

**TWO-DOSE METHOTREXATE REGIMEN FOR TREATMENT OF CESAREAN SECTION SCAR PREGNANCY****IBRAHIM A. ABDELAZIM<sup>1,2</sup>, S.U. SHIKANOVA<sup>3</sup>, B. ZH. KARIMOVA<sup>3</sup>**<sup>1</sup>Ain Shams University, Cairo, Egypt<sup>2</sup>Ahmadi hospital, Kuwait Oil Company (KOC), Kuwait<sup>3</sup>West Kazakhstan Marat Ospanov Medical University, Aktobe, KazakhstanIbrahim A. Abdelazim – <http://orcid.org/0000-0002-7241-2835>Svetlana Shikanova – <https://orcid.org/0000-0003-2261-4559>Bakyt Karimova – <https://orcid.org/0000-0001-5658-3995>

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Абделазим Ибрахим А, Шиканова СЮ, Каримова БЖ. Случай успешно пролеченной беременности на рубце после кесарева сечения двумя дозами метотрексата. West Kazakhstan Medical Journal.2020;62(4):265-269

**Two-dose Methotrexate Regimen for Treatment of Cesarean Section Scar Pregnancy**Ibrahim A. Abdelazim<sup>1,2</sup>, S.U. Shikanova<sup>3</sup>, B. Zh. Karimova<sup>3</sup><sup>1</sup> Ain Shams University, Cairo, Egypt.<sup>2</sup> Ahmadi hospital, Kuwait Oil Company (KOC), Kuwait.<sup>3</sup> West Kazakhstan Marat Ospanov medical university, Aktobe, KazakhstanCesarean section scar pregnancy (CSSP) at 5 weeks+2days and initial  $\beta$ -hCG 4361 mIU/ml was diagnosed in a 44-year-old patient (previous 3 vaginal deliveries and one cesarean section) by trans-vaginal ultrasound (TVS).She refused methotrexate (MTX) treatment at the beginning, and she decided to repeat  $\beta$ -hCG after two days, which came as 5378 mIU/ml.She agreed for MTX treatment later, after she noticed the rising  $\beta$ -hCG titer. The repeated  $\beta$ -hCG was 6758 and 6132 mIU/ml on the 4th and 7th day; respectively following first MTX-dose, therefore, she was given the second MTX-dose.The  $\beta$ -hCG decreased from 6132 mIU/ml to 4335 mIU/ml on the 4th day following the second MTX-dose (>15% drop of  $\beta$ -hCG).Follow-up  $\beta$ -hCG showed gradual drop from 2736 mIU/ml on 7th day following second MTX-dose, to 682.8 mIU/ml on 2nd week following second MTX-dose, then to 20.2, and 83.1 mIU/ml on 3rd and 4th week; respectively following second MTX-dose.Furthermore,  $\beta$ -hCG dropped to 35.6 and 15.26 mIU/ml on 5th and 6th week; respectively following second MTX-dose and returned to non-pregnant level 4.07 mIU/ml on the 8th week following second MTX-dose.

This report represents variant of CSSP successfully treated with two-dose MTX regimen with no side effects and/or complications.

