



Case report

Methotrexate for management of twin pregnancy with complete hydatidiform mole and co-existing live fetus: A case report

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ABSTRACT

Introduction and importance: Here, we discuss novel management with methotrexate for the rare case of a complete hydatidiform mole with a co-existing fetus (CHMCF).

The management of CHMCF is controversial, and methotrexate might represent a solution.

CHMCF management with methotrexate needs more study, especially its side effects, safe dosage, and the permissible period of pregnancy.

Case presentation: A 23-year-old Syrian primigravida came to our hospital with vaginal bleeding. The patient was diagnosed with a complete hydatidiform mole with a co-existing fetus. The mother had no complications but elevated B-HCG. After counseling, the decision was made to continue pregnancy with methotrexate to control B-HCG levels. The outcome was favorable though the infant had tetralogy of Fallot.

Clinical discussion: In our case, the patient was stable except for the elevation of B-hCG levels, so we considered methotrexate to control it. On the other hand, methotrexate is considered a human teratogen. Case reports and case series of exposure to it during pregnancy began appearing in the 1960s. The sensitive period is suggested to be 6 to 8 weeks after conception. After discussing the choices with the patient, she elected to continue pregnancy and accepted methotrexate exposure to control B-hCG levels despite its risks.

Conclusion: Methotrexate usage within a safe dosage should be studied more to determine the benefits and risks it carries in cases such as ours.

1. Introduction

A complete hydatidiform mole with co-existing fetus (CHMCF) is a rare obstetric condition [1]. It was first described in laker in 1914 [1]. The prevalence varies widely from one in 22,000 to one in 100,000 pregnancies [1]. The complete hydatidiform mole is not fully understood. Vaginal bleeding was the main symptom in our case, the same as in most cases in the literature [1–4].

Mothers with CHMCF are likely to suffer from complications such as pre-eclampsia, vaginal bleeding, and hyperemesis [5,6].

Patients with CHMCF are at high risk of Gestational trophoblastic diseases (GTD) [7]. The risk does not increase with the continuation of pregnancy [4]. So, the decision depends on many aspects like maternal status, complications, and whether the pregnancy is highly desired or not. However, the chance of a live term birth is less than 50 % [4,6,7].

The management of CHMCF is controversial and puts doctors in the

dilemma of ending pregnancy. The one thing researchers agreed on for the management of CHMCF is observation [7].

Chemotherapy is a proposed but questionable option for management.

In this case of CHMCF, which was in a private hospital, we present methotrexate as a medication for CHMCF management.

Methotrexate is used in conditions such as malignancy, ectopic pregnancy, and psoriasis [8].

We administered methotrexate when the human chorionic gonadotropin (HCG) level elevated during week 22 and after.

The outcome was favorable, although the newborn suffered from tetralogy of Fallot.

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Fig. 1. A female newborn weighing 2200 g. A normal placenta (thin arrow). A hydatidiform mole (thick arrow).

2. Case presentation

A 23-year-old Syrian primigravida woman came to our hospital with vaginal bleeding. On ultrasound examination, we revealed a normal-appearing female fetus at 21 weeks, with two placentas. The first was normal. But the second was larger, multivesicular, and hyperechogenic with a snowstorm appearance, which suggested a complete hydatidiform mole with co-existing fetus (CHMCF) or partial hydatidiform mole (Figs. 2 and 3).

The pregnancy was spontaneous. There is no medical history and no family history of a molar pregnancy but a twin pregnancy. After counseling, she elected to continue pregnancy. After resting in bed, the bleeding stopped. Laboratory tests were within normal ranges, except serum B-human chorionic gonadotropin (B-hCG) level was 700,000 IU

\mL. We administered 50 mg of methotrexate intramuscular (IM) once \weekly for two weeks. She remained asymptomatic without any complications and had normal blood pressure. At 25-gestational-week, serum B-hCG was 124,000. Again, we administered 50 mg of methotrexate IM once \weekly for two weeks. At 28-gestational-week, the B-hCG level was 51,700 and we did not need more methotrexate.

At 31-gestational-week, molar pregnancy declined. Her blood pressure was 120\80 mmHg.

