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Improved Post-Stillbirth Depression and Medical Adherence during Embryo Preservation Resulting in a Livebirth in a Woman with Chronic Hypertension and Systemic Lupus Erythematosus: A Case Report

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Abstract

Blood Pressure (BP) control, before conception or since early pregnancy, is important in pregnancy with Chronic Hypertension (CH). We present a woman with CH and Systemic Lupus Erythematosus (SLE), whose Fertility Preservation (FP) in pregnancy-prohibited phase may have contributed to BP control and a livebirth. A 33-year-old woman with CH and SLE conceived twins in SLE remission, without BP control. Both SLE flare and superimposed preeclampsia occurred, and the pregnancy was terminated because of renal dysfunction at 20 weeks. She presented with depression and decreased medical adherence, resulting in prolonged hypertension and pregnancy prohibition. FP was started 40 weeks after stillbirth, and a blastocyst was preserved at the fifth oocyte retrieval. Her medical adherence improved, and her BP became 120-130/90-100 mmHg. After thawed embryo transfer, she conceived a singleton pregnancy. Her BP was 120-130/70-90 mmHg during this pregnancy. At 32 weeks, she delivered a baby due to abnormal findings in Cardiotocogram. In this case, FP may have contributed to BP control and a livebirth. To our knowledge, this is the first report of FP in a pregnancy-prohibited woman with CH or SLE.

Keywords: Autoimmune disease; Fertility preservation; Hypertension; Pregnancy; Systemic lupus erythematosus

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Introduction

Pregnancy with Chronic Hypertension (CH) is a high-risk pregnancy because the incidence of Superimposed Preeclampsia (SPE), preterm birth, Fetal Growth Restriction (FGR), fetal/neonatal death, maternal death, and maternal cardiovascular morbidities such as heart failure, renal failure, stroke, and pulmonary edema are 3 to 10 times more frequent in patients with CH than in normotensive women [1]. It is well accepted that Blood Pressure (BP) control, before conception or since early pregnancy, is important. However, the target BP is controversial. The International Society for the Study of Hypertension in Pregnancy (ISSHP) states that the target BP should be in the range of 110-140/80-85 mmHg [2], and the National Institute for Health and Care Excellence (NICE) recommends a target BP of 135/85 mmHg [3]. In contrast, in 2019, the American College of Obstetricians and Gynecologists (ACOG) recommended that anti-hypertensive therapy for CH should be started when pregnant women have a BP ≥ 160/110 mmHg, and that the target BP should be 120-159/80-109 mmHg [4]. This recommendation is based on the finding that strict control of diastolic BP did not improve maternal/fetal outcomes. In April 2022, however, ACOG revised the target BP to 140/90 mmHg [5], based on the results of the Chronic Hypertension and Pregnancy study.

Pregnancy with Systemic Lupus Erythematosus (SLE) is also a high-risk pregnancy [6-8]. A study including patients with active and inactive disease at conception, showed a significantly higher incidence of hypertension, renal disease, preeclampsia, preterm delivery, cesarean delivery, FGR, and neonatal death in women with SLE than in women without SLE [8]. For women with SLE, conception is recommended after at least 6 months disease remission, which is based on reports showing that pregnancy loss is significantly higher in women who had active SLE during 6 months

before conception than in those who were in remission for >6 months before conception [6,7,9]. In Japan, the criteria for pregnancy in women with autoimmune disease are based on renal function. The estimated Glomerular Filtration Rate (eGFR) should be ≥ 60 mL/min/1.73 m^2. No such criteria for BP exist [10].

Here we present the case of a woman with CH and SLE who had a healthy baby after BP was controlled before pregnancy. It was suggested that embryo preservation during pregnancy-prohibited period may have contributed to improvement in depression and medical adherence, resulting in BP control and a livebirth. To our knowledge, this is the first report on the embryo preservation in pregnancy-prohibited woman with CH or SLE.

Case Presentation

A 21-year-old woman presented to our hospital with cheek erythema, oral ulcers, finger arthralgia, and thrombocytopenia; she was subsequently diagnosed with SLE at the department of rheumatology in our hospital. Her BP was normal, and her medical history was uneventful. An evaluation of the patient's family history showed that her mother had hepatic cancer, but there was no family history of autoimmune diseases, hypertension, thrombosis, or sudden death. The patient showed positive results in autoantibody tests for anti-DNA, anti-RNP, anti-Smith, anti-SSA, anti-SSB, and Lupus Anticoagulant (LA), and negative results for anti-cardiolipin and anti-β2 Glycoprotein I (β2-GPI). SLE flares were observed twice during the following 2 years. During the second flare, her BP was 130/80 mmHg. Subsequently, she was in remission and was taking 7 mg/day Prednisolone (PSL) and 4 mg/day Tacrolimus (TAC). She got married at the age of 30 years, and her disease remained in remission. She conceived spontaneously at 31 years of age, but the pregnancy resulted in a miscarriage at 7 weeks. LA and anti-β2-GPI tests were repeated 8 weeks after the miscarriage, but both showed negative results.

