Efficacy of the combined administration of low dose aspirin and low molecular weight heparin in unexplained recurrent miscarriages with occasional antiphospholipid antibody positivity: A case report and literature review

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Case Report

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Abstract

Background: Recurrent miscarriage (RM), defined as three or more miscarriages, is estimated to occur in 1–3% of couples trying to conceive. Although several established causes of RM have been reported, the causes for half of all cases remain unexplained. Occasional antiphospholipid antibody (aPL)-positivity not diagnosed as antiphospholipid syndrome (APS) could be a risk factor for unexplained RM. However, no established treatment has been documented for patients with occasional aPL-positivity.

Case presentation: This patient with unexplained infertility underwent in vitro fertilization (IVF) and experienced three continuous miscarriages, including chemical pregnancy. The general screening for RM detected only aPL-IgG. However, the negative result obtained by the retest 12 weeks later suggested the case as an unexplained RM with occasional aPL-positivity not diagnosed with APS. Low-dose aspirin (LDA; enteric-coated aspirin tablet, 100 mg once daily) as an anticoagulant was administered on the day of embryo transfer (ET) and continued until a successful clinical pregnancy was determined. Although implantation was achieved with this intervention, a successful clinical pregnancy could not be achieved. Thereafter, low-molecular-weight heparin (LMWH; 10,000 IU every 12 h) and LDA (enteric-coated aspirin tablet, 100 mg once daily) were administered everyday starting on the day of ET and continued till 14 and 28 weeks of gestation, respectively. On day 16 post-ET, the serum β-human chorionic gonadotropin concentration was elevated to 2562.0 IU/L, and an ultrasound confirmed the pregnancy. The patient successfully completed the course of pregnancy and delivered a viable female neonate (3010 g) at 40 weeks and 3 days of gestation.

Conclusions: This case demonstrated that the combination therapy of LMWH and LDA led to a successful pregnancy and live birth in a patient with occasional aPL-positivity but not APS. However, further clinical trials are required to confirm the efficacy of the combined therapy of LMWH and LDA in patients with unexplained RM associated with occasional aPL-positivity.

Background

Recurrent miscarriage (RM) is defined as the loss of two or more pregnancies according to the most recent guidelines of the European Society of Human Reproduction and Embryology (ESHRE) [1] and the American Society of Reproductive Medicine (ASRM) [2]. It is a disorder of early gestation that affects approximately 1–3% of couples expecting a child [3]. Moreover, Antiphospholipid antibodies (aPLs) directed against phospholipid-binding proteins are complexly secreted during pregnancy, increase the risk of RM by activating the immune system leading to blood to clot abnormally and finally placental blood supply insufficiency due to thrombophilia[4]. Antiphospholipid syndrome (APS), an autoimmune disorder, is characterized by thrombotic events and/or pregnancy loss in the presence of aPL [5, 6]. According to the international criteria to define APS [6], patients are diagnosed with APS when lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL) are tested positive (in medium or high titer) persistently for 12 weeks. However, if aPL-positivity does not persist for 12 weeks on general screening for RM, patients are diagnosed as occasional aPL-positive without APS [7].

Treatment with anticoagulants such as low-dose aspirin (LDA) and low molecular weight heparin (LMWH) has been shown to benefit women with APS and, therefore, has also been used for thrombophilia [8]. In particular, the rationale for prescribing LDA and LMWH is based on their potential ability to promote both implantation and subsequent placentation, anti-inflammatory and immunomodulatory action [9], and safety during pregnancy for both mother and child [9–11]. On the contrary, occasional aPL-positivity without APS could also be a risk factor for unexplained RM— studies have reported occasional positivity of aPLs in 11.4–16.4% of women with a history of RM [12]. However, no established treatment method has been documented to treat patients with occasional aPL-positivity. Nevertheless, Sugiura-Ogasawara et al. demonstrated the efficacy of anticoagulants, such as LDA, to achieve successful pregnancies and live births in patients with unexplained RM experiencing occasional aPL-positivity [7]. On the contrary, Rai et al. demonstrated no benefits of anticoagulants in improving the subsequent live birth rate among women with unexplained RM [13]. These contradictory results could be attributed to the heterogeneous nature of the patients with unknown causes of RM. In addition, the efficacy of LMWH alone or the combination of LDA and LMWH for unexplained RM with occasional aPL-positivity has not been explored. Therefore, it is unclear what kind of treatment should be administered to patients with unexplained RM showing occasional aPL-positivity.

