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Review Article

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Protocol Details and Outcome Analysis of 5 Years of Continuous Infertility Treatment in A Patient with Premature Ovarian Insufficiency/Failure and Complex Crohn's Disease Utilizing Her Own Oocytes and Outcome of 3 Pregnancies

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ABSTRACT

Treatment options of POI patients wishing to increase the likelihood of conceiving with their own oocytes are limited. Current ASRM guidelines state no such interventions have demonstrated efficacy. Over the last three decades we have utilized techniques including ethinyl estradiol for follicular sensitization, that have resulted in successful pregnancy and live offspring in POI/POF and even menopausal patients. This case report is a final follow-up of a patient with Crohn's disease and POI/POF from endometriosis first described by us in 2008. She successfully had two healthy daughters (one of whom is a co-author of this report) via IVF with her own oocytes and a gestational carrier. She recently transferred the final remaining frozen embryo to a different GC, who is 15 weeks pregnant with her son. Herein, using her original lab records, we detail each and every cycle, the interventions used and reasoning behind them, and the ultimate outcome of all transfers of all embryos. Our objectives are to increase awareness and understanding of these techniques and improve treatment options for POI/POF patients.

Introduction

The updated 2025 ASRM guidelines on premature ovarian insufficiency state "there are no interventions that have been reliably shown to increase ovarian activity and natural conception rates" and recommend "oocyte donation as an established option to achieve pregnancy." We strongly disagree with the first statement. Based on our and others published experience in hundreds of patients over 40 years, beginning with follicular sensitization protocols using ethinyl estradiol, the statement is simply incorrect/misleading.

For patients with POI/POF who strongly desire at least one of their own genetic offspring at completion of infertility therapy, there are absolutely methods to increase the likelihood of eventually succeeding using this definition. Unfortunately, providers and patients may still be unaware of these techniques, may not believe them, or find them too complex, time consuming, and unprofitable compared to IVF with donor oocytes. Yet, it has been clearly demonstrated and widely accepted by reproductive endocrinologists that most patients with POI have evidence of remaining follicular activity. More recently, studies have also shown that in humans as well as mice, de novo folliculogenesis can occur after birth. Therefore, patients with POI/POF may actually have numerous chances of producing a competent oocyte, and therefore, the simple mathematics of probability are actually in their favor for at least one genetic child. Managing the infertility aspect of POI/POF may be approached better as a chronic endocrine disorder, such as hard to control diabetes, benefitting from very close monitoring and individualized cycle adjustments to promote follicular recruitment, maturation, ovulation, and pregnancy, rather than counting IVF cycles. Most patients with POI/POF as the only cause of infertility would not even need IVF, but may need follicle boosting, or ovulation induction, relatively easy endocrine manipulations, and

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optimally timed SI, but potentially very different between each monthly cycle. Some patients, with POI/POF and multifactor infertility/complex medical issues may be a true challenge, but success with such patients demonstrate the concepts are valid.

To this end, we submit this case report, a final follow-up of our physician/scientist-patient (reproductive immunologist/gastroenterologist) reported in 2009, who developed POI/POF after surgeries for bilateral ovarian endometriomas with high CA-125, in the setting of complex Crohn's disease [1]. She was fully aware of the donor oocyte option, but absolutely desired her own genetic offspring. She was refused treatment at multiple tertiary IVF referral centers, and only by conducting a literature review found our publications on ethinyl estradiol [2,3,4]. She was warned by her GYN specialists that these treatments were "futile", "dangerous", that it was "untrue" that ethinyl estradiol could not interfere with serum estradiol measurement, and that our goal was to "take her house." She relayed all this to the author (JHC) at consultation, but committed to try until succeeding or it became futile.

Ultimately, she successfully had two healthy daughters (one of whom is the lead author of this report) using her own oocytes and a gestational carrier [5]. She transferred the last frozen embryo 4/2026 to another GC, who is 15 weeks pregnant with her son. Herein, using her original lab records, we detail each and every cycle, the interventions used and reasoning behind them, and the ultimate outcome of all transfers of all embryos (Table 1). It is hoped that physicians managing POI/POF may better understand and utilize the details of these interventions to offer patients who desire their own genetic offspring an additional and more accurate assessment of their options.

Results

See Table 1.