The patient subsequently visited a private fertility clinic, and her BP that time was 137/89 mmHg. She conceived dichorionic diamniotic twins after intrauterine insemination in a natural ovulatory cycle at 33 years of age. At 5 weeks of gestation, her BP was 138/102 mmHg. At 9 weeks, she presented with thrombocytopenia and skin erythema, and an SLE flare was diagnosed. Her PSL and TAC doses were augmented, and treatment with Hydroxychloroquine sulfate (HCQ) was initiated (Figure 1). At 13 weeks, she was referred to our Obstetrics and Gynecology (OBGY) department, a tertiary perinatal care center, and was subsequently managed in cooperation with the rheumatology department at our institute. At 13 weeks, LA test again showed negative result. Hypertension (150/110 mmHg) was observed at 13 weeks, and methyldopa, labetalol, and amlodipine were administered; however, her BP remained around 150/90 mmHg. She was admitted at 17 weeks because thrombocytopenia had not improved. Although intensive immunosuppression therapy, including intravenous immunoglobulin, augmentation of PSL, and initiation of Cyclosporin A (CyA) and azathioprine, was administered for the SLE flare, the thrombocytopenia did not improve. At 20 weeks, rapid progression of renal dysfunction was observed, which was indicated by changes in the serum creatinine levels (from 0.86 mg/dL to 1.19 mg/dL) and the eGFR (from 62.0 mL/min/1.73 m^2 to 43.4 mL/min/1.73 m^2). Her serum uric acid levels were also elevated (6.8 mg/dL). Because the patient's thrombocytopenia and renal dysfunction did not improve despite intensive immunosuppressive therapy, we concluded that SPE was complicated with the SLE flare, although the gestational age was only 20 weeks. Considering the gestational age, we recommended termination of pregnancy for maternal safety. After obtaining informed consent, therapeutic termination was performed

