Successful term pregnancy using oral DHEA to restore serum estradiol in a 39 year old with 5 recurrent pregnancy losses including a fetal demise at 19 weeks: a case report

Cynthia Barco, MD, CCFP; Ulrika Drevniok RN(C), MScA

Abstract

- 39-year-old female with nine previous pregnancies including 4 live births and 5 pregnancy losses
- low progesterone in the luteal phase was found after the 4th pregnancy loss (PL)
- 5th PL occurred at 8 weeks despite progesterone supplementation and ASA
- Estradiol levels were found to be low during this 9th pregnancy
- In our care, hypoandrogenemia was also discovered
- RRM multifactorial approach to treatment included follicle stimulation with letrozole and DHEA
- Estradiol levels were followed and DHEA titrated through the 10th pregnancy
- Healthy baby girl delivered at 38+3 weeks
- Low estradiol levels as a cause for RPL should be considered and treated with DHEA supplementation

Introduction

- Recurrent pregnancy loss (RPL) or recurrent miscarriage is a common but devastating occurance in pregnancy and affects at least 2% of all couples (using the definition of 2 or more losses)[1]
- RPL needs to be investigated and underlying causes treated due to the high physical, psychological and economic burden of future obstetrical complications
- Thorough investigation generally identifies contributing factors in about 50% of cases
- Likely that a significant number of causative factors remain unexplained and further study is needed
- Restorative reproductive medicine (RRM) seeks to manage infertility and RPL from a systematic multifactorial approach by finding and treating all potential underlying factors contributing to reproductive dysfunction[2]
- RRM has been shown to be at least as successful in achieving live births as compared to assisted reproductive technologies (ART)[3,4]
- DHEA supplementation has been shown to improve follicular function, spontaneous pregnancy, and live birth rates while hypoandrogenemia (low DHEA) has been associated with increased risk of miscarriage[5]
- Low estradiol levels during pregnancy are associated with a higher risk of miscarriage and likewise using DHEA orally during pregnancy has been shown to improve estradiol levels and decrease risk of PL[6]

History and Clinical Presentation

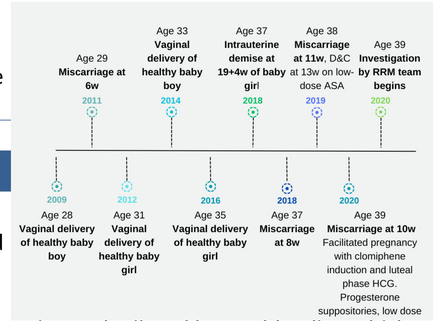
First attended our clinic in June 2020. At that time she was 39 years old. Her husband was 40 years old. She worked as a school nurse and he as a teacher. Both were non-smokers, exercised regularly and generally healthy. Both had minimal alcohol use and no illicit drug use. At that time, she had a total of 9 pregnancies with 4 live births and 5 pregnancy losses.
#6: PL, normal placental pathology, no autopsy or chromosomal testing done
#7: PL, no chromosomal testing done
#8: PL, on low dose ASA, D&C done, no tissue sent for chromosomal testing
#9: PL, faciltated pregnancy after 4 cycles of ovulation induction with Clomiphene and HCG for luteal phase support. On ASA 81mg and progesterone Suppositories (400 mg qhs) during the pregnancy,
no tissue sent for chromosomal testing

Positive family history of autoimmune disease
Normal parental karyotypes
Normal thrombophilia screen, thyroid panel, prolactin and no insulin resistance
Normal hysterosalpingogram (HSG)

Table 1. Estradiol monitoring during pregnancy #9

Adjusted gestational age (weeks)	Estradiol (pmol/L)	Progesterone (nmol/L)	Treatment
4	~1,800	63.9	ASA Progesterone
6	~900	49.6	
8	430	60.8	Fetal heartbeat on US
9	560	54.9	
10	232	39.1	miscarried

Image 1. Historical Timeline



Investigations and Treatment

Salivary cortisol and DHEA testing
-blunted cortisol curve indicating chronic stress burden and HPA axis dysfunction
-low DHEA indicating immune dysregulation, ovarian aging
Menstrual cycle charting revealed dysmenorrhea, dyspareunia, premenstrual spotting and tail-end brown bleeding which could indicate endometriosis, luteal phase deficiency and/or endometritis