Table 1: Cycle outcomes over 5 years of continuous treatment of iatrogenic POI/POF, multifactor infertility (tubal and multiple implantation failure), severe fistulizing Crohn's disease/malabsorption, and high CA-125 ovarian endometriosis. Learning from failure with persistence towards success. Patient has 2 healthy genetic daughters (18y and 9y) and final embryo/pregnancy with son is ongoing in GC at 15 weeks.

Date and Age	IVF to Retrieval Attempt	Serum Hormone Levels	Medical Issues	Treatment Regimen	Cycle Outcome	Conclusion
8/2001 32y8m	-	Random E2=233	Recurrence of endometriosis symptoms (dx 1989 age 20y); anti-TNF induced vasculitis	Steroids for vasculitis; central line for access required	-	Pt should be counseled at time of initial dx (age 19) and at regular f/u of risks to fertility, including recurrence, POF/POI; individualized options for treatment; better surveillance
1/2002 33y1m	-	Day3 E2=34.8 FSH=8.1	8 cm endometrioma on right ovary (12 cm left ovarian endometrioma and L FT was resected age 20y 6m at open colectomy and ileostomy)	Preop- Fertility preservation/ IVF denied by all centers consulted (OH, NY, MA)	-	Preop fertility preservation options should be discussed and offered. At this point there was DOR but no POF/POI. AMH level should be done.
5/2002 33y 4m	-	Day 3 E2=37.3 FSH=14.2	Post op removal of R endometrioma and R hydrohemosalpinx	Placed on progesterone OCP (ovrette)	-	Will require IVF due to TF but now with POI and in most centers not an iVF candidate. Donor sperm required as no partner.
8/2002 33y7m	-	Day 3 E2=83.9 FSH 6.10	Diminished ovarian reserve and bilateral TF infertility	Levels done on OCP. REI consultation at in MA center (hospital)	-	-
11/2002 33y11m	MICR ODOSE FLARE	At cancellation E2=0 FSH=38.6		Lupron, 4 Gonal F, 4 Repronex "long protocol"	CANCELED no follicles on u/s MA refused further "futile" and "dangerous" attempts; NYC/OH refused "futile"	Follicle development was inhibited by this common regimen for "poor responders".
12/2002 33y11m	-	Day 26 E2=185 Day 31 E2=486	Acute right sided pelvic pain	Off all meds Ultrasound+ "3 cystic structures" in R ovary	"functional ovarian cysts" or??? follicles Literature review. Consult Cooper REI-NOT hospital based and out of state requiring travel.	"Release" of inhibition allowed follicle development.