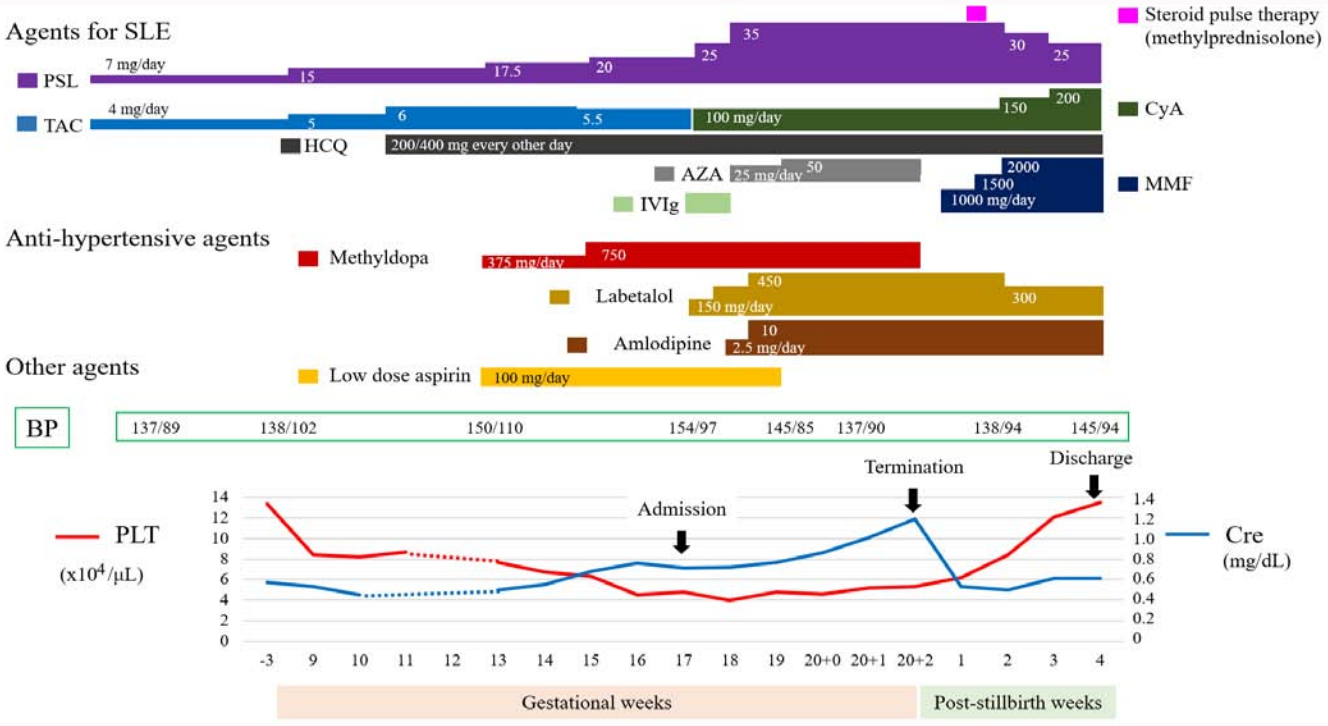

Figure 1: The clinical course of the second pregnancy with twins, which ended in therapeutic termination at 20 weeks.
SLE: Systemic Lupus Erythematosus; PSL: Prednisolone; TAC: Tacrolimus; HCQ: Hydroxychloroquine Sulfate; CyA: Cyclosporin A; AZA: Azathioprine; IVIg: Intravenous Immunoglobulin; MMF: Mycophenolate Mofetil; BP: Blood Pressure; PLT: Platelet Count; Cre: Creatinine

