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First Successful Pregnancy Outcome after Intrauterine Insemination in a Woman with Primary Infertility and Essential Thrombocythemia Treated with Interferon-Alpha and Aspirin

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SUMMARY

Introduction The management of pregnancy in young women with essential thrombocythemia is complex and may present a difficult problem. An adverse pregnancy outcome due to thrombosis or bleeding is a common complication. In addition, little is known about fertility in these women prior to the disease.

Case Outline We present the first case of a young woman with primary infertility and essential thrombocythemia who had uneventfully delivered a healthy boy in the fortieth week of pregnancy. Her platelet count was normalized during treatment with interferon-alfa.The patient failed to become pregnant in the natural way and after three attempts of programmed intercourse. She conceived only following intrauterine insemination. During pregnancy, the patient was carefully controlled by a hematologist and gynecologist.

Conclusion Natural course and prognosis of essential thrombocythemia is not adversely affected by pregnancy. In these women, the pregnancy should be planned only after normalization of platelet count. The interferon-alpha should be administered before the pregnancy to regulate and maintain the platelet count within the normal range. Intrauterine insemination with minimal hormonal stimulation due to the risk of thrombosis could be recommended as the safest treatment option of infertility in women with essential thrombocythemia.

Keywords: essential thrombocythemia; pregnancy; interferon-alpha; intrauterine insemination

INTRODUCTION

Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by an elevated platelet (Plt) count in the peripheral blood and the increased risk of vascular complications [1]. Patients with ET are predominantly women and 15% to 20% of them are diagnosed during the childbearing age [2]. Maternal and fetal complications during pregnancy in patients with ET are well documented [3, 4]. The causes of these complications are thrombosis of placental vessels leading to chronic blood flow insufficiency and placental infarctions [5]. However, little is known about the fertility in these patients before the onset of ET. Decision-making on pregnancy is therefore a frequent issue in the clinical management of young women with ET imposing on physicians difficulties in relation to treatment.

To the best of our knowledge, we report the first case of a young woman with ET who normalized the Plt count during treatment with interferon-alpha (INF-α) but failed to conceive in the natural way. The successful intrauterine insemination (IUI) was carefully followed up by a hematologist and gynecologist and she uneventfully delivered a healthy male newborn in the fortieth week of pregnancy.

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CASE REPORT

A 23-year-old woman was referred to the Clinic for Hematology, Clinical Center of Serbia in April 2005 because of a high Plt count. She has already experienced episodes of gingivorrhagia when tooth brushing over previous few years. Her physical examination revealed a mild splenomegaly (+1 cm below the left costal margin) which was later confirmed by abdominal ultrasonography. The initial complete blood cell count (CBC) showed white blood cells of 10.7×10^9/L, with normal cell differentiation, hemoglobin value of 132 g/L, and Plt count of 1748×10^9/L. Serum iron (24.5 μmol/L), total binding capacity (49.3 μmol/L), ferritin (53.5 μg/L) and other biochemical analyses were normal. A bone marrow (BM) aspirate showed numerous sheets of megakaryocytes and normal iron stores. A BM trephine biopsy revealed megakaryocytic hyperplasia without signs of fibrosis. Most megakaryocytes had abundant cytoplasm and showed hyperlobulation with a tendency to form clusters. In vitro culture of hematopoietic progenitors from the BM disclosed spontaneous CFU-E and spontaneous BFU-E growth. Conventional cytogenetic analyses showed a normal female karyotype 46, XX. Mutation of JAK2V617F was not de-

tected in the granulocytes of peripheral blood. Based on these findings, the diagnosis of ET was made following the World Health Organization criteria.

The treatment with anagrelide was started 3 months after the diagnosis was made, within a multicentre clinical study when her Plt count was 1866×10^9/L [6]. A complete hematological response was achieved after 3 weeks. Thereafter, her Plt count was maintained within the normal range (from 265 to 457×10^9/L), without any thrombotic or hemorrhagic complications. The patient was on initial and continuous anagrelide treatment with 1.5 mg per day for 6 years.

During the first 3 years of anagrelide treatment in clinical study, the patient was advised to use contraception during intercourse with her fiancé. After the multicentre clinical study was ended, and over the next 3 years of treatment with anagrelide, the patient did not enforce any contraception with expectation if she became pregnant to immediately stop with anagrelide. However, the pregnancy did not occur. She decided to discontinue anagrelide treatment after 6 years. In the next three months, she was taking only aspirin 100 mg daily. Assessment of fertility in both spouses was conducted after two years of primary infertility. Routine infertility investigations (serum FSH and LH concentrations, hysterosalpingography and semen analysis) detected no signs of perturbation, except for unilateral tubal obstruction. Basal body temperature was biphasic. Ureaplasma infection was treated in the male partner with an epididymal cyst. He was found to have normozoospermia.

