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Prognostic Impact of Recurrent Pregnancy Loss

For many years, recurrent pregnancy loss (RPL) has been defined as 2 or 3 consecutive losses; now, some researchers and scientific societies think the definition should be 2 or 3 losses that are not necessarily consecutive. Egerup et al from Copenhagen University Hospital, Denmark, investigated whether the prognostic impact is the same if the prior losses are consecutive or if they occur both before and after a birth.

Selected for the study were 168 women aged ≤41 years who had been participating in 3 randomized controlled trials of intravenous immunoglobulin for treatment of RPL and had been followed for ≥5 years. Those whose losses had all occurred before gestation week 22 and who had no live birth or stillbirth were classified as primary RPL. The majority of the cohort (n = 127) had ≥1 pregnancies progressing to ≥22 weeks resulting in live birth or stillbirth followed by ≥3 consecutive losses before week 22; these were classified as secondary RPL. For 124 of the women, the consecutive losses followed a live birth; 45 also had losses before a birth. Three women had consecutive losses after an unexplained stillbirth but no prior losses.

When early and late losses were separated according to whether they occurred before or after the last birth, the analyses showed that neither early nor late loss had an impact on the risk of subsequent pregnancy loss if it occurred before a birth (incidence rate ratio [IRR] 0.88 [95% confidence interval {CI}, 0.70–1.11] and IRR 1.31 [95% CI, 0.62–2.77], respectively). If the losses occurred after the last birth, however, both early and late previous losses had a significant negative impact (IRR 1.14 [95% CI, 1.04–1.24] and IRR 2.15 [95% CI, 1.57–2.94], respectively).

Conclusions and Clinical Implications

These analyses showed that among women with secondary RPL, a live birth seems to eradicate the negative prognostic impact of losses prior to the birth. Although the study was limited by the small sample size and retrospective design, the authors concluded that only consecutive pregnancy losses should be included in the definition of RPL. The study also confirmed the hypothesis that the number of losses had a prognostic impact.

Egerup P, Kolte AM, Larsen EC, et al. Recurrent pregnancy loss: what is the impact of consecutive versus non-consecutive losses? Human Reprod 2016;31:2428-2434.

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Table 1. Embryo transfer characteristics and pregnancy outcomes

Characteristic	Vaginal deliveries only	History of CD	*p* value
Transfer time (seconds)	157 (128–190)	187 (142–309)	.002
Mucus on catheter	29/109 (27)	38/85 (45)	.010
Blood on catheter	9/109 (8)	18/85 (21)	.012
Retained embryo	1/109 (1)	2/85 (2)	.582
Easy transfer	104/109 (95)	62/82 (76)	<.001
Positive hCG	61/109 (56)	45/85 (53)	.771
Clinical pregnancy	53/109 (49)	35/85 (41)	.313
Live birth	42/109 (39)	27/85 (32)	.366

Values reported as median (interquartile range) or fraction (%). Blood and mucus on catheter include microscopic blood and mucus contamination. Three charts in the history of the CD group did not report the difficulty of the transfer.

Embryo Transfer And Pregnancy Outcome After Cesarean Delivery

Increased risk of subfertility among women with a history of cesarean delivery (CD) has been widely reported. Several potential contributing factors have been cited, including the impact of the surgical scar. In as many as 58% of these women, routine transvaginal ultrasounds or saline sonograms have shown an anterior lower uterine segment defect, often with fluid within the hysterotomy site. The role of the defect and how it may affect embryo transfer (ET) and pregnancy outcome was investigated by Patounakis et al from the National Institute of Child Health and Human Development, Maryland.

Women awaiting transvaginal oocyte retrieval before in vitro fertilization (IVF) and ET and who had ≥1 previous deliveries at >20 weeks gestation were enrolled in the study; 109 had vaginal deliveries only, and 85 had a history of ≥1 CDs. There were no statistically significant differences between the 2 groups (mean age, 35.3 ± 4.2 years and 35.6 ± 4.3 years, respectively) in baseline or cycle characteristics.

The primary outcome measure was live birth at >24 weeks gestation. Secondary outcome measures were

- positive serum human chorionic gonadotropin (hCG) level (>5 mIU/mL)
- clinical pregnancy
- time taken to perform ET

Only the first fresh ET was considered for patients who had had >1 ET.