Here, we report a case of unexplained RM with occasional aPL-positivity. The patient with unexplained infertility underwent freeze-thawed blastocyst transfer and experienced three continuous miscarriages, including chemical pregnancy. On general screening for RM, only aPL-IgG was detected occasionally, and the patient was diagnosed with unexplained RM with occasional aPL-positivity. A regimen of combined administration of LMWH and LDA simultaneously at the time of vitrified-warmed blastocyst transfer followed by their administration till 14 and 28 weeks of gestation, respectively, led to a successful pregnancy and live birth.

Case Presentation

The patient was a 36-year-old G0P0 woman who presented to our fertility center seeking fertility treatment. The body mass index of the patient was 16.4 kg/m^2 (body weight, 38.2 kg). The patient had no prior surgical history, known allergies, or medications, including prenatal vitamins. The patient denied any history of sexually transmitted infections and had normal hysterosalpingogram and saline sonohysterograms. The levels of anti-Müllerian hormone was 8.56 ng/mL, and on day 3 of the menstrual cycle estradiol (E2), follicle-stimulating hormone, and luteinizing hormone were 55.0 pg/mL, 6.6 mU/mL, and 10.9 mU/mL, respectively. The partner of the patient was diagnosed with male factor infertility. Therefore, the patient was scheduled for in vitro fertilization (IVF). The first IVF cycle used a fixed gonadotropin-releasing hormone (GnRH) antagonist stimulation protocol. Clomiphene citrate (50 mg/day for 5 days) and recombinant human follicle-stimulating hormone (Gonal-F®, Merck Serono, Tokyo, Japan) at 150 IU every alternative day and on day three of the menstrual cycle, respectively were used for stimulation. On days 10 and 11 of the menstrual cycle, human menopausal gonadotropin (225 IU, Ferring Pharma, Tokyo, Japan) with a GnRH antagonist, cetrorelix acetate (0.25 mg, Cetrotide; Merck Serono,

Tokyo, Japan), was administered. Final follicular maturation was induced with a nasal spray of GnRH agonist (600 μg, Buserecure, Fuji Pharma, Tokyo, Japan). On the day of the trigger, the concentrations of E_2, progesterone, and luteinizing hormone were 4,328 pg/mL, 0.9 ng/mL, and 11.8 mIU/mL, respectively. Oocyte retrieval was performed 35 h after the trigger under general anesthesia. A total of 14 cumulus-oocyte complexes were retrieved, and 14 oocytes reached the MII stage. Because of the high E_2 concentration on the day of trigger, the dopamine agonist cabergoline (0.5 mg) was also administered daily after oocyte retrieval to prevent ovarian hyperstimulation syndrome. Conventional IVF and intracytoplasmic sperm injection were performed according to semen parameters. Blastocysts were evaluated according to Gardner's classification [14]. Three blastocysts (4BB, 4BC, and 6BC) were obtained and cryopreserved by vitrification using a Cryotop carrier system (Kitazato Biopharma Co., Tokyo, Japan) according to the manufacturer's instructions. Afterward, vitrified-warmed ET was scheduled, and endometrial preparation was performed using a hormone replacement cycle (HRC). In the HRC, transdermal estradiol (0.72 mg, ESTRANA TAPE, Hisamitsu Pharmaceutical, Tokyo, Japan) was administered from cycle day 3. Progesterone treatment with vaginal progestin tablets (300 mg/day, LUTINUS Vaginal Tablet, Ferring Pharmaceuticals Co., Ltd., Tokyo, Japan) and oral dydrogesterone tablets (30 mg/day, Duphaston, Mylan EPD, Tokyo, Japan) was administered at an endometrial thickness of 8 mm. Vitrified-warmed ET was performed five days after the start of progesterone treatment. Progesterone treatment was continued for 10 weeks after confirming positive serum β-human chorionic gonadotropin (β-hCG).

After the first frozen single ET (FET) of 4BB blastocyst following the HRC protocol described above (Fig. 1A), intrauterine fetal death was diagnosed at 19 weeks of gestation, and the patient eventually had a stillbirth. The baby and the placenta showed no obvious congenital abnormalities. The patient refused further examinations for stillbirth, such as placental pathological examination and genetic analysis. Thereafter, the patient experienced two spontaneous abortions at 9 and 4 weeks of gestation after each FET of 6BC (Fig. 1B) or 4BC (Fig. 1C) blastocysts following the HRC protocol described above. Therefore, she underwent a standard RM workup, including an investigation of the coagulation factors such as protein C, protein S, antithrombin III, LA, and aCL- IgG and aCL-IgM to rule out possible potential prothrombotic causes. Hysteroscopy was performed on the patient, and karyotypes of the patient and her partner were analyzed. The results showed that only aCL-IgG was positive and elevated to 22.0 U/mL, whereas other parameters were unremarkable. Hysteroscopy did not reveal any remarkable findings, and karyotypes were normal. According to the classification criteria for definite APS [6], aCL-IgGs were re-examined 12 weeks later to determine whether they were continuously positive, which revealed negative results suggesting an occasional aPL-positivity. Therefore, it was inferred that the unexplained RM in the patient could be due to occasional aPL-positivity but not APS. We discussed the next strategy with the patient to avoid miscarriage and succeed in pregnancy. Accordingly, ET using a single embryo and simultaneous treatment with LDA, LMWH, or combined therapy of LMWH and LDA was planned based on the results obtained in previous studies [7].

