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Case Reports

Bicornuate uterus with recurrent miscarriage treated with Sitagliptin and PRP: A Case Report of a Successful Pregnancy

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Research has shown that recurrent miscarriage can be due to loss of endometrial mesenchymal stem-like progenitor cells (eMSC) and excessive decidual senescence. Sitagliptin has been shown to increase eMSC in the endometrial tissue and decrease decidual senescence.

Case

This is a case report for a 31-year-old woman with a bicornuate uterus who suffered recurrent miscarriages with IVF treatment. IVF treatment was done due to male factor infertility in a modified stimulation protocol using oral clomifene and human menopausal gonadotrophin. A total of 10 blastocysts were cryopreserved. The couple could not afford to do a PGT-A testing on the cryopreserved embryos. Initial three frozen embryo transfers were done in a natural cycle but resulted in biochemical pregnancies. Thyroid function test and Anti-phospholipid Syndrome tests were negative. Her Protein C level was slightly low at 63%. Hysteroscopy showed no abnormalities in both the uterine horns. A fourth embryo transfer was done in a medicated cycle which resulted in no pregnancy. She was started on oral Sitagliptin 100mg once daily for 3 months. Following this, a fifth embryo transfer was done in a natural cycle. Endometrial PRP infusion was done in this cycle. She successfully became pregnant and delivered a baby girl via LSCS in August 2023.

Conclusion

Sitagliptin can be a cost-effective adjunct treatment for patients with recurrent miscarriage. While the absence of PGT-A may raise questions regarding the underlying cause of her recurrent miscarriages, oral Sitagliptin can be an option in cases of financial constraint or limited resources.

BACKGROUND

Pregnancy loss is a complication of early pregnancy. It is estimated to affect between 5%-15% of pregnancies.[1] Recurrent pregnancy loss (RPL) is less prevalent as it is estimated to affect between 1%-2% of women.[1] Pregnancy loss can be due to cytogenetic causes, Anti-phospholipid Syndrome, uterine anatomical abnormalities, hormonal or metabolic causes, infection, or related to male factors.[2]

Although abnormal fetal karyotype is one of the main contributors to recurrent miscarriage, research has also shown that the frequency of normal embryonic karyotypes significantly increases with the number of previous abortions.[3]

This research finding implies that the uterine factor contributes to recurrent miscarriages.

A successful embryo implantation requires decidualization of the endometrium. This is a multi-step procedure, driven by the post-ovulatory rise in progesterone and intracellular cyclic adenosine monophosphate levels, which leads to the differentiation of endometrial stromal cells (EnSC) into specialized decidual cells.[4,5] A portion of EnSC becomes acute senescent cells.[6] Acute senescent cells are involved in wound healing, tissue repair, and embryo development. These cells typically self-eliminate by recruiting innate immune cells such as natural killer cells (NK).[7-9]

In women with RPL, there is a reduction of mid-luteal endometrial mesenchymal stem-like progenitor cells (eMSC) and excessive decidual senescence, representing a

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loss of endometrial plasticity.[10] This imbalance predisposes the formation of a pro-inflammatory and intrinsically unstable placenta-decidual interface in pregnancy.

Decidual cells, but not senescent cells, are dependent on progesterone signaling. In the absence of embryo implantation, endometrial tissue breakdown occurs. Regeneration of the endometrium partly depends on the recruitment and engraftment of bone marrow-derived cells (BMDC) and their differentiation into non-hematopoietic endometrial lineage, including endothelial, stromal, and epithelial cells.[11,12]

Stromal cell-derived factor-1 alpha (SDF-1) mediates mobilization of BMDC and homing to the endometrium in response to injury and rising estradiol levels.[13,14]

SDF-1 is inactivated by dipeptidyl-peptidase IV (DPP4), thus can reduce the mobilization of BMDC.

Sitagliptin is a DPP4 inhibitor and increases the bioavailability of SDF-1,[15] and this helps to promote tissue regeneration and decidualization in the endometrium.

Preconception usage of Sitagliptin (100mg daily) over 3 consecutive menstrual cycles effectively increases the abundance of clonal eMSC during the mid-luteal phase of the menstrual cycle.[16]

CASE PRESENTATION

MK is a 31-year-old woman who presented with primary infertility in 2020. She has been trying to conceive for 1 year.

She has no underlying medical illnesses. She had a laparoscopic cholecystectomy in 2016. She has a regular menstrual cycle of 30 to 32 days cycle length. A hysterosalpingography (HSG) test showed a bicornuate uterus with a single cervix.

Her partner's semen analysis showed Oligoasthenoteratospermia (OATs) with a sperm concentration of 3.9 million/ml. A repeated semen analysis revealed the same findings months after oral antioxidants. He has no significant medical illnesses and no modifiable lifestyle factors contributing to this.