No statistically significant differences were found between the groups in live births (42/109 [39%] vs 27/85 [32%], respectively; $p = .366$), positive hCG level or clinical pregnancy. ET took longer for the CD group (157 vs 187 seconds), and the catheters were almost 3× as likely to have blood and almost 2× as likely to have mucus on them (Table 1).

Conclusions and Clinical Implications

This study showed no significant effect of a previous CD on pregnancy outcomes for women undergoing IVF cycles. The authors believed the data should be reassuring to patients and providers. An explanation for the apparently more difficult ET in these patients remains to be determined.

Patounakis G, Ozcan MC, Chason RJ, et al. Impact of a prior cesarean delivery on embryo transfer: a prospective study. Fertil Steril 2016; 106:311-316.

Tubal Occlusion vs Salpingectomy

Tubal pathology is one of the main indications for in vitro fertilization (IVF) treatment in subfertile women. The most severe form of distal tubal pathology, hydrosalpinges, is associated with poorer ongoing pregnancy rates after IVF, compared with other forms. Both laparoscopic salpingectomy and laparoscopic proximal tubal ligation have been shown to improve IVF outcomes.

As an alternative to invasive surgery and its attendant risks, an intratubal device has been developed that occludes the tube and prevents leakage of hydrosalpingeal fluid into the uterine cavity. Studies published since 2005 have shown that use of the intratubal device is feasible and safe, but its effectiveness when compared with salpingectomy has

not been demonstrated by any randomized clinical trials. Dreyer et al from VU University Medical Centre, the Netherlands, conducted such a trial to test the hypothesis that the tubal device would not be inferior to laparoscopic salpingectomy.

Study participants included 85 women (age range, 18–41 years) with unilateral or bilateral hydrosalpinges confirmed by hysterosalpingography (HSG) or laparoscopy who were scheduled for IVF or intracytoplasmic sperm injection (ICSI). They were randomly assigned to undergo insertion of the device ($n = 42$) or laparoscopic salpingectomy ($n = 43$) and to begin IVF or ICSI treatment 12 weeks later. Of these, 37 received the device, 29 of whom started the fertilization treatment; 36 underwent the surgery, with 35 starting the treatment.

Several women from both groups dropped out or were eliminated from the study for a variety of reasons, including difficulty inserting the device followed by a crossover to salpingectomy, or were lost to follow-up. Results were determined by intention-to-treat (ITT) analysis, which included all 85 participants, and by per protocol (PP) analysis, which excluded those who underwent both tubal insertion and salpingectomy and those who showed leakage along the device on HSG.

The primary outcome was the rate of ongoing pregnancy following a single IVF or ICSI treatment. ITT analysis found a significant difference between the groups in the rate: 26.2% (11 of 42) for the intratubal device group vs 55.8% (24 of 43) for the salpingectomy group ($p = .008$; Table 2). The median time to ongoing pregnancy was

- 12.0 months (range, 7.9–19.5 months) for women receiving the tubal device
- 6.7 months (range, 5.3–9.5 months) for those undergoing laparoscopy ($p \leq .001$)

PP analysis found the ongoing pregnancy rate to be 33.3% (9 of 27) for the intratubal device group and 59.4% (19 of 32) for the salpingectomy group, a difference that did not reach statistical significance (χ^2 $p = .067$). The median time to pregnancy was

Table 2. Primary and secondary outcome measures: pregnancy outcomes following 1 IVF/ICSI treatment cycle (intention-to-treat analyses)