Using the same protocol for HRC, as described above, the vitrified-warmed blastocyst graded 4AB (Fig. 1D) was transferred, and only LDA (enteric-coated aspirin tablet, 100 mg once daily) (Bayaspirin; Bayer Pharmaceutical Co., Ltd., Tokyo, Japan) was administered starting on the day of ET and continued until a successful clinical pregnancy was determined using ultrasound. Although the serum hCG concentration was elevated to 9.9 IU/L two weeks after the ET, a clinical pregnancy with the gestational sac in the uterus was not confirmed afterward. On the next ET cycle, the vitrified-warmed blastocyst graded 4AB was transferred (Fig. 1E), and the combined intervention of LMWH (10,000 IU every 12 h; Mochida Pharmaceutical Co., Ltd., Tokyo, Japan) and LDA (enteric-coated aspirin tablet, 100 mg once daily) was performed on the day of ET using the same protocol of HRC and luteal support and continued for 14 and 28 weeks of gestation, respectively (Fig. 2). Sixteen days post-ET, serum HCG concentration was elevated to 2562.0 IU/L, confirming a pregnancy. A transvaginal ultrasound was performed 3–4 weeks later to confirm a clinical pregnancy with a viable fetal heartbeat. A repeat ultrasound scan performed at 12 weeks of gestation ensured the viability of the fetus. The patient successfully completed the course of pregnancy, went into spontaneous labor at 40 weeks of gestation, and gave birth to a viable female neonate (3010 g) at 40 weeks and 3 days of gestation. The neonate had an Apgar score of 8/9 out of 10. The postpartum course was stable, and the patient was discharged five days after delivery (Fig. 2).

Discussion

Occasional aPL-positivity is categorized as an unexplained RM. Hence, no treatment has been established, and it is clinically difficult to intervene with anticoagulants, such as LDA or LMWH. The patient experienced three continuous failures in active pregnancy, including a miscarriage at 19 weeks after transferring a vitrified-warmed good-quality embryo. The general screening for RM detected aCL-IgG as temporally positive, indicating a case of unexplained RM with aPL-positivity but not with APS. After an unsuccessful attempt with LDA alone, LMWH combined with LDA was administered on the day of the transfer of the vitrified-warmed blastocyst and continued till 14 and 28 weeks of gestation, respectively. The combined regimen led to a successful pregnancy and live birth.

LMWH or LDA is used clinically to prevent miscarriage when LAs or aPL are detected persistently, and placental circulation was suspected to be impaired by thrombotic inclination[15]. Approximately 70–80% of RM with the causal factor of APS treated with combined LDA and LMWH have had successful pregnancies and live births [16] because miscarriages associated with APS have been ascribed to thrombosis and infarction of the uteroplacental vasculature [17]. LMWH are a class of anticoagulant agents with an average molecular weight of < 8000 Da. Studies showed that LMWH improves pregnancy outcomes by modulating several physiological processes required for blastocyst adherence, implantation, and trophoblast invasion [18, 19]. Therefore, several studies have suggested that LMWH has a strong benefit in preventing unexplained RM and improving pregnancy outcomes, as LMWH enhances the inhibitory effect of anticoagulation, anti-inflammatory, and immunoregulation [18–22]; however, several contradictory studies demonstrating no evidence of benefits have also been reported [23–26]. For instance, Wang et al. included five randomized control trail (RCT) studies in their review and concluded

that LMWH treatment decreases the incidence of miscarriage in women suffering a history of three or more unexplained miscarriages; however, it cannot reduce the risk of women suffering a history of two or more unexplained miscarriages [27]. On the contrary, Yan et al. reviewed seven RCTs to compare the effects of LMWH or LMWH combined with aspirin on unexplained RM and concluded that LMWH combined with LDA did not improve the pregnancy outcome in women with unexplained RM and aPL-negativity [28]. Taken together, the administration of anticoagulants such as LMWH or LMWH with LDA to women with unexplained RM, including aPL-positive patients, is controversial.