This report suggests the two-dose MTX regimen for treatment of CSSP diagnosed at 5-6 weeks, with no viable fetus, and initial  $\beta$ -hCG between 5500-6000 mIU/ml.**Keywords:** Two-dose, Methotrexate, Regimen, Treatment, CSSP.**Метотрексаттың екі еселенген дозасымен кесар тілігінен кейінгі тыртықтағы жүктілікті нәтижелі емдеу жағдайы**Ибрахим А.Абделазим<sup>1,2</sup>, С.Ю. Шиканова<sup>3</sup>, Б.Ж. Каримова<sup>3</sup><sup>1</sup>Айн Шамс университеті, Каир, Египет.<sup>2</sup>Ахмади ауруханасы, Кувейт мұнай компаниясы, Кувейт.<sup>3</sup>Марат Оспанов атындағы Батыс Қазақстан медицина университеті, Ақтөбе, Қазақстан.44 жастағы науқаста (анамнезінде 3 кынаптық және 1 кесар тілігімен босану) трансвагинальды ультрадыбыстық зерттеуде (TVS)  $\beta$ -АХГ бастапқы мөлшері 4361 мМе/мл кесар тілігі операциясынан кейінгі тыртықта жүктіліктің 5 аптасы+2 күні анықталды.Науқас қайталап тексеруде  $\beta$ -АХГ титрінің жоғарылауы (5378 мМе/мл) анықталғанда метотрексатпен (МТ) емделуге келісін берді.Метотрексаттың бірінші дозасын қабылдағаннан кейін  $\beta$ -АХГ титрі 6758 мМе/мл, 4-ші және 7-ші күндері 6132 мМе/мл құрады. Науқаста метотрексаттыңShikanova S.Yu  
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екінші дозасын қабылдағаннан кейін  $\beta$ -АХГ титрі 4 күндері 6132 мМЕ/мл-ден 4335 мМЕ/мл дейін төмендеді ( $\beta$ -АХГ титрінің төмендеуі 15%). Кезекті бақылауда  $\beta$ -АХГ титрінің деңгейі 7-ші күні 2736 мМЕ/мл-ден метотрексаттың екінші дозасын қабылдағаннан кейінгі екінші аптада 682,8 мМЕ/мл дейін, кейін 3-ші және 4-ші аптада 20,2 мен 83,1 мМЕ/мл сәйкес төмендеді. Зерттеудің 5-ші және 6-ші апталарында  $\beta$ -АХГ титрінің 35,6 мМЕ/мл және 15,26 мМЕ/мл төмендеп, метотрексаттың екінші дозасын қабылдағаннан кейінгі 8-ші аптада жүкті емес әйелдердегі мөлшермен теңесті, яғни 4,07 мМЕ/мл құрады. Бұл зерттеуде  $\beta$ -АХГ бастапқы деңгейі 5500-6000 мМЕ/мл және кесар тілігі операциясынан кейінгі тыртықтағы жүктілікте әлі өмірге қабілеттілігі жоқ ұрықтың 5-6 апталық кезеңінде метотрексаттың екі еселенген дозасымен емдеу кестесі ұсынылған.

**Негізгі сөздер:** екі доза, метотрексат, кесте, емдеу, кесар тілігінен кейінгі тыртықтағы жүктілік.

#### Случай успешно пролеченной беременности на рубце после кесарева сечения двумя дозами метотрексата

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У 44-летней пациентки (в анамнезе 3 вагинальных родов и одно кесарево сечение) диагностирована беременность на рубце после кесарева сечения с помощью трансвагинального ультразвукового исследования (ТВУЗИ) в сроке 5 недель+2 дня и начальном уровне  $\beta$ -ХГЧ 4361 мМЕ/мл.

Пациентка согласилась на лечение метотрексатом после повышения титра  $\beta$ -ХГЧ (5378 мМЕ / мл) при повторном определении.

После первой дозы метотрексата титр  $\beta$ -ХГЧ составил 6758 и 6132 мМЕ/мл на 4-й и 7-й день. Пациентка получила вторую дозу метотрексата, после которой уровень  $\beta$ -ХГЧ на 4-й день снизился с 6132 мМЕ/мл до 4335 мМЕ/мл (падение уровня  $\beta$ -ХГЧ > 15%).

При последующем наблюдении уровень  $\beta$ -ХГЧ показал постепенное снижение с 2736 мМЕ/мл на 7-й день до 682,8 мМЕ/мл на 2-й неделе после второй дозы метотрексата, затем до 20,2 и 83,1 мМЕ/мл на 3-й и 4-й неделе соответственно. Далее, уровень  $\beta$ -ХГЧ снизился до 35,6 и 15,26 мМЕ/мл на 5-й и 6-й неделе соответственно и вернулся к уровню небеременных 4,07 мМЕ/мл на 8-й неделе после второй дозы метотрексата.

В этой публикации предлагается схема с двумя дозами метотрексата для лечения беременности на рубце после кесарева сечения, диагностированного на 5-6 неделях при отсутствии жизнеспособного плода, и начальном уровне  $\beta$ -ХГЧ в диапазоне 5500-6000 мМЕ / мл. .

**Ключевые слова:** две дозы, метотрексат, схема, лечение, беременность на рубце после кесарева сечения.

## Introduction

Cesarean section scar pregnancy (CSSP) is an intrauterine pregnancy, and it may result in a live offspring if not terminated [1]. To date there were 27 live births reported following conservative treatment of CSSPs [1]. CSSPs occur after implantation of the fertilized ovum over the previous cesarean section (CS) or hysterotomy scar(s) [2].

The CSSP is often misdiagnosed as ongoing inevitable miscarriage, because of the low position of the gestational sac (GS) near the uterine cervix [3].

The number of previous scars is not risk factor for CSSP, and it occurs following elective CS [4]. The true incidence of CSSP estimated as 1/1800-1/2500 of all cesarean deliveries [5]. The incidence of CSSP increased due to increased CSs rate, and improved diagnostic imaging tools [6].