	Intratubal device ($n = 42$)	Salpingectomy ($n = 43$)	Absolute difference (95% CI)	p value (χ^2)
Primary outcome				
Ongoing pregnancy				
Per included patient	11/42 (26.2%)	24/43 (55.8%)[a]	29.6% (7.1–49.1)	.008
Per embryo transferred	11/78 (14.1%)	22/60 (36.7%)[a]	22.6% (7.1–37.7)	.003
Secondary outcome				
Implantation rate				
Per embryo transferred	13/78 (16.7%)	23/60 (38.3%)	21.6% (5.7–37.0)	.006
Clinical pregnancy rate				
Per included patient	13/42 (31.0%)	25/43 (58.1%)	27.1% (4.4–47.0)	.016
Miscarriage rate				
Per included patient	2/42 (4.8%)	1/43 (2.3%)	2.5% (–8.3 to 14.1)	.616
Per embryo transferred	2/78 (2.6%)	1/60 (1.7%)	0.9% (–6.7 to 7.5)	≥.99
Ectopic pregnancy rate				
Per included patient	0/42 (0%)	0/43 (0%)	N/A	N/A
Per embryo transferred	0/78 (0%)	0/60 (0%)	N/A	N/A
Live-birth rate				
Per included patient	9/42 (21.4%)	20/43 (46.5%)[a]	25.1% (3.4–44.5)	.022
Per embryo transferred	9/78 (11.5%)	18/60 (30.0%)[a]	18.5% (4.0–33.1)	.009

CI, *confidence interval*; N/A, *not applicable*.
[a]*One twin pregnancy following single embryo transfer, calculated as 1 pregnancy and 1 live birth.*

8.9 months (range, 7.6–15.3 months) for the women who received the device and 6.6 months (range, 5.3–8.6 months) for those who underwent laparotomy.

Conclusions and Clinical Implications

This study failed to demonstrate that proximal tubal occlusion with an intratubal device was noninferior to salpingectomy in women with hydrosalpinges who were to undergo IVF/ICSI. ITT analysis showed that salpingectomy resulted in a significantly higher rate of ongoing pregnancy; PP analysis also showed a higher rate, although the difference was not statistically significant. The authors concluded that salpingectomy should remain the procedure of choice for infertile patients with hydrosalpinges.

Dreyer K, Lier MCI, Emanuel MH, *et al*. *Hysteroscopic proximal tubal occlusion versus laparoscopic salpingectomy as a treatment for hydrosalpinges prior to* IVF *or* ICSI: *an* RCT. Human Reprod 2016;31:2005-2016.

Fertility Trends For Young Patients with Lupus and Vasculitis

Some cases of impaired fertility, both male and female, may be a result of treatment with gonadotoxic agents received in childhood, not only for cancer but for rheumatic and other diseases. An example is cyclophosphamide (CTX), which is a standard therapy for systemic lupus erythematosus (SLE), granulomatosis with polyangiitis and other types of vasculitis.

Now that several fertility preservation (FP) options are available, the American Academy of Pediatrics and other groups have recommended counseling adolescents and young adults, before they undergo such therapy, about the possibility of fertility loss, and offering them referrals to specialists to discuss their options. The focus has usually been on patients with childhood cancers. Nahata et al from Nationwide Children's Hospital, Ohio, evaluated fertility counseling and FP practices among patients with rheumatic diseases who had received CTX at a large pediatric academic center.

Review of medical records identified 53 individuals, 13 male and 40 female, who met the study criteria. They had been diagnosed at a median age of 14 years (range, 4–18 years) and had begun treatment at age 15 years (range, 4–21 years). The indication for CTX was SLE in 33 cases and granulomatosis or other vasculitis in 20 cases.

Fertility counseling was documented for only half of these patients, 4 male and 22 female:

- For the female patients, the only FP option discussed was leuprolide acetate, which was pursued by all of these patients. Some of the charts included statements that this would protect against infertility.
- For the male patients, most of whom were postpubertal, 3 were offered sperm banking; 2 declined and 1 provided a semen sample after beginning treatment that was azoospermic. Sperm banking was not discussed with some of the male patients.
- Only 1 of the 53 patients was referred to a fertility specialist.

Conclusions and Clinical Implications

These findings were consistent with results of a national survey of pediatric nephrologists showing inconsistencies in fertility counseling and underutilization of fertility referrals. The study's authors urged physicians treating childhood rheumatic disease to be more aware of infertility risk and FP options, and called for development of disease-specific guidelines for fertility counseling of pediatric populations beyond oncology.

Nahata L, Sivaraman V, Quinn GP. *Fertility counseling and preservation practices in youth with lupus and vasculitis undergoing gonadotoxic therapy*. Fertil Steril 2016;106:1470-1474.

In the next issue of Infertility Treatment Update™

Single-embryo transfer and birth rates; counseling young cancer patients about fertility preservation; endometriosis and pregnancy complications

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