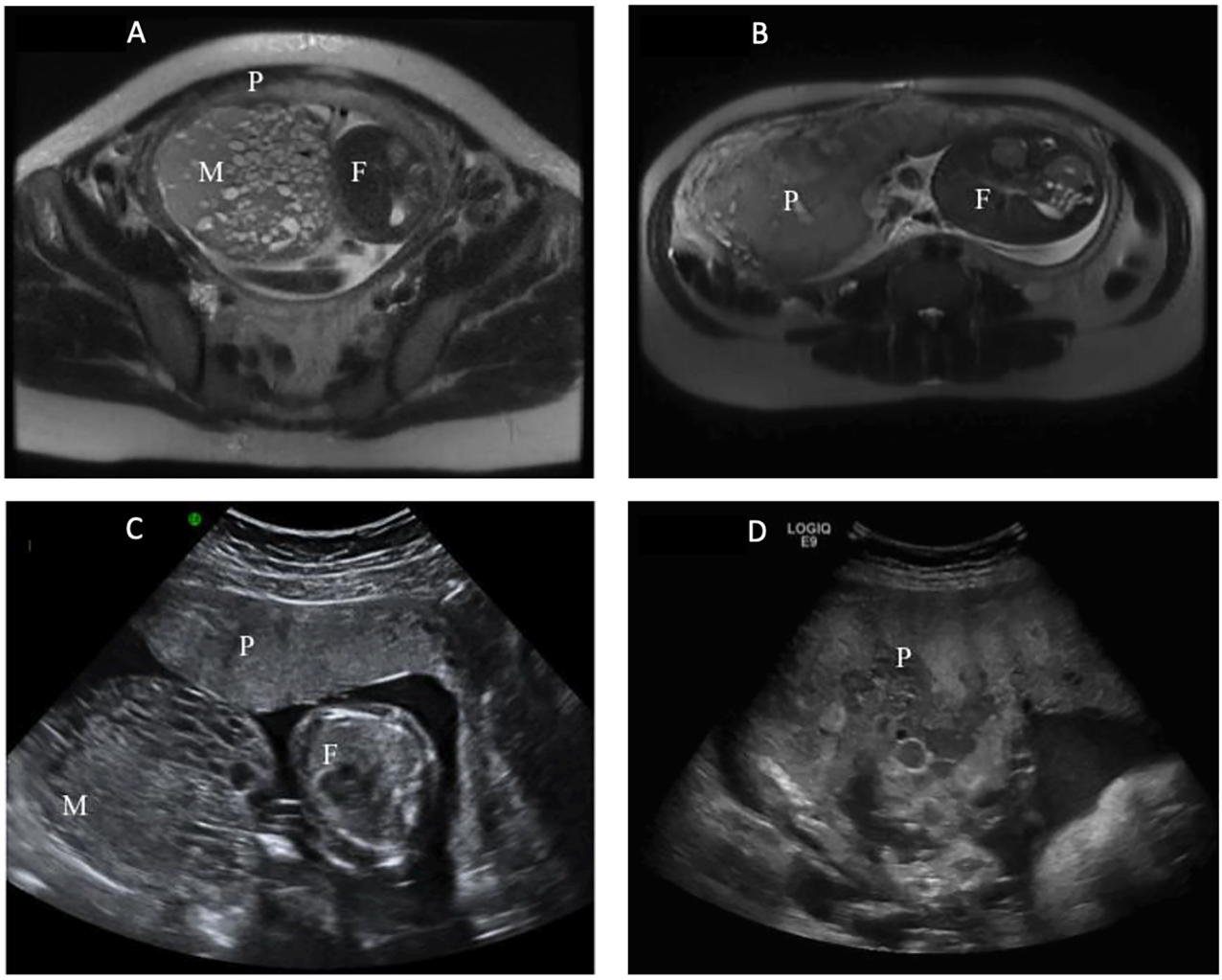

Fig. 1. A. Axial T2 weighted MRI of the abdomen and pelvis demonstrating twin molar pregnancy. Normal placenta (P), Molar pregnancy (M), and Fetus (F). B: Axial T2 weighted MRI of the abdomen and pelvis demonstrating PMD. There is no clear plane separating the cystic component and normal placenta. Placenta (P), Fetus (F). C: Transverse abdominal ultrasound demonstrating twin molar pregnancy. Normal placenta (P), Molar pregnancy (M), and Fetus (F). D: Transverse abdominal ultrasound demonstrating PMD. Again no clear plane is seen between the cystic component and normal placenta. Placenta (P).

36.2% of patients went on to develop GTN, with 27.5% of patients with live births developing persistent GTN. Thus, continuing with the pregnancy does not appear to increase the risk of persistent GTN. Of the patients who develop GTN, most are cured with single agent chemotherapy (Sebire et al., 2002).

Estimates of live birth in these twin-mole cases ranges from 40 to 60% (Sebire et al., 2002; Lin et al., 2017). Although a live birth may be possible, many of these births are pre-term, so that the implications of postnatal morbidity need also be addressed. In terms of following patients after delivery, we recommend using the same guidelines as for patients with singleton complete molar pregnancy (Committee on Practice Bulletins-Gynecology ACoO, 2004).

In patients with PMD, there are generally more fetal complications than maternal complications. Given the up to 23% association with fetal BWS, patients should be offered genetic testing. This generally should be done by amniocentesis, so that epigenetic testing of chromosome 11p15.5- the gene that most commonly has an alteration in its imprinting in BWS- can be performed (Cooper et al., 2005). Additionally, because of the risk of fetal growth restriction and intrauterine demise, the patient should be followed by a Maternal Fetal Medicine specialist who can determine the best regimen for antenatal testing and growth scans.