In this case, LMWH and LDA were expected to affect implantation and invasion at first; however, LMWH and LDA effectively overcame unexplained RM due to occasional aPL-positivity, finally leading to a successful pregnancy and live birth. aPL may cause miscarriage through insufficiency in the blood supply resulting from uteroplacental thrombosis [29] and directly inhibit the proliferation and differentiation of trophoblast cells, leading to placental defects [30]. Therefore, the benefit of the combination therapy of LMWH and LDA could be attributed to their efficiency to improve placental circulation. Furthermore, due to an abnormal signaling event in the implantation and placentation site of aborters [31], a history of two or more miscarriages might be associated with a higher incidence of placenta-related complications, such as preeclampsia (PE), placenta previa, placental abruption, and obstetric complications, such as fetal growth restriction, gestational diabetes mellitus (GDM), premature rupture of the membrane, and caesarean section (CS) [32–35]. Only in unexplained RM, which is associated with maternal-fetal interface immune system or micro-thrombosis [36, 37], the incidence risk of GDM and CS has been shown to be higher; however, the underlying mechanisms remain unknown [38]. Recently, Cruz-Lemini et al. conducted a meta-analysis of 15 RCTs that assessed the effectiveness of LMWH for the prevention of placenta-related complications in women with RM and found that LMWH use was associated with a significant reduction in the risk of placenta-mediated complications when treatment was started before 16 weeks of gestation [39]. The study also showed that the combination of LMWH and LDA was associated with a significant reduction in the risk of PE compared to LDA alone [39]. Li et al. reviewed eight RCTs to compare the efficiency of treatment with LMWH alone or LMWH combined with aspirin and concluded that the combination of LMWH and aspirin increased the live birth rate in women with unexplained RM compared to LMWH alone [40]. In this case, the combination of LMWH and LDA may have been successful in obtaining live births without placenta-related and obstetric complications. Nevertheless, whether the intervention of anticoagulants has specific efficiency for unexplained RM with occasional aPL-positivity remains elusive.

Conclusions

In this case, the transfer of good quality freeze-thawed vitrified embryo by IVF or intracytoplasmic sperm injection was unsuccessful, and the patient had three continuous miscarriages, including chemical pregnancy. Subsequently, the patient was diagnosed with unexplained RM with occasional aPL-positivity but not APS. After an unsuccessful attempt with LDA, the combination therapy of LMWH and LDA achieved a successful pregnancy and live birth. These findings suggest that a combination of LDA with LMWH could help achieve successful pregnancy in patients experiencing unexplained RM with

occasional aPL-positivity but not APS. However, no clinical trials of LMWH alone or a combination of LMWH and LDA for unexplained RM with occasional aPL-positivity have been reported. Therefore, RCTs are required to confirm the efficacy of LMWH alone or a combination of LMWH and LDA in patients with occasional aPL-positivity without APS. Furthermore, proposing a set of criteria to define unexplained RM with occasional aPL-positivity but not APS is also required to identify such cases.

Abbreviations

aCL
Anticardiolipin antibody
aPL
Antiphospholipid antibody
APS
Antiphospholipid syndrome
ASRM
American Society of Reproductive Medicine
B-HCG
β-human chorionic gonadotropin
E2
Estradiol
ESHRE
European Society of Human Reproduction and Embryology
ET
Embryo transfer
GnRH
Gonadotropin-releasing hormone
IVF
In vitro fertilization
LA
Lupus anticoagulant
LDA
Low-dose aspirin
LMWH
Low-molecular-weight heparin
RCT
Randomized control trial
RM
Recurrent miscarriage

Declarations

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study did not require Institutional Review Board approval. Written informed consent was obtained from the patient to publish this paper.

Competing interests

The authors declare that they have no conflict of interest.

Consent for publication

Written informed consent as opt-out was obtained from our patient for publication of her case and accompanying images.

Author's contribution

Conceptualization: K.O. and K.K.; data collection: Y.T., M.T., and K.H.; writing—original draft preparation: K.O. and J.M.; writing—K.O.; supervision: T.T. and K.K. All authors have read and agreed to the published version of the manuscript.