The couple decided to proceed with an IVF treatment in 2021. A modified stimulation protocol using clomiphene citrate 200mg daily and alternate-day human menopausal gonadotrophin (Humog 150iu + Foliculin 150iu) was used. No GnRH antagonist was used.

A total of 12 oocytes out of 15 follicles were retrieved. Ten oocytes were mature and ICSI was done. All 10 oocytes fertilized. All 10 embryos grew to the blastocyst stage and were cryopreserved. The couple could not afford to do PGT-A on the embryos due to financial constrain.

Her first frozen embryo transfer (FET) was done in a natural cycle. She was given oral Nolvodex (Tamoxifen) 20mg daily for 5 days, starting from day 3 of menses to stimulate single follicle growth. On Day 18 of her period cycle, the dominant follicle on her right ovary was 20mm, with an endometrial thickness on the right and left uterine horn of 8.5mm and 8mm, respectively. Ovulation was triggered with Hucog (Hcg 5000iu). Embryo transfer was done with a single blastocyst to the right uterine horn 6 days after the trigger injection with a single blastocyst (grade 5AA). Guardia Access, an embryo transfer catheter, was used.

Post-embryo transfer, she was started oral Duphaston 10mg twice daily until her serum beta-hCG test. The beta-hCG pregnancy test performed 10 days after embryo transfer showed a 96 Miu/ml level.

She developed uterine cramps a few days later, and the repeated serum beta-hCG level showed a downward trend.

Her second frozen embryo transfer was done in a similar natural cycle regime in the subsequent month. On Day 14 of her period cycle, the right dominant follicle was 26mm, and her right horn's endometrial thickness was 7mm. Embryo transfer was done 6 days post-trigger injection into the right uterine horn with a single blastocyst (Grade 5AA). She was started on oral Duphaston 10mg twice daily and vaginal Uterogestan 100mg twice daily.

Her serum Beta-hCG result, 10 days post-embryo transfer showed a level of 186 Miu/ml. An ultrasound scan was done at 5+6 weeks of gestation which showed a yolk sac of 2.2mm. A repeat ultrasound scan in 2 weeks showed a yolk sac of 6mm with no fetal pole seen. A diagnosis of a miscarriage was made. She had spontaneous bleeding about a month later.

During the review in the clinic, PGT-A was again suggested but the couple declined the test due to the cost.

After two months, a third embryo transfer was done in a natural cycle. On day 12 of her cycle, the right dominant follicle was 21mm, with an endometrial thickness of 7mm on the right uterine horn. Embryo transfer was done 6 days post HCG trigger with a single blastocyst (Grade 5AA), into the right uterine horn. Post-embryo transfer, she was started oral Duphaston 10mg twice daily, oral aspirin 100mg daily, and intramuscular Hiprogin (Hydroxyprogesterone Caproate) 250mg on the day of embryo transfer and a week later.

Her beta-hCG results, 10 days post embryo transfer, showed a level of 38 Miu/ml and a repeat level 2 days later came down to 14 Miu/ml.

Following three miscarriages, a blood test for thyroid function, Anti-nuclear antibody and Anti-phospholipid Syndrome was done. All tests were normal except for the Protein C level which is slightly low at 63%. A hysteroscopy procedure was also done. Both uterine horns are accessible and there were no endometrial polyps.

Subsequently, a fourth embryo transfer was done in a hormone replacement cycle. She needed 14 days of 6mg oral Progynova daily. An endometrial thickness of 7mm was reached on both uterine horns. Embryo transfer was done 6 days after starting vaginal Crinone gel (90mg daily) with a single blastocyst (Embryo Grade 4AA).

However, her serum beta-hCG level returned negative, 10 days after embryo transfer.

A trial of oral Sitagliptin was discussed with the couple. The couple was informed about limited evidence and off-label use of oral Sitagliptin for recurrent miscarriage. The couple consented to the use of oral Sitagliptin.

She was started on oral sitagliptin 100mg daily for 3 consecutive period cycles.

The fifth embryo transfer was done in a natural cycle. On Day 15 of her period cycle, the right dominant follicle was 17mm with an endometrial thickness of 7mm on both uterine horns. Ovulation was triggered with Hucog 5000iu.

A platelet-rich plasma (PRP) infusion into the uterine cavity was done 2 days prior to embryo transfer. PRP was prepared using a RegenLab centrifuge tube and centrifuge equipment. Embryo transfer was done 6 days post ovulation trigger with a single blastocyst (Grade 3AA)

Post-embryo transfer, the patient was given oral Duphaston 10mg twice daily, aspirin 100mg daily, prednisolone 5mg twice daily, and Hiprogin IM (on the day of embryo transfer).