In conclusion, in patients with suspected twin mole or PMD, we recommend assessing for maternal symptoms, checking quantitative β-hCG levels, and performing routine antenatal ultrasound. Consideration can also be given to MRI if ultrasound interpretation does not yield a clear diagnosis. Patients with either twin mole or PMD should be followed by a Maternal Fetal Medicine specialist to optimize fetal outcomes as well as a Gynecologic Oncologist to optimize maternal outcomes. Patients with twin mole who would like to continue with the pregnancy should be allowed to do so with close surveillance for known complications.

The authors have nothing to disclose.

Informed Consent Statement

IRB approval was obtained in order to perform this study through the UCSF Committee on Human Research, IRB # 15–16359. This study was exempt from requiring written consent.

CRediT authorship contribution statement

Leah McNally: Conceptualization, Investigation, Project administration. **Joseph T. Rabban:** Investigation, Writing - review & editing. **Liina Poder:** Investigation, Writing - review & editing. **Shilpa Chetty:** Investigation, Writing - review & editing. **Stefanie Ueda:** Investigation, Writing - review & editing. **Lee-may Chen:** Conceptualization, Methodology, Investigation, Writing - review & editing.

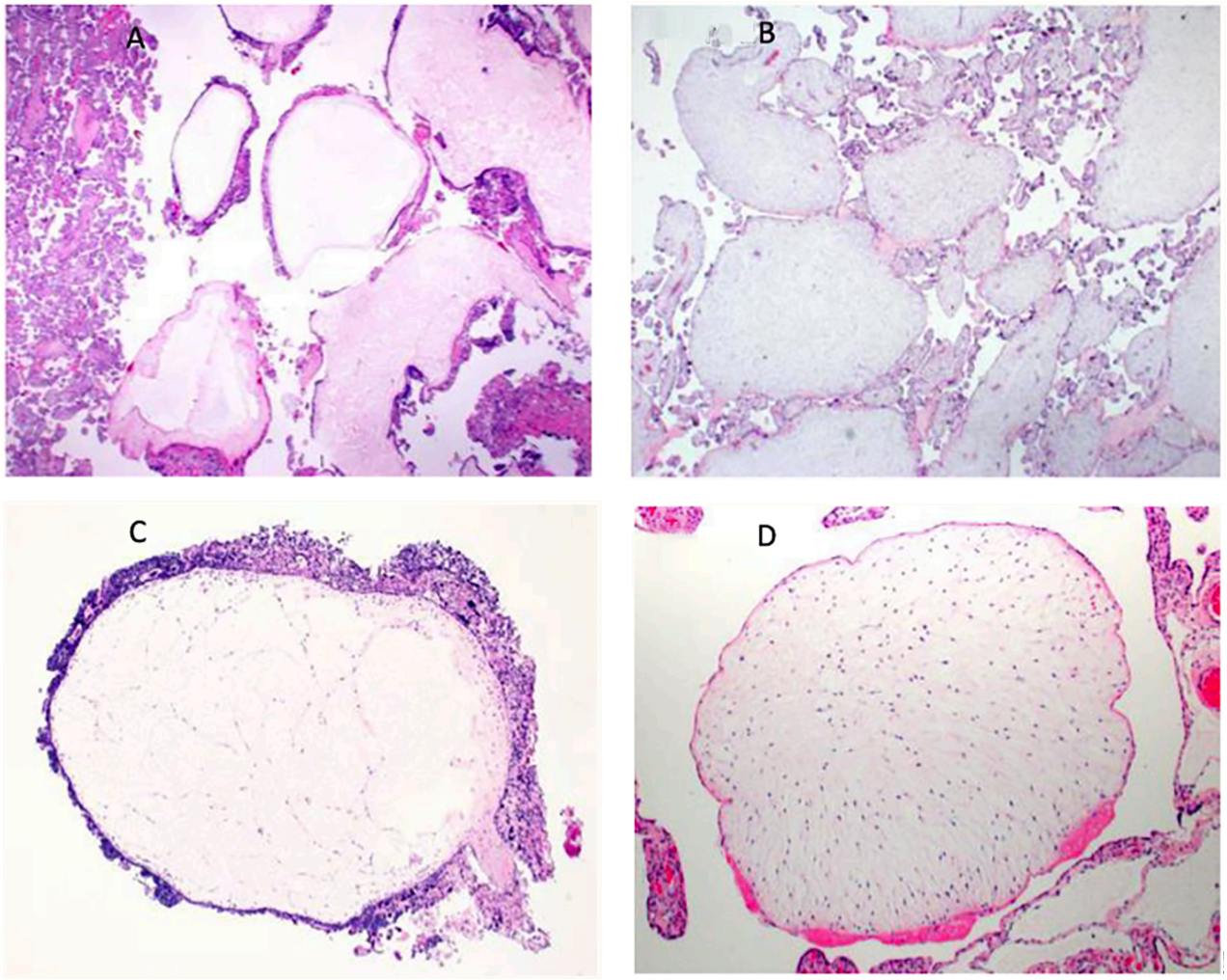

Fig. 2. A: Villi from twin conception of a non-molar gestation (uniform small villi, left half of image) and a complete mole (massively enlarged villi with cisterns and trophoblast proliferation, right half of image). B: Villi from placental mesenchymal dysplasia shows massively enlarged villi and a background of uniform small normal villi. In contrast to the complete mole (Fig. 2A) there are no cisterns or trophoblast proliferation. C and D: The villous trophoblast exhibits exuberant proliferation in complete mole (Fig. 2C) whereas there is no trophoblast proliferation in placental mesenchymal dysplasia (Fig. 2D).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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