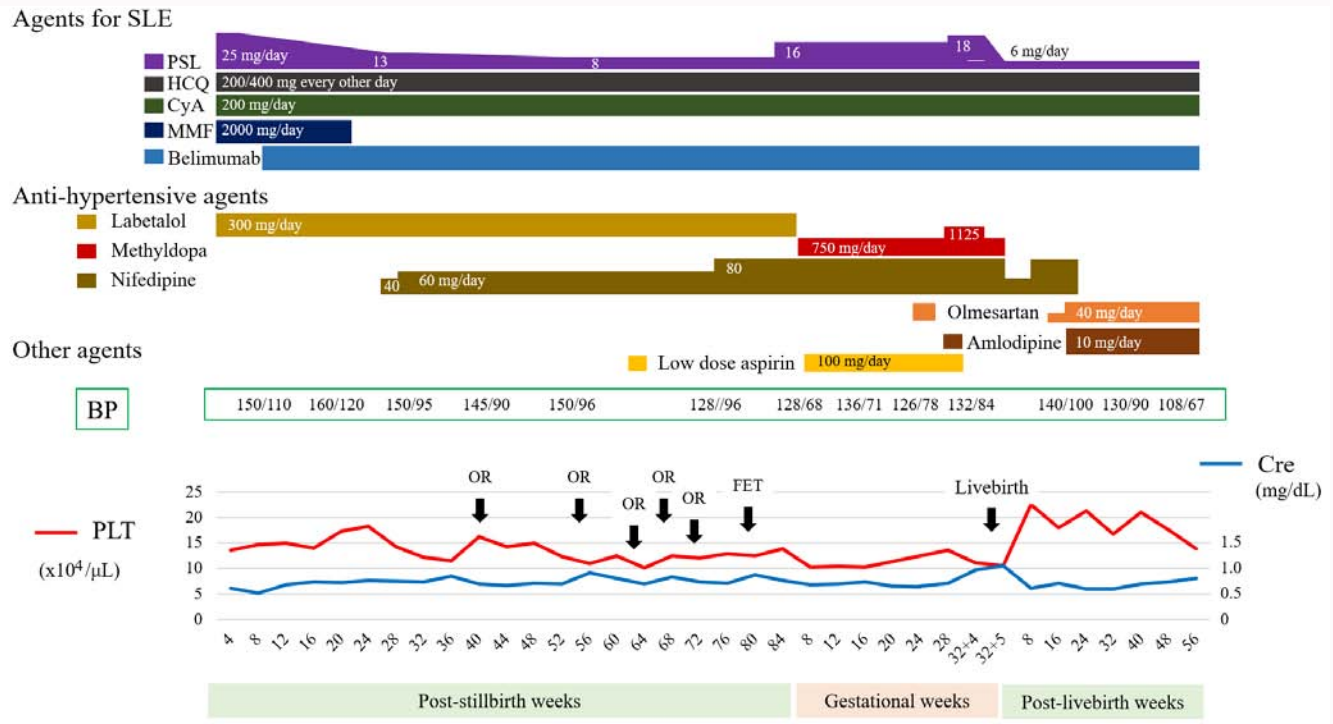

Figure 2: Clinical course post-stillbirth, including embryo preservation, and the third pregnancy, which ended in livebirth.
SLE: Systemic Lupus Erythematosus; PSL: Prednisolone; HCQ: Hydroxychloroquine Sulfate; CyA: Cyclosporin A; MMF: Mycophenolate Mofetil; BP: Blood Pressure; PLT: Platelet Count; Cre: Creatinine; OR: Oocyte Retrieval; FET; Frozen-Thawed Embryo Transfer

Table 1: Summary of embryo preservation trials.

Trial	Weeks after the still birth	Stimulation	Number of oocytes retrieved	Number of preserved trophoblasts
1st	40	Short	4	0
2nd	56	CC	1	0
3rd	64	CC	2	0
4th	68	CC	2	0
5th	72	CC	2	1

CC: Clomiphene Citrate

at 20+2 weeks using a cesarean section, and two babies (292 g and 272 g) were delivered.

After the stillbirth, immunosuppression therapy was administered more intensively, including steroid pulse therapy (intravenous methylprednisolone, 1,000 mg/day for 3 days), initiation of mycophenolate mofetil (which is contraindicated during pregnancy), and augmentation of CyA. As a result, her serum creatinine levels decreased, and platelet counts increased. Although her hypertension was prolonged, she was discharged 28 days after stillbirth.

Following the discharge, SLE was treated with PSL, CyA, HCQ, and belimumab, and renal function test results and platelet counts were controlled within normal ranges (Figure 2). However, her BP remained around 150-160/100-110 mmHg; therefore, pregnancy was not permitted. She became depressed soon after the stillbirth; at approximately 20 weeks after stillbirth, her depression became severe, and she stopped taking prescribed medicines. She contemplated suicide, but it was avoided with the help of a psychiatrist.

As we could not predict when pregnancy would be permitted, a prenatal team of doctors suggested embryo preservation to the fertility treatment team. We proposed that the couple undergo embryo preservation 36 weeks after the stillbirth to preserve fertility. The couple chose to proceed with the embryo preservation. Embryo preservation started 40 weeks after the stillbirth (Figure 2). The stimulation methods and outcomes are shown in Table 1. The first trial used the "short" protocol, and the following trials used administration of Clomiphene Citrate (CC). A blastocyst with good morphology was preserved for the first time at the fifth trial 72 weeks after the stillbirth. Following the embryo preservation trials, the patient's depression had ameliorated, and her adherence of medicines improved. Her BP was 120-130/90-100 mmHg, with the systolic BP falling into the normal range. SLE was in remission, and LA was negative once again. Rheumatology and OBGY doctors had a conference and permitted her pregnancy 76 weeks after the stillbirth.

After obtaining informed consent from the couple regarding the risks of pregnancy that included a possibility of twin pregnancy (2% in single blastocyst transfer), an SLE flare, preterm birth which could result in a neonatal mortality/morbidity, and the risk of mortality/morbidity to the patient, a thawed Embryo Transfer (ET) was performed in a spontaneous ovulatory cycle 80 weeks after the stillbirth. The patient developed a singleton pregnancy. In this pregnancy, her BP was maintained around 120-130/70-90 mmHg. However, serum creatinine was elevated to 0.97 mg/mL at 32+4 weeks, and she was subsequently admitted. At 32+5 weeks, elevated serum creatinine (1.06 mg/dL), decreased eGFR (53 mL/min/1.73 m^2), and abnormal findings on Cardiotocogram (loss of variability) were observed; therefore, an emergency cesarean was performed. A 1,580 g baby was delivered with a 5-min Apgar score of 9. After delivery, the serum creatinine levels became normal. Both the mother and baby were in good health 1 year after the delivery.

Discussion

We presented the case of a woman with CH and SLE whose first

pregnancy resulted in a miscarriage, the second pregnancy (without pre-conceptional BP control) resulted in therapeutic termination at 20 weeks, and the third pregnancy (with pre-conceptional BP control) resulted in a livebirth.

First, we estimated that the patient's hypertension was drug-induced due to administration of PSL and TAC for approximately 10 years.