Intercourse programming was attempted for three times. Afterwards, treatment with INF-α was started in the patient, at a dose of 3 MU s. c. three times per week, when the patient's Plt count was 1060×10^9/L. A month later her Plt count was still increased (922×10^9/L) and the dose of INF-α was intensified to 3 MU s. c. four times per week. Thereafter, her Plt count was normalized but the patient still could not get pregnant spontaneously. After four months of INF-α treatment and almost one year of conservative gynecological medical treatment, the gynecologist decided to conduct intrauterine insemination (IUI) with a minimal hormonal stimulation of the patient in the attempt to conceive. The ovarian stimulation was done by administration of clomiphene citrate tablets, 50 mg twice a day, starting day 2, for five days. The follicle was 18 mm on day 11 and endometrium was 9 mm, with adequate morphology. Ovulation triggering with human chorionic-gonadotrophin (hCG) 5000 IU was administered on the same day. Fallopian sperm perfusion (FSP) was performed 34 hours later. The "swim-up" method was used for sperm preparation. After swim-up, there were 110×10^6/ml of spermatozoa, which were used with 15 ml of Medicult media for FSP. Two weeks later the beta hCG test was positive (130 IU/L). Four weeks after FSP, intrauterine 18 mm gestational sac was identified, with 3 mm embryoblast. Fetal heart activity was confirmed one week later. The hematologist continued to monitor patient's Plt count once monthly. Following the normalization of her Plt count, the dose of IFN-α was continued thrice weekly until delivery. During further pregnancy monitoring regular laboratory analyses were performed. A double test for chromosome abnormalities screening was performed at 12th gestational week. Fetal morphology, fetal and utero-placental circulations and dynamics were assessed on monthly basis, continuously showing normal fetal growth and unaffected uteroplacental circulation. At 22nd week, there was an episode of abdominal pain with diarrhea, so that micronized progesterone was administered vaginally, 200 mg twice a day. At 27th gestational week, a 75 gr. OGTT revealed glucose intolerance, so that she was recommended diet with a low carbohydrate intake. At 40th week of gestations the Bishop score was 3, and Misgav Ladach Cesarean section was performed, with normal operative and postoperative outcome. A healthy baby boy was born, weighting 3.4 kg with a normal blood count. Starting from the delivery, the patient was given danaparoid sodium over the next seven days for the prevention of thrombosis, and INF-α was continued. The boy is now two and a half year old, with normal growth and development.

DISCUSSION

Available data about pregnancy in women with ET are mainly related to the complications arising during gestation, without evidence about their premorbid fertility. The most frequent complication is the fetal loss in the first trimester occurring in 31-35% women with ET. Estimated prevalence of the fetal loss in the general population is approximately 15 and 20% [4]. Moreover, the overall risk of fetal loss in women with ET is 3.4-fold higher than expected for an age-matched healthy population [7]. Live birth rate recorded in ET pregnancies was 63%, while full-term normal delivery was in 51%. [8]. Fetal complications occurred in 40% of ET pregnancies, whereas maternal complications, such as pre-eclampsia and arterial hypertension, developed in 9% of them.

Regarding the data from large patient series, the predictive risk factors for pregnancy outcome have not been identified in patients with ET [4, 9]. The presence of the JAK2 mutation in patients with ET was not clearly defined as a predictor of pregnancy complications. Other possible risk factors, such as age >35 years, Plt count or leukocytosis did not significantly influence the pregnancy outcome.

However, irrespective of the treatment modalities, the proportion of live births was higher (74%) in treated pregnancies than in untreated ones (43%) [10]. In respect to this finding it could be assumed that control of Plts may correlate positively with a successful pregnancy outcome. Thrombophilia is also known to play an important role in the development of complications in pregnancy in general population, but there is not enough data that could indicate the impact of thrombophilia in pregnant women with ET [11].

There is limited information concerning the fertility of women with ET. So far as we know, only a single case was reported of a 37-year-old woman with ET who developed massive intra-abdominal bleeding after transvaginal oocyte retrieval during in vitro fertilization [12].