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Figures

Figure.1

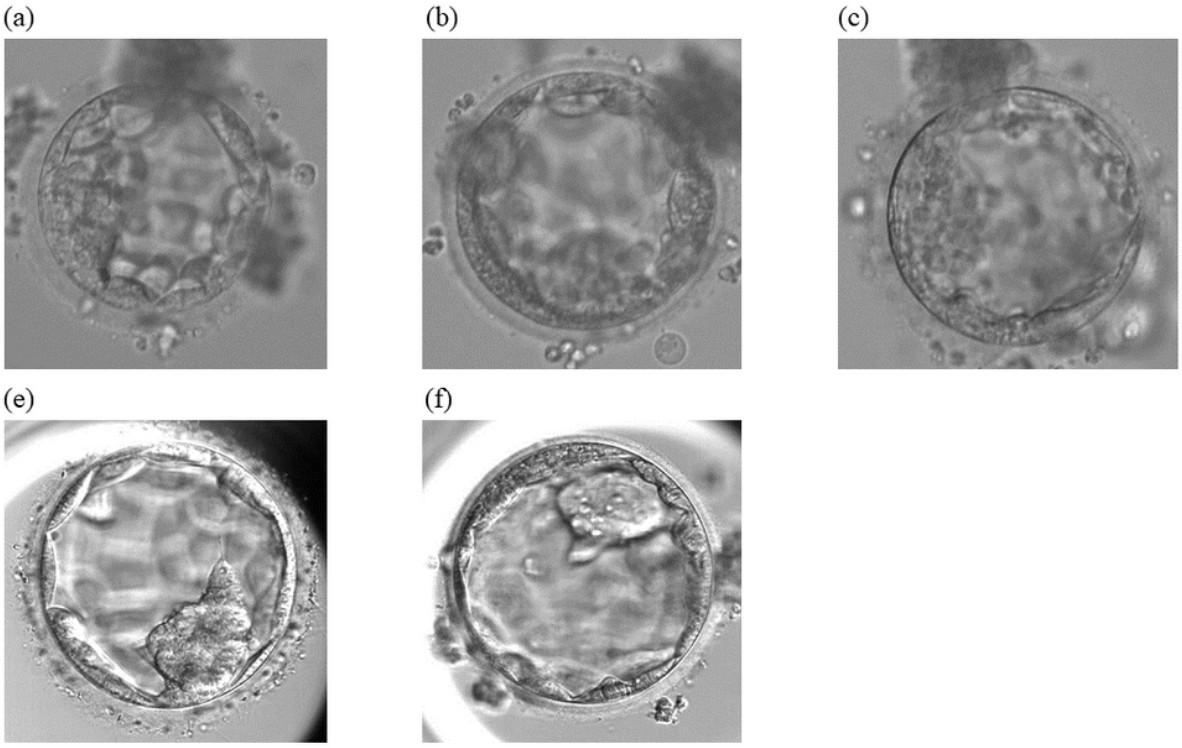

Figure 1

Photographs of the vitrified-warmed blastocyst transferred in this patient

Figure.2

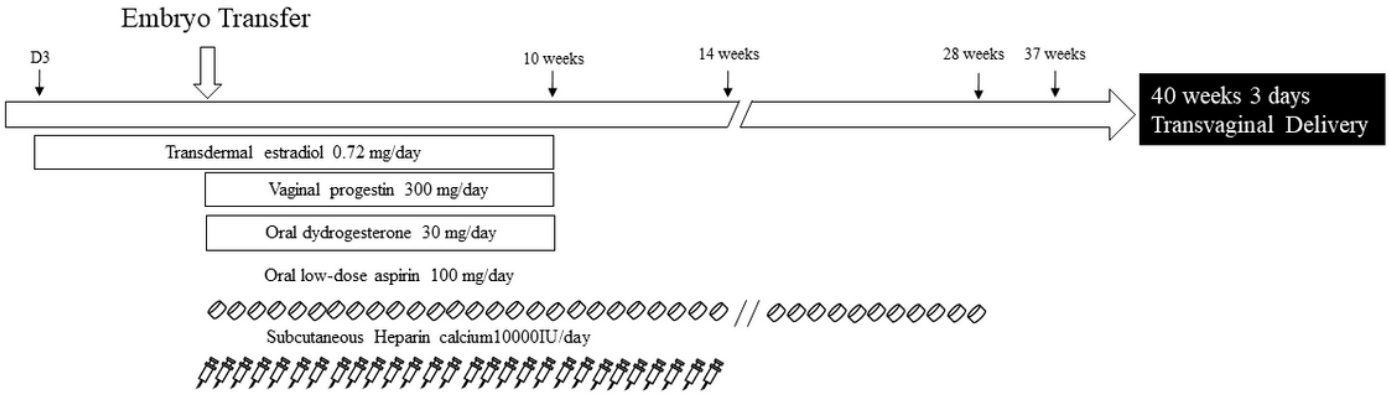

Figure 2

Clinical intervention with low-dose aspirin and low molecular weight heparin from embryo transfer to delivery.