Her beta-hCG results, 10 days post embryo transfer, showed a level of 277 Miu/ml.

An ultrasound scan 2 weeks later showed a CRL of 2.1mm (5+5 weeks) size, but no obvious fetal heart activity was seen. Ultrasound scan a week later showed a CRL of 4.1mm (6+1 weeks gestation) with a fetal heart rate of 123 bpm. In addition to oral medications, she was also given Hiprogin injections twice weekly. At 9 weeks of gestation, she was referred to a tertiary Feto-Maternal unit for antenatal follow-up in anticipation of a preterm delivery.

At the time of writing this case report, she has successfully delivered a healthy term baby girl on 30th of August 2023 via lower segment cesarean section for fetal distress.

DISCUSSION AND CONCLUSION

Pregnancy loss is a common complication in early pregnancy with the prevalence ranging from 5%[17] to 10%-15%.[18] The prevalence of recurrent pregnancy loss is lower, between 1-3%.[19,20]

A woman with a bicornuate uterus has a higher risk of first-trimester and second-trimester miscarriage.[21] MK in this case report, has an increased risk of recurrent miscarriage due to a bicornuate uterus. Even in a woman with a bicornuate uterus, we should always consider endometrial factors associated with recurrent miscarriage.

The issue of endometrial receptivity has been studied with no conclusive evidence.

However, research by Shreeya Tewary[10] and the team revealed the underlying mechanisms involved in transforming the endometrium to be more receptive to embryo implantation. This research also has shown that the usage of a simple intervention (oral Sitagliptin) may hold the answer to improve the receptivity of the endometrium in a cost-effective manner.

In this case, it can be argued that all her embryos were not tested (PGT-A) for genetic abnormalities, thus her recurrent miscarriages could be due to embryo aneuploidy. The recent ESHRE (draft for review) guideline for Good Practice recommendations for add-ons in reproductive medicine, states that PGT-A does not improve live birth rate, thus confirming that embryo euploidy cannot be considered as the only main factor in determining a successful pregnancy. Furthermore, PGT-A testing is costly and could not be done by many couples, who need to pay the entire cost of an IVF treatment. PGT-A testing is prevalent in countries where IVF treatment is subsidized by the government.

The couple in this case report could not afford to spend money for the PGT-A testing because they knew that their risk of a miscarriage was high and thus, they decided to allocate the money instead for multiple embryo transfers.

All tests for recurrent miscarriage done were negative, limiting the role for medical intervention.

After 3 early miscarriages, the usage of oral Sitagliptin was discussed with the couple. It was made clear to them that the available evidence for this intervention is limited and this intervention has not been tested in many women with recurrent miscarriage.

The usage of sitagliptin in non-diabetic women has not shown any adverse effects. Furthermore, Gliptins have been used in other medical specialties such as for coronary disease for myocardial cell repairs.

In patients with recurrent miscarriage and treatment options are limited by financial constraints, usage of oral Sitagliptin is to be considered. Its usage has no known adverse effects. However, patients undergoing IVF treatment require to wait for at least few menstrual cycles before subsequent embryo transfer can be attempted.

The usage of Sitagliptin for improving endometrial receptivity can be expanded because the intervention is simple and cost effective. Current research on the usage of Sitagliptin has not conclusively concluded the effect on pregnancy rate or live birth rate. A large-scale randomized control study is needed to answer this question. Until then, widespread usage of Sitaglitin in recurrent miscarriage should only be considered in a research setting. Future research suggestions are to investigate the effect of Sitagliptin usage in In-vitro fertilization (IVF), both in fresh and frozen-thawed embryo transfer.

The success story of this couple highlights the importance of considering endometrial factors as one of the main possible reasons for recurrent miscarriage, even in a woman with a uterine anomaly. Current medical advances in the field of recurrent miscarriage have not given doctors a 'formidable' treatment option. In our daily clinical practices, we face the difficult task of formulating a logical treatment plan for the minority of women with recurrent miscarriages. In our list of possible interventions, we should strongly consider including the usage of Sitagliptin, especially where the doors seem to be closed for any other treatment modalities.

AUTHORS' CONTRIBUTION PER CREDIT

Conceptualization: Agilan Arjunan (Lead). Data curation: Agilan Arjunan (Lead). Formal Analysis: Agilan Arjunan (Lead). Investigation: Agilan Arjunan (Lead). Project administration: Agilan Arjunan (Lead). Visualization: Agilan Arjunan (Lead). Supervision: Agilan Arjunan (Lead). Writing – original draft: Agilan Arjunan (Lead), Charlotte Sundaraj (assist). Writing – review & editing: Agilan Arjunan (Lead), Charlotte Sundaraj (assist).

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