She delivered a 2200-gram alive female infant with uncomplicated cesarean delivery at 38 gestational age. On macroscopic examination, there were two placentas. The first was normal. The second was remnants of the molar placenta. After birth, the baby was cyanotic, cardiologist examined her and diagnosed tetralogy of Fallot. Pathohistological examination revealed a complete hydatidiform mole with a co-existent live fetus (CHMCF) (Fig. 1).

By following up, B-hCG levels decreased gradually.

3. Discussion

CHMCF is a rare obstetric condition, and there is still controversy about the management of these cases.

Most of the cases ported in the literature said that continuation of CHMCF is an acceptable option, and pregnancy may continue until term if normal fetal anatomy is assured and maternal complications are under control [4,7].

Current guidelines for the management of CHMCF recommend close clinical monitoring if the mother and fetus are stable and have urgent delivery in case of complications [7].

In our case, the patient was stable except for the elevation of B-hCG levels, so we considered methotrexate for management.

Methotrexate, which is a folic acid antagonist, blocks the synthesis of thymidine and inhibits DNA synthesis. Therefore, methotrexate can disrupt dividing cells. Methotrexate has been used in malignant diseases, rheumatic disorders, ectopic pregnancy, and psoriasis [8]. In malignant diseases, methotrexate is effective because of its ability to inhibit cellular proliferation [10]. It has recently become a standard treatment

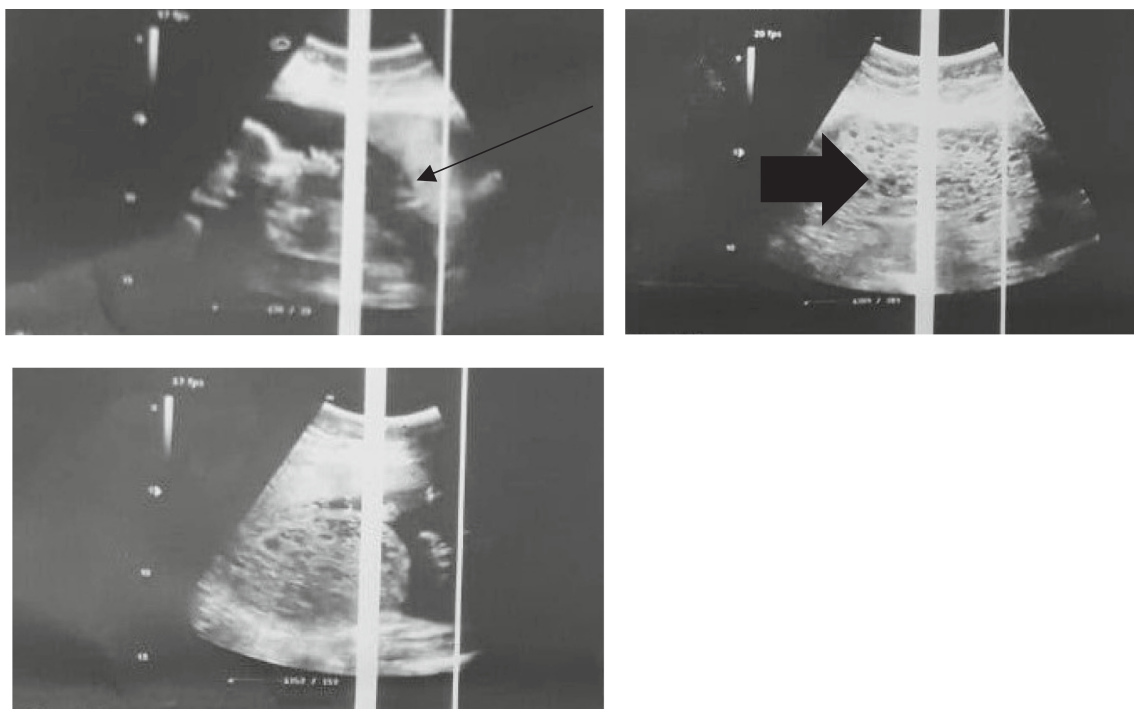


Fig. 2. An ultrasound image showing a live fetus aged 20 weeks 5 days. Two placentas, the anterior one is normal (thin arrow), the posterior one is large and has a snow-storm appearance consistent with Hydatidiform Mole (thick arrow).