Second, we diagnosed an SLE flare and SPE during the second pregnancy. In the management of pregnancy in patients with SLE, differential diagnosis of SLE flares and Hypertensive Disorders of Pregnancy (HDP) is important because the treatment for an SLE flare is immunosuppression, while the final treatment for HDP is termination of pregnancy [9]. However, a differential diagnosis may be challenging for clinicians because both conditions present with proteinuria, hypertension, and lower-extremity edema, and may also have systemic effects [9]. In this case, we concluded that both SLE flare and SPE were present because immunosuppressive therapy did not control the disease; therefore, therapeutic termination at 20 weeks was done. A twin pregnancy is a strong possible cause of SPE at an early gestational age. Postpartum improvement of renal dysfunction and thrombocytopenia supports this diagnosis.

Third, we discussed the safety of Assisted Reproductive Technology (ART) in women with SLE. The most serious complication associated with ovarian stimulation and ovarian hyper stimulation syndrome is thrombosis [11,12]. To avoid thrombosis, selection of appropriate ovarian stimulation, a "freeze all" strategy, and appropriate heparin administration should be performed, especially for those with Anti-Phospholipid Antibodies (APAs) [11,12]. To avoid thrombosis in thawed ET, a natural ovulatory cycle is the first choice. If hormone replacement is necessary, non-oral natural estradiol and progesterone should be administrated [12]. Furthermore, single ET should be performed to avoid the risks associated with multifetal pregnancy [12]. ART is not indicated in the women with acute flare, poorly controlled arterial hypertension, pulmonary hypertension, advanced renal disease, severe valvular or heart diseases, or major previous thrombotic events [11]. In this case, we considered that the patient had a low risk of thrombosis, because her anti-mullerian hormone was low (0.84 ng/mL), her APAs were negative, and she had no previous episode of thrombosis. In addition, because her platelet count was $>10 \times 10^4$ /μL, the risk of ovarian bleeding with Oocyte Retrieval (OR) was low. Therefore, we concluded that ovarian stimulation and OR were acceptable in this case.

Fourth, we discussed the validity of ET in this case as the patient's BP was 120-130/90-100 mmHg with a relatively high diastolic BP. As mentioned in the introduction, the target BP is controversial in pregnancy in women with CH, with ISSHP, NICE, and ACOG having different guidelines. In a retrospective analysis of 215 women with CH, Ueda et al. showed that systolic BP<130 mmHg within 14 weeks of gestation reduced the risk of developing early-onset SPE [13]. We (Kurashiki Central Hospital) participated in this study and recognized the importance of systolic BP control. In this case ET was performed in 2020 when the international guidelines for target diastolic BP ranged from 85 mmHg to 110 mmHg. Therefore, we believed ET to be acceptable in this case.

Lastly, we discussed Fertility Preservation (FP) in women with SLE, who are prohibited from getting pregnant. It is well accepted that SLE itself is not a cause of infertility [6,7,11,12]. However, administration of Cyclophosphamide (CPA) decreases ovarian reserve, resulting in decreased fertility [6,7,11,12]. Additionally, when a woman with SLE is advised not to conceive for a long period, her fertility decreases because of a decreased ovarian reserve and oocyte ageing [12]. It is demonstrated that clinicians should give information on FP, including cryopreservation of embryos/oocytes/ovarian tissue, to the female patients with SLE who are going to be administrated with CPA, in European Society of Human Reproduction and Embryology (ESHRE) guidelines [14] and American Society for Reproductive Medicine (ASRM) guidelines [15]. Accordingly, FP counseling before CPA administration is a common practice at present. In Japan, there have been reports on this issue since 2015. However, FP counseling for women with SLE who are advised not to conceive for a long period is not yet a common practice; FP counseling for these women is not present in the ESHRE or ASRM guidelines. A review by Italian doctors showed that FP should be considered for women who are advised not to conceive for a long period [12], suggesting that FP had been practical in Italy or European nations in these cases. However, we could not find such reports in English. We believe that FP for women prohibited from pregnancy is not yet a common practice because it is undetermined whether ART in women with SLE during a pregnancy-prohibited period is safe and effective. Additionally, we could not find the reports on FP in women with CH.

In conclusion, we present a woman with CH and SLE, in whom post-stillbirth depression and medical adherence improved during embryo preservation, resulting in systolic BP control and a livebirth. We reported this case because it provides information on FP in women with CH or SLE during pregnancy-prohibited period. However, the safety and effectiveness on this approach is undetermined, and careful consideration is necessary on a case-by-case basis.

Ethical Consideration

We have obtained the written informed consent from the patient for the publication of this report. The ethical committee of Kurashiki Central Hospital approved this report.

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