12/2002 33y11m	-	Day 3 E2=224 FSH=2.5 Day 33 E2=51 FSH=18.7 P<.2	-	20 mcg EE day 4; IVIG day 38	Evidence follicular activity; no ovulation	Follicular activity; Need to add HGC to trigger ovulation
2/2003 34y1m	-	Day 3 E2=22 FSH=18.3 Day11 E2 = 267 FSH 16.9	-	20 mcg EE-> 40 mcg day 3; 75 Gonal F day 8 ; HGC day 12	u/s +17 mm follicle Day 11; Day 12 no follicle on u/s and P=4.4, LH=45.7c/w sp. ovulation	Mature Follicle demonstrated & Ovulation successfully induced; due to TF need to prevent sp. release; will need GNRH antagonist
2/2003 34y 2m	YES	Day 4 E2=45 FSH 19.8	-	Off meds day 0- 3; 20 EE-> 40; 75 rhFSH day 11; Antagon 250 mcg and 10,000 HCG day 13; IV antibiotics postretrieval; very difficult to reach R ovary due to adhesed bowel	17mm follicle day 14; successful retrieval of single oocyte; Failure of natural fertilization	Oocyte obtained; ICSI will be needed to ensure fertilization
3/2003 34y 3m	YES	Day 2 E2=23, FSH=22; Day 17 E2=283 FSH=17.2	-	20 EE day 3-> 40 day 7; rhFSH 75-225 days 12-16; Antagon day 14 ;HCG 10,000 DAY 17 ; Very difficult to reach ovary; IV antibiotics	u/s + 2x10mm follicles day 14; retrieval attempt day 19 "EFS" no oocytes retrieved	Empty follicle syndrome can occur; the ovary must be surgically relocated for easier retrieval access
3/2003 34y 3m	-	-	Crohns surgery attempt at J pouch failed due to mesenteric reach; right ovary moved lower into pelvis	No gyn meds	-	-
4/2003 34 y 4m	-	Day 14 E2=95 FSH=14.8	TPN for Crohns	No gyn meds	-	-
5/2003 34Y 5 m		Day 5 E2=52 FSH=11.8	Central line with fever	IV antibiotics; no gyn meds	-	-
6/2003 34y 6m	-	Day 4 E2=139; FSH=3.3	Essential fatty acid deficiency	No gyn meds	2 10 mm follicles on u/s day 29	No follicular development off gyn meds; but follicles present
7/2003 34y 7m	-	Day 2 EE=35 FSH=10.4; Day 19 E2=<12 FSH=3.8	Crohns flare required prednisone	EE 40 mcg day 1, decreased to 20 MCG DAY 32 maintenance; IVIG given day 32	u/s day 19 no follicles seen	Continuous EE can inhibit follicle development. EE does not affect serum E2 measurement.
9/2003 34y 8 m	YES	Day 3 E2<12; FSH=7.1 Day 7 E2<12 FSH=25.3 Day 29 E2=355 FSH=17	9	EE 0-40 mcg; Antagon 125-> 50 ; Follistim 150->225; Toradol days 27-29 30mg; HCG 10,000 DAY 29	U/S day 29 17 mm follicle; 1 oocyte retrieved day 31; icsi successful; fresh transfer 7 cell day 3 A1 embryo to patient; implantation failure EMBRYO #1	This process is not futile-> high quality/high potential embryo can be obtained. There may be another factor (?immunlogic/ inflammatory endocrine?) leading to failure of implantation in the patient
10/2003 34 Y 10m	YES	Day 3 E2=27 FSH=26 Day 14	Toradol 30 mgx1 day 2 for painful period	Day 3: 20 mcg EE->40; 250 Antagon, 150>225 Follistim; HCG 10,000 day 13; Toradol 15 mg x3 days 11-13	u/s + 17 mm follicle; successful retrieval 1 oocyte; successful icsi; fresh transfer to patient day 3 4 cell A1 embryo; luteal support with po& IM P and estrace; implantation failure. HCG - EMBRYO #2	Second implantation failure but low blastomere number in this embryo also a factor.