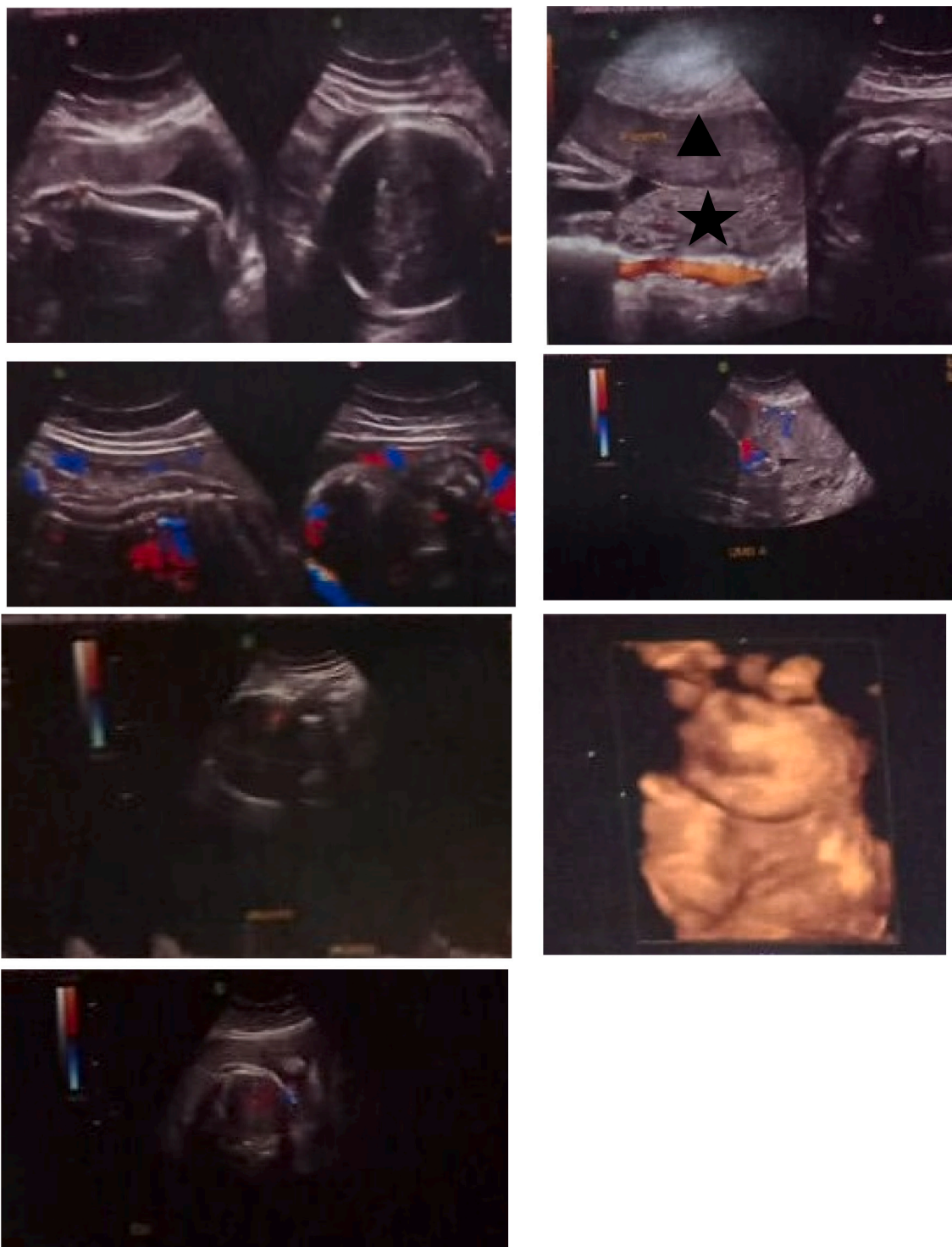


Fig. 3. A pulsed and colored Doppler image showing a live fetus aged 31 weeks 5 days according to BPD. A mature placenta on the anterior wall of the uterus (triangle). A hydatidiform mole with a diameter of 60 mm and a thickness of 15 mm (star).

for ectopic pregnancy, as it can interrupt the growth of trophoblastic cells [8,11]. All the above raise the hypothesis that methotrexate can stop molar pregnancy. Methotrexate can stop the uncontrolled proliferation of the placenta [12] and molar pregnancy is a type of this proliferation.

On the other hand, methotrexate is considered a human teratogen. Case reports and case series of exposure to it during pregnancy began appearing in the 1960s [8].