This report represents variant of CSSP successfully treated with two-dose Methotrexate (MTX) regimen.

## Case Report

Cesarean section scar pregnancy (CSSP) at 5 weeks+2days was diagnosed in a 44-year-old patient (previous 3 vaginal deliveries and one cesarean section) by trans-vaginal ultrasound (TVS), which showed that GS (gestational sac) is located in the lower uterine anterior quadrant close to the site of the previous CS scar (with yolk sac inside), and initial  $\beta$ -hCG 4361 mIU/ml on 31st July 2020.

She refused MTX treatment at the beginning, and she decided to repeat the  $\beta$ -hCG after two days, which came as 5378 mIU/ml on 2nd August 2020.

On 3rd of August she decided to receive the first MTX-dose after she noticed the rising  $\beta$ -hCG titer. The repeated

$\beta$ -hCG was 6758 and 6132 mIU/ml on the 4th (7th August 2020) and 7th (10th August 2020) day; respectively following first MTX-dose, therefore, she was given the second MTX-dose.

The  $\beta$ -hCG decreased from 6132 mIU/ml on 10th August 2020 (day of second MTX-dose) to 4335 mIU/ml on the 4th day following second MTX-dose (>15% drop of  $\beta$ -hCG), so no more MTX-doses were given to the studied woman.

Follow-up  $\beta$ -hCG showed gradual drop from 2736 mIU/ml on 7th day following second MTX-dose, to 682.8 mIU/ml on 2nd week following second MTX-dose, then to 20.2, and 83.1 mIU/ml on 3rd and 4th week; respectively following second MTX-dose.

Furthermore,  $\beta$ -hCG dropped to 35.6 and 15.26 mIU/ml on 5th and 6th week; respectively following second MTX-dose and returned to non-pregnant level 4.07 mIU/ml on the 8th week following second MTX-dose (Figure 1).

Studied woman counselled regarding the risk of pregnancy in the first 6 months following the MTX regimen, and possibility of the CSSP recurrence. Departmental approval and written consent taken from the studied woman to publish her data as case report.

**Discussion**

CSSP usually diagnosed in women with previous uterine scar(s) based on positive pregnancy test, and ultrasound criteria of CSSPs which include [7]: 1) empty uterus with closed cervical canal; 2) GS located in lower uterine segment (LUS) below the bladder close to the internal os and previous scar(s) with yolk sac and/or embryo (Figure 2); 3) Thin myometrium layer between the GS and urinary bladder, and 4) Numerous blood vessels around the GS (Figure 3).

The risk of CSSP recurrence is 1%, and treatment of CSSP should be individualized based on the future desired fertility and patient’s age [7].

CSSPs with no yolk sac or fetal cardiac activity can be managed by ultrasound, and  $\beta$ -hCG follow-up until the  $\beta$ -hCG returns to non-pregnant level with or without MTX.

CSSPs with yolk sac and/or fetal cardiac activity can be managed either by termination or continuation of pregnancy. Women decided to continue the pregnancy, should counselled regarding the risks of hemorrhage, uterine rupture, morbid adherent placenta (MAP) and possibility of emergency hysterectomy [2].

Termination of CSSPs should be individualized based on desired future fertility, patient’s age, and clinicians’ experience.

1) Surgical approaches: Suction aspiration is the traditional choice, but it usually associated with major bleeding which may necessitate life-saving hysterectomy. Insertion of Foley’s catheter at the CSSP site inflated with saline as tamponade is potentially useful technique and can be combined with the suction aspiration [2].

Traditional dilatation and curettage (D&C) often complicated by hemorrhage. The reported emergency

Date	Time	Result	Units	Reference
13/10/20	13:52	2.71	mIU/mL	0.0-10.0
7/10/20	11:09	4.07	mIU/mL	0.0-10.0
24/9/20	10:45	15.26 H	mIU/mL	0.0-10.0
17/9/20	10:58	35.63 H	mIU/mL	0.0-10.0
9/9/20	09:03	83.61 H	mIU/mL	0.0-10.0
2/9/20	12:01	201.2 H	mIU/mL	0.0-10.0
26/8/20	12:19	682.8 H	mIU/mL	0.0-10.0
18/8/20	10:38	2736 H	mIU/mL	0.0-10.0
14/8/20	09:16	4335 H	mIU/mL	0.0-10.0
10/8/20	21:34	6132 H	mIU/mL	0.0-10.0
7/8/20	21:22	6758 H	mIU/mL	0.0-10.0
2/8/20	23:24	5378 H	mIU/mL	0.0-10.0
31/7/20	23:47	4361 H	mIU/mL	0.0-10.0