11/2003 34y 11 m	-	Day 3 E2<5 FSH=40 Day 36 E2=718 FSH=5	Crohns flare New dx cervical polyp Severe pelvic pain High CA-125=99	40 mcg EE added day 4; decreased to 20 day 8; stopped day 14; period induced with medroxyprogesterone day 22-33	U/S day 35 24x17 R cyst	MEN0PAUSA L LEVELS
1/2004 35y 0m	-		Cyst drainage	10,000 given day 2	Cyst aspirated day 3 no oocyte	Functional Ovarian cyst vs EFS
1/2004 35 Y 0m		Day 4 E2=20 FSH=28 Day 25 E2<5 FSH 69		20 mcg EE day 4; siladenafil day 8x1; EE40 day 8, antagon 250 day 11.Follistim 75 day 14, off all day 19; 10 P and 40 EE days 27-40, 40 EE – end. Period induced	-	Viagra no help
2/2004 35 y 2 m		Day 5 E2<5 FSH=23		EE 20-40 mcg days 5-20; prog with EE dys 21-41. EE continued. Period induced.	-	-
4/2004 35 y 4 m	YES	Day 25 E2<5 Day 37 E2=251; FSH 21	Crohns flare SBO/ vomiting, acidosis day 36. Patient admitted via ER for pelvic sepsis/ abscess day after transfer. IV zosyn required. ID consulted, Iv zosyn pre retrieval and for full 7 days after recommended for all further retrieval/ transfer attempts.	20 mcg EE day 7; antagon 250 follistim 150 day 25; HCG 10,000 day 38	2x 5 mm follicles day 25; 16 mm follicle day 37; oocyte retrieved, icsi, Fresh transfer of day 3 14 cell morula; IM /po P and estrace. Oral antibiotics used as no IV available in time from out of state pharmacy. EMBRYO #3	Pt hx + rectovaginal fistulae and tortuous /strictured cervical canal. Transfers very difficult. Will keep supply of zosyn unconstituted and bring to retrievals. Confirmed that risk of IVF is increased in outpatient IVF setting.
6/2004 35y 5 m	-	Day 25 E2=14; FSH=18.5	Completed IV zosyn, abscess resolved, pt discharged; perianal crohns flare	EE 20 mcg day3 Prednisone 5 days; period induced with progertone 10 mg withdrawal	-	-
7/2004 35 Y 6 m	YES	Day 3 E2=<12; FSH 18.4 Day 16 E2=423; FSH=24	Active perianal Crohns disease Prednisone for 1 week given	20 mcg EE day 4, antagon 250, and Follistim150>225 ; ASA 81 mg day 8-13; HCG 10,00 day 16	u/s day 16 one 18 mm follicle; zosyn IV; no oocyte obtained	Empty Follicle Syndrome; Baby ASA no help
8/2004 35y 7m	-	Day 3 E2=42 FSH=23 Day 17 E2<5; FSH 16	-	EE 20 mcg day 3, FSH 150, Cetrotide; progesterone withdrawal to induce period	-	-
9/2004 35y 8m	YES	Day 4 E2=733; FSH=4	-	10,000 HCG only med day5; estrace & IM/po for luteal support	Oocyte retrieved, icsi, 6 cell A2 embryo fresh transfer to pt; implantation failure HCG- EMBRYO #4	Multiple implantation failures with fresh transfers. Gestational carrier and freeze all going forward.
10/2004 35y 9m	-	Day 4 E2=<5; FSH=43 Day 23: E2<5	-	EE 20 mcg day 4; Antagon 250 and 75->150 follistim day11; progesterone added day 23 and period induced	-	-
11/2004 35 y 10m	YES	DAY 9 E2=190; FSH 24	Crohns flare-Toradol and Prednisone days 4-8	Antagon 250 and Follistin 150 day 9, HCG 10,00 day 12	Successful retrieval of oocyte and icsi; 2PN embryo frozen. EMBRY0 #5	Embryo defrosted and 6 cell embryo transferred as part of DET to GC MK 2013 HCG- ? PREDNISONE IN EARLY FOLLICULAR PHASE helpful