Feldkamp and Carey (1993), suggested the sensitive period to be 6 to

8 weeks after conception based on the reports of six malformed infants. They also proposed the dose to produce malformation is 10 mg/week or more [8]. Here, we present some literature.

Avile's et al. [14] presented the outcome of women treated during gestation for acute leukemia. Nine of the women received methotrexate as part of their regimens. Only five of them were treated during the first trimester. They did not report the dose or gestational weeks of exposure. There were no malformations reported [8].

Donnenfeld et al. [15] surveyed 63 teratology information services

and identified 21 prospectively ascertained cases of methotrexate exposure before or during pregnancy. Five exposures occurred during pregnancy, four of which occurred between 0 and 6 weeks after conception, and one of which occurred in the third trimester [8].

All babies exposed during pregnancy were normal. Four of nine women with methotrexate exposure during the year preceding pregnancy had spontaneous abortions and one child had a cavernous hemangioma. The authors concluded that the normal outcomes in the four children with first-trimester exposure were consistent with the report by Feldkamp and Carey [17], because the exposures were less than 10 mg/week or because the treatment was discontinued by 6 weeks after conception [8].

Østensen et al. [20] presented four women who received methotrexate during early pregnancy and before 6 weeks after conception. The result was one spontaneous abortion and three normal infants [8].

Chakravarty et al. [19] used a questionnaire to solicit information about pregnancies exposed to disease-modifying antirheumatic drugs. Among 38 methotrexate-exposed pregnancies with known outcomes, there were two children and one abortus with unspecified malformations [8]. Unfortunately, the results are not clear because the response rate to the questionnaire is only 29 %, and it is not clear how and by whom the pregnancy outcomes were ascertained [8].

Lowden et al. [21] conduct a 9-year study about methotrexate for the treatment of rheumatologic or chronic inflammatory disorders in pregnant women. There were 28 pregnancies with follow-up among 27 women. Only two women took methotrexate after 6 weeks after conception, one of them elected abortion, while the other had a child with an eyelid angioma and bilateral metatarsus varus. The result was five electives and four spontaneous abortions and 19 liveborn infants with no major malformations [8]. This study does not contradict the conclusions of Feldkamp and Carey [17], inasmuch as only one continuing pregnancy was exposed during the sensitive period proposed by them [8].

Poggi and Ghidini [16] reported a case where methotrexate was used for a misdiagnosis of ectopic pregnancy less than 4 weeks after conception. The pregnancy continued and resulted in a child with tetralogy of Fallot [8]. Management of ectopic pregnancy with methotrexate involves high doses during the 2 or 3 weeks after implantation.

Nurmohamed et al. [18] reported a case series of eight intrauterine pregnancies with methotrexate treatment for misdiagnosis of ectopic pregnancy. Two pregnancies continued to viability and had tetralogy of Fallot. These pregnancies had been exposed to methotrexate at 3 and 4 weeks after conception [8].

As the characteristic of methotrexate embryopathy was derived from case reports, we cannot prove if any malformation in infants exposed to methotrexate was surely caused by methotrexate [8].

However, by going back to the cardiac embryology, we found that the major embryologic development of the cardiac structure is complete by the end of the seventh postconceptual week in the human (day 49). Thus, most of the congenital cardiac defects recognized at birth have their origin during these critical early weeks of cardiac embryogenesis [13]. If, for example, congenital heart disease occurs in nearly 1 % of newborns, it might reasonably be expected that congenital heart disease will occur in nearly 1 % of methotrexate-exposed newborns, even if methotrexate does not cause congenital heart disease [8].

Thus, on one hand, we had the risk of complications associated with the high level of B-hCG, and on the other hand, we had the teratogen effect of methotrexate. After discussing the choices with the patient she elected to continue pregnancy and accepted methotrexate exposure to control B-hCG levels despite its risks. We obtained informed consent and administered 3 courses of methotrexate. The outcome was favorable without complications. The newborn was diagnosed with tetralogy of Fallot.

4. Conclusion

In the lack of clinical guidelines to manage such cases, we recommend that pregnant patients with a complete hydatidiform mole with a co-existing fetus who do not develop complications should be advised to continue pregnancy.

As for methotrexate use in such cases, we should do more research to determine its benefits and risks if it is used in a safe dosage within the permissible period of pregnancy.