Figure 1.  $\beta$ -hCG levels of the studied woman after two Methotrexate (MTX)-dose regimen

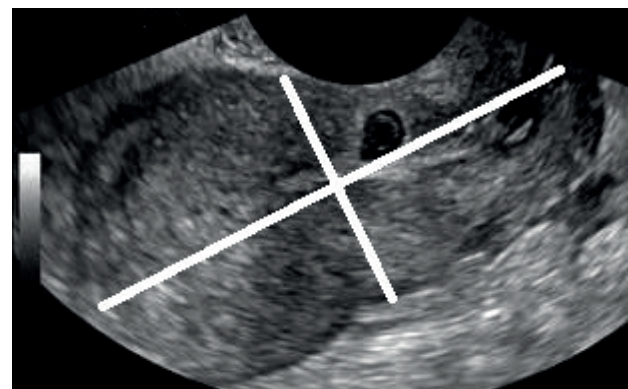


Figure 2. Trans-vaginal ultrasound image of the cesarean section scar pregnancy (CSSP) shows gestational sac (GS) with yolk sac inside



Figure 3. Trans-vaginal ultrasound image shows the blood vessels around the CSSP gestational sac (GS)

hysterectomy rate was 14% following traditional D&C in CSSPs series [8].



Hysteroscopic resection has reported for CSSPs treatment at initial  $\beta$ -hCG of 28,333 mIU/ml [9]. Hysteroscopic resection is not preferred for CSSPs treatment when the residual myometrium  $<3$  mm (risks of uterine perforation and bladder injury are high).

Transabdominal excision of CSSPs, allows revision of LUS and reduces risk of recurrence. Laparotomy indicated in CSSPs complicated by life-threatening hemorrhage and/or uterine rupture.

2) Local injection of MTX or KCl (ultrasound guided) is the most effective treatment for CSSPs between 6-8 weeks' (it stops the cardiac activity) and should be considered with desired future fertility [2].

3) Systemic MTX: Systemic intramuscular (IM) multi-dose MTX regimen for CSSPs treatment combined with ultrasound, and  $\beta$ -hCG follow-up [10].

Oral ulcers with decreased hematological parameters were recorded as side effects following multi-dose MTX treatment for CSSPs and ectopic pregnancies (EPs) [10].

4) Uterine artery embolization with local intragestational MTX or systemic MTX with intragestational MTX were similarly effective in treating CSSP, and both treatments likely to fail when the GS  $>5$  cm in diameter [11].

The studied CSSP case managed successfully by two-dose MTX regimen, and  $\beta$ -hCG decreased from 6132 mIU/ml to 4335 mIU/ml on the 4th day following second MTX-dose ( $>15\%$  drop of  $\beta$ -hCG), so no more MTX doses were given to the studied woman. Successful treatment following MTX indicated by decreased  $\beta$ -hCG by  $\geq 15\%$  on the 4th day following second MTX-dose, and this explains why the studied woman was given only two MTX-doses.

She was followed by  $\beta$ -hCG, vaginal ultrasound, and blood picture, till the  $\beta$ -hCG return to non-pregnant level (4.07 mIU/ml) on the 8th week following second MTX-dose.

Abdelazim et al. found the  $\beta$ -hCG dropped to zero, and the GS completely disappeared on the 5th week following multi-dose MTX regimen for CSSP treatment [2].

Uludag et al. found the  $\beta$ -hCG returned to non-pregnant level 6 weeks after the multi-dose MTX regimen for CSSP [10].

The studied woman did not develop any side effects and/or complications following two-dose MTX regimen for CSSP treatment. Two-dose MTX regimen has been proposed by Barnhart et al. with 87% success rate in treatment of EPs [12].

A retrospective study reported 87% success rate for the single-dose MTX versus 90% success rate for the two-dose MTX in treatment of EPs [13].

A meta-analysis reported 89% success rate for MTX in treatment of EPs; the multi-dose MTX was significantly more successful than single-dose MTX (93% versus 88%) but caused more side effects [14].

This report represents a variant of CSSP successfully treated with two-dose MTX regimen with no side effects and/or complications.

### Conclusion

1. The regimen using two doses of methotrexate for the treatment of cesarean section scar pregnancy, diagnosed at 5-6 weeks, with no viable fetus, and initial  $\beta$ -hCG between 5500-6000 mIU/ml is effective.
2. The two-dose MTX regimen is recommended as an option for termination of pregnancy on the cesarean section scar pregnancy.
3. The two-dose MTX regimen has demonstrated high efficiency, absence of side effects, in contrast to the use of surgical methods for abortion or topical application of methotrexate.

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