RRM diagnoses: hypoandrogenemia, luteal phase deficiency, adrenal fatigue, endometritis, possible endometriosis and autoimmune factors
The pre-conception treatments used were:
1. Naltrexone 4.5 mg, nightly
2. DHEA 25 mg, twice daily
3. 21 day course of doxycycline + azithromycin of both partners
4. Letrozole 2.5mg x 7 tablets (17.5 mg) on day 3 of cycle
5. HCG 2,500/2,000/1500 IU on days 3, 5, and 7 post-ovulation

Monthly blood tests were done to confirm optimal estradiol and progesterone levels on day 7 post-ovulation until pregnancy was confirmed in January 2021, on the third cycle of targeted intercourse

Post-conception treatments used were naltrexone and DHEA (titrated to estradiol levels) continued as above and:
1. ASA 162mg daily
2. subcutaneous dalteparin injections daily
3. prednisolone 20mg from weeks 5-9, tapered and discontinued by 12 weeks
4. progesterone 400mg PV twice daily

Table 2. Estradiol and Progesterone monitoring and treatments during pregnancy #10

Adjusted gestational age (weeks)	Estradiol (pmol/L)	Progesterone (nmol/L)	Beta HCG (IU/L)	Treatment
3	670	63.9		On DHEA 25 mg QD and luteal phase HCG preconception
5	1,005	49.6		Progesterone 300 mg pv BID and 100 mg po QD started Dalteparin SC 5,000 IU daily started, ASA 162 mg daily started
6	947	60.8	31,757	Prednisolone 20 mg qd added, DHEA increased to 50 mg
7	3,282	54.9	105,058	
8	7,580	39.1	194,243	Progesterone changed to 400 mg pv BID, DHEA decreased to 25 mg
9	8,686	85.9	220,247	
11	7,326	80.6	7,9561	DHEA increased to 50 mg
12	6,687	103.2		Prednisolone tapered and discontinued at 20 weeks
13	11,517	89.2		
15	16,915	85.6		
17	16,965	101.3		
19	16,928	100.3		Dalteparin SC increased to 7,500 IU daily at 20 weeks
21	30,360	168.9		Reduced DHEA to 25 mg QD
25	34,640	184.1		Reduced DHEA to 25 mg every other day
29	25,590	298.2		Increased DHEA to 25 mg QD
33	> 36,700	314.2		Dalteparin SC reduced to 5,000 IU daily and discontinued at labour

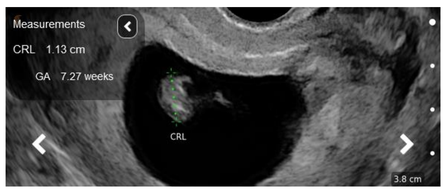


Image 2: Transvaginal US on 6 Feb 2021 at 7 weeks 4 days gestation, Pregnancy #10, RRM treatment protocol

Discussion

- Etiology of RPL is multifactorial and treating all identifed abnormalities is an effective RRM approach to treating infertility and recurent miscarriage.(2)
- During pregnancy #9 low estradiol levels were found but not treated. Low estradiol levels have been shown to be associated with PL.(6,7)
- Other potential underlying causes included adrenal insufficiency (blunted cortisol curve), endometritis (tail-end brown bleeding), autoimmune factors (family history) and endometriosis (clinically).
- chronic endometritis was treated with 21 days of antibiotics in both partners
- Low dose naltrexone 4.5 mg QD to treat possible endometriosis and inflammation.
- Poor follicle function was treated with Letrozole 17.5 mg on day 3 of the cycle.
- Luteal phase deficiency was treated with HCG SC 2500 IU, 2000 IU and 1500 IU on days 3, 5 and 7 respectively post ovulation.
- DHEA was started pre-conception to improve follicular function and to increase estradiol levels after conception.(6)
- Progesterone was added following a positive pregnancy test and titrated to keep progesterone levels in the right zone.
- Prednisolone was started after positive pregnancy test to treat adrenal fatigue and autoimmunity.
- Due to the recurrent pregnancy losses including a late loss, dalteparin was added to ASA as empirical treatment despite negative thrombophilia work-up.

Conclusions

By treating all the potential underlying causative factors, we were able to help this couple successfully conceive and deliver a healthy baby after her 5 pregnancy losses one of which was a late loss. Of particular note is the use of DHEA during pregnancy to titrate and maintain estradiol levels sufficiently high to reduce the risk of miscarriage.
Further studies need to be done to establish estradiol thresholds for gestational age and treatment guidelines as low estradiol levels can be a significant factor in RPL.

Contact Information

Dr. Cynthia Barco
Email: cyn.barco@gmail.com
Phone: 250-217-1787

Ulrika Drevniok
Email: ulrika.drevniok@gmail.com
Phone: 778-977-0993

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