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The authors declared that they have no conflict of interest.

Ethical approval

Ethical approval is not required.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Nazih Tawashi: The Supervisor, patient care, revising critically.

All authors discussed the content of the manuscript, read and approved the final manuscript.

Research registration

This is not a first in man case report. This registration is not required.

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Declaration of competing interest

None.

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References

- [1] N. Zilberman Sharon, R. Maymon, Y. Melcer, E. Jauniaux, Obstetric outcomes of twin pregnancies presenting with a complete hydatidiform mole and coexisting normal fetus: a systematic review and meta-analysis, *BJOG* 127 (12) (2020) 1450–1457.
- [2] T.J. Ferraz, C.M. Bartosch, C.M. Ramalho, F.A. Carvalho, B.C. Carvalho, O. G. Brandão, et al., Complete mole in a dichorionic twin pregnancy after intracytoplasmic sperm injection, *Rev. Bras. Ginecol. Obstet.* 35 (1) (2013) 39–43.
- [3] P. Fatima, M.M. Hossain, S. Ishrat, D. Rahman, H.B. Hossain, Outcome of triplet pregnancy with hydatidiform mole and coexisting twin live fetus following ICSI, *Mymensingh Med. J.* 23 (3) (2014) 590–594.
- [4] M. Suksai, C. Suwanrath, O. Kor-Anantakul, A. Geater, T. Hanprasertpong, T. Atjimakul, et al., Complete hydatidiform mole with co-existing fetus: predictors of live birth, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 212 (2017) 1–8.

- [5] M.L. Sánchez-Ferrer, F. Hernández-Martínez, F. Machado-Linde, B. Ferri, P. Carbonel, A. Nieto-Díaz, Uterine rupture in twin pregnancy with normal fetus and complete hydatidiform mole, *Gynecol. Obstet. Investig.* 77 (2) (2014) 127–133.
- [6] E. Arsène, E. Clouqueur, M. Stichelbout, L. Devisme, P. Vaast, D. Subtil, Twin pregnancy with complete mole and coexisting fetus: reach fetal viability is possible, *J. Gynecol. Obstet. Biol. Reprod. (Paris)* 44 (9) (2015) 887–890.
- [7] L.B. Lipi, L. Philp, A.K. Goodman, A challenging case of twin pregnancy with complete hydatidiform mole and co-existing normal live fetus - a case report and review of the literature, *Gynecol. Oncol. Rep.* 31 (2020), 100519.
- [8] S.C. Hyoun, S.G. Običan, A.R. Scialli, Teratogen update: methotrexate, *Birth Defects Res. A Clin. Mol. Teratol.* 94 (4) (2012) 187–207.
- [9] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, *Int. J. Surg.* 84 (2020) 226–230.
- [10] E.S. Chan, B.N. Cronstein, Methotrexate—how does it really work? *Nat. Rev. Rheumatol.* 6 (3) (2010) 175–178.
- [11] K.T. Barnhart, G. Gosman, R. Ashby, M. Sammel, The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens, *Obstet. Gynecol.* 101 (4) (2003) 778–784.
- [12] J.J. Candelier, The hydatidiform mole, *Cell Adhes. Migr.* 10 (1–2) (2016) 226–235.
- [13] M.D. Reller, R.W. McDonald, L.M. Gerlis, K.L. Thornburg, Cardiac embryology: basic review and clinical correlations, *J. Am. Soc. Echocardiogr.* 4 (5) (1991) 519–532.
- [14] Avile's, *Am. J. Hematol.* (1991), <https://doi.org/10.1002/ajh.2830360404>.
- [15] Donnenfeld, *Teratology* (1994), <https://doi.org/10.1002/tera.1420490202>.
- [16] Poggi, *Fertil. Steril.* (2011), <https://doi.org/10.1016/j.fertnstert.2011.06.014>.
- [17] Feldkamp, *Teratology* (1993), <https://doi.org/10.1002/tera.1420470605>.
- [18] Nurmohamed, *Am. J. Obstet. Gynecol.* (2011), <https://doi.org/10.1016/j.ajog.2011.07.002>.
- [19] Chakravarty, *J. Rheumatol.* (2003).
- [20] Ostensen, *J. Rheumatol.* (2000).
- [21] Lewden, *J. Rheumatol.* (2004).