12/2004 35y 11m	YES	Day 3 E2=86; FSH=13	Crohns flare, IVF needed, Liposyn 2 for EFA deficiency, Prednisone for 5 days end day 2	Antagon 250, Follistim150 day 6, HCG 10,000 day 8	u/s day 7 + 15 mm follicle, oocyte retrieved, icsi, 2PN embryp frozen EMBRYO #6	Embryo defrosted and 7 cell embryo transferred as part of DET to GC JB 6/2007. HCG-
1/2005 36 y 0m	YES	Day 3 E2=16; FSH=32	ELECTIVE prednisone 40/30/20/10	40 mcg EE ONCE day6, then 20 mcg; antagon 250 day	Oocyte retrieved day 19, icsi, 2PN frozen.	Embryo defrosted and 5 cell embryo transferred as part off DET
11/2005 36y 10 m	yes	Day 3 E2=<5; FSH=30 Day 15 E2=187; FSH=11.8	IV fluids and Lipsyn for Crohns; perianal disease active; IV zosyn	Cetrotide 250 day 7 decreased to 0 day 11, 20 mcg EE days 11, 13; antagon 250 day 15-19; follistim150 days 15-19; HCG 10, 000 day 20	18 mm follicle day 20. No oocyte retrieved at aspiration.	EFS
12/2005 36y 11m	-	Day 7: E2=291; FSH=11	ELECTIVE prednisone days 3-7 40/30/20/10		40 mm cyst on ovary	Functional ovarian cyst
1/2006 37y 0m	-	Day 6: E2=63 FSH=38 Day 14 E2=255; FSH=24 Day 15 E2=155	ELECTIVE prednisone 40/30/20/10/5/ 5 ays 1-6	20 mcg EE day 9x1 then cetrotide 250, follistim 100- >300 day 10-14. Period induced with 20 EE and progesterone	u/s day 11 17,11, 9, 7 mm	? Follicles vs cycts
2/2006 37y 1m	yes	Day 2 E2=<5, FSH=21 Day 12 E2=116; FSH=10.7	ELECTIVE prednisone days 2-6 40/30/20/10/5	DHEA 10 mg days 2-6; 20 mcg EE day 612; 150 Follistim and 250 cetrotide days 13-15; Toradol day 18; 15,000 HCG day 16	u/s 3 follicles<10m m on R day 12; oocyte retrieved day 14, icsi, 2 PN embryo frozen EMBRYO #12	Embryo defrosted and 2 cell embryo transferred in DET 2007 to GC MK. This resulted in singleton birth. However, it was most likely from the other embryo (8 cell)
3/2006 37y 2m	-	Day 4 E2=13; FSH=40.6 Day 8 E2<1; FSH=33	ELECTIVE prednisone days 1-5 40/30/20/10/5	DHEA 25 mg days 1-5; EE 20 mcg day 5-19. Period induced with 20 EE and progesterone.	-	DHEA not helpful.
4/2006 37y 3m	-	Day 5 E2<5; FSH=53	Crohns sbo	Period induced with 20 EE and progesterone	-	-
5/2006 37 y 4 m	-	Day 11 E2=<5; FSH=34	ELECTIVE prednisone 40/30/20/10/5 Days 1-5	EE 20 mcg days 6-10, 40 mcg days 11. Period induced with 20 EE and progesterone.	-	-
6/2006 37y 5 m	-	Day 5 E2<1; FSH:NT Day 21 E2- =24; FSH=9.8; LH=14.9	ELECTIVE prednisone 40/30/20/10/5 Days 2-7	20 mcg EE day 5-28; Cetrotide 250 day 9-20; follistim 150200 days 9-12. Period induced with 20 EE and progesterone.	-	-
7-8/2006 37 y 6m	-	Day 6 E2<5; FSH=51	ELECTIVE prednisone days 1-6 40/30/20/10/5	250 cetrotide x1 day 6. Period induced with 20 EE and progesterone.	-	-
9-10 /2006 37y 8m	-	Not done		Period induced with 20 EE and progesterone		SIXTH CONSECUTI VE MONTH OF PERIODS ONLY WHEN INDUCED WITH E/P MENOPAUS E
11/2006 37y 10 m	-	Not done	Elective prednisone days 1-4 40/30/20/10	DHEA 25 MG TID from last 3 days of 9-2006 cycle to day 7; EE 20 mcg days 8-27. Period induced with 20 EE and progesterone.	u/s Day 7 <5 mm follicles	-

12/2006 37y 11 m	-	Day 10: E2=323		3 doses 20 mcg EE; cetrotide x1, Follistim 100 x2 10,000	35 mm Ovarian cyst drained day 20.	-

Discussion

The patient states that she viewed the process as a probability equation. Probability of one genetic offspring (providing you can obtain a normal oocyte) = (p) of successful fertilization to 2 PN stage x (p) survival freezing x (p) implantation –(p) loss by miscarriage (usually due to aneuploidy). The overall probability will increase the more chances you have (with each individual oocyte obtained).

Using our interventions we obtained multiple oocytes, one at a time and the patient began this process relatively young (age 32). So, the probability of at least one genetic offspring in the end was actually very high. Using ICSI, fertilization approached 100% (failed once) and survival of freezing was 100%- supportive of excellence in embryology at our center.

Probability of implantation using a proven GC and a high-quality embryo is about 60% in the literature. In the case of our patient if the A1-A2 embryo had 8-9 cells 100% resulted in viable pregnancy. If the embryo at day 3 transfer had any other number of blastomeres implantation rate was zero. There was no miscarriage.

The above extremely challenging case demonstrates that interventions to increase the probability of having genetic offspring in POI/POF patients exist, and should be taught and offered to patients. Without IVF, our patient would never have been able to have a child, and without the detailed treatments she would not have been able to acquire even one oocyte for IVF to have her own genetic child. The process overall took a long period of time due to the need for, and difficulty finding, gestational carriers, especially during and after the COVID epidemic. Most POI/POF patients would need neither. In the end, our patient was able to have two healthy genetic daughters, and is expecting a healthy genetic son. Thus, with 3 children, she completes her infertility journey with a fertility rate almost double the USA average (1.7 children per woman). Thus, this 57-year-old physician will have her third child at the age of 57 with the first sibling twenty years older than her youngest sibling a brother without the rise one one's health of delivering a baby at 58 years old by using a gestational carrier.

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