Infertility is defined as a failure to achieve pregnancy during a year or more without use of contraception during the childbearing period and commonly affects 10–15% of the couples [13]. In our case, few factors influenced fertility. The patient had clogged Fallopian tube and myeloproliferative neoplasm with increased Plt count (ET) while the male partner had ureaplasma infection and epididymal cyst. An additional factor could be the psychological effect on fertility in both spouses. Oddens et al. [14] reported that infertile women had symptoms of depression and anxiety four times more frequently than fertile ones, which may negatively affect the outcome of treatment for infertility.

Currently, the IUI is the recommended method for the treatment of moderate male infertility and unexplained infertility [15]. The therapeutic procedure involves placing washed spermatozoa transcervically into the uterine cavity. The pregnancy rate after the IUI is 10–20% [16]. The known limitations of IUI are the potential risk of infection, ectopic pregnancies and miscarriages which arise at the same frequency as in application of other infertility treatment modalities. In our case, the IUI was the safest method of assisted fertilization, since it could be applied with minimal hormonal stimulation due to the risk of thrombosis since ET and its prothrombotic influence. Due to failure of prior therapy, our patient received selective estrogen receptor modulator, clomiphene citrate, which by binding to estrogen receptors increases endogenous production of pituitary gonadotropins. Ovulation triggering was achieved giving highly purified human chronic gonadotropin (hCG). This is significantly less aggressive method of ovulation stimulation than the usually used combination of recombinant follicle-stimulating hormone (FSH) and luteinizing hormone (LH) with recombinant hCG, which is the standard way of ovarian stimulation for the complex infertility treatment.

Our patient was treated before the conception and during the pregnancy with INF-α. According to the data from literature and also form our experience, INF-α is highly effective in normalization of the Plt count, and produce favorable response in 90% of pregnant woman with myeloproliferative neoplasms associated with thrombocytosis [17, 18]. It has been shown that INF-α lowers the Plt count by a direct effect on megakaryocytopoiesis. Based on results from the in vitro studies, INF-α neither crosses the placental barrier or affects fertility [19]. It also does not increase the risk of maternal and fetal complications during treatment.

It is important to provide young women with ET an opportunity to become mothers since the pregnancy itself does not adversely affect the natural course and prognosis of ET. The presented case also highlights the need for the assessment of fertility in this group of patients. The IUI can be recommended as the safest treatment option for infertility in women with ET. The INF-α should be applied before the pregnancy in order to achieve a favorable response and to maintain a normal Plt count. The pregnancy should be planned only after the Plt count has been normalized. Doppler ultrasonography of uteroplacental circulation in pregnancy should be conducted at monthly basis. Disease control achieved in this way provides a good opportunity for a normal course and a favorable outcome of pregnancy for both mother and child. In these women multidisciplinary approach is needed in order to achieve the most optimal treatment results.

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Прва успешна трудноћа након интраутерине инсеминације код болеснице с примарним инфертилитетом и есенцијалном тромбоцитемијом лечене алфа-интерфероном и аспирином

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КРАТАК САДРЖАЈ

Увод Лечење младих жена с есенцијалном тромбоцитемијом током трудноће је комплексно. Проблем представљају могуће тромбохеморагијске компликације које могу утицати на неповољан исход трудноће. Поред тога, мало се зна о плодности ових жена пре болести.

Приказ болесника Приказујемо први случај младе болеснице с примарним инфертилитетом и есенцијалном тромбоцитемијом која је успешно порођена у 40. недељи трудноће, при чему је родила здравог дечака. Код болеснице је нормализован број тромбоцита применом алфа-интерферона. Болесница није могла да затрудни природним путем, као ни након три покушаја програмираног односа. Она је остала трудна тек након интраутерине инсеминације. Детаљне и учестале контроле од стране хематолога и гинеколога током трудноће су биле неопходне.

Закључак Трудноћа нема негативан утицај на природни ток и прогнозу есенцијалне тромбоцитемије. Код ових болесница трудноћу треба планирати само након нормализације броја тромбоцита. Лечење алфа-интерфероном треба започети пре трудноће до нормализације броја тромбоцита, и наставити током трудноће уз одржавање броја тромбоцита у референтном опсегу. Интраутерина инсеминација с минималном хормонском стимулацијом због ризика од тромбозе може се препоручити као најсигурнија метода за лечење неплодности код жена с есенцијалном тромбоцитемијом.

Кључне речи: есенцијална тромбоцитемија; трудноћа; алфа-интерферон; интраутерина инсеминација

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