Title: THE CARDINAL PROTOCOL: INVESTIGATING A LOW-COST OPTION FOR OOCYTE CRYOPRESERVATION IN A NON-INFERIORITY CLINICAL TRIAL

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Background:
The 2025 strategic plan of American Society of Reproductive Medicine (ASRM) prioritizes equitable access to reproductive healthcare as a priority, calling for cost-effective treatments accessible to patients otherwise excluded by financial barriers(1). However, methods to achieve affordability without sacrificing efficacy have not been rigorously studied. In response to this, we designed the novel Cardinal protocol—a low cost, simplified version of routine high-cost protocols for oocyte cryopreservation (OC).

Objective: The purpose of this study was to determine if the Cardinal protocol could achieve non-inferior clinical outcomes, specifically the number of mature oocytes (MIIs), compared to routine, high-cost protocols.

Materials and Methods: Patients undergoing planned OC were prospectively recruited at a single academic institution between 2023-2024. Participants were allowed to choose between the routine high-cost protocols vs. the low-cost Cardinal protocol. The Cardinal protocol is limited to 2 ultrasounds (baseline and stimulation day 9 [SD9]), no bloodwork, standardized FSH dosing (AMH $\leq$ 4: 300 IU, AMH > 4: 225 IU), scheduled progestin start on SD6 in place of antagonist, and auto-trigger when $\geq$ 3 follicles are projected $\geq$ 18mm. Routine high-cost protocols (antagonist, microdose flare) include up to maximum dose gonadotropins, 5-6 ultrasounds, and 3-5 blood draws. We hypothesized that Cardinal would be non-inferior to routine, based on a non-inferiority margin of 5 oocytes(2–4). Inclusion criteria included ovary-bearing individuals aged 18-40 with AMH $\geq$ 0.3 and $\leq$ 7 ng/ml. Exclusion criteria included patients needing time-sensitive gonadotoxic therapy, concern for severe ovarian hyperstimulation syndrome (OHSS), or contraindications to stimulation or outpatient retrieval. The primary outcome was the number of MIIs retrieved. Secondary outcomes included total number of oocytes retrieved, premature ovulation, OHSS, adverse events, and total charges. Continuous variables were compared using Wilcoxon rank sum test; categorical variables were tested using Chi-squared or Fisher's Exact tests, as appropriate. Multivariable linear regression with generalized estimating equations was used to assess non-inferiority(5).

Results:
Of 105 participants, 50 enrolled in Cardinal and 55 opted for routine. Fifteen patients did a second cycle, of which 6 patients switched protocols from both Cardinal to routine and vice-versa. No significant differences existed between groups. The median AMH was 2.56 in Cardinal vs. 3.30 in routine (p=0.062), and median AFC was 15 in Cardinal vs. 17 in routine (p=0.063). A total of 119 cycles (57 Cardinal, 62 routine) were compared. The median number of MIIs retrieved was 10 (IQR 7-15) in Cardinal and 11 (IQR 7-16) in routine. Adjusted for age and ovarian reserve, the mean difference in MIIs between groups was +1.3 (95% CI -1.0, 3.6), demonstrating non-inferiority of the Cardinal protocol. Premature ovulation did not occur in either group. OHSS rates were lower in Cardinal (3.5% vs. 23%, p=0.002); no other significant differences in adverse events were noted. The average cost of the Cardinal cycles was $5,040

(p<0.001) less than that of the routine protocols.

Conclusions:
The Cardinal protocol is non-inferior to the routine high-cost protocols in terms of mature oocytes retrieved. Moreover, it considerably reduces costs by $5,000, making it a cost-conscious protocol that should be seriously considered for OC cycles.

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Table 1

	Cardinal	High-Intensity	
Participants	50	55	--
Median Age	33 (32, 35)	32 (31, 34)	p=0.2
Median AFC	15 (9, 19)	17 (12, 22)	p=0.063
Median AMH (ng/ml)	2.56 (1.48, 3.51)	3.30 (1.78, 4.66)	p=0.062
Cycles	57	62	--
Median BMI	23.8 (21.6, 26.2)	23.3 (21.8, 26.3)	p>0.9
Median starting FSH dose (IU)	300 (300, 300)	375 (300, 450)	p<0.001
Median # of US visits	2 (2,3)	5 (5, 6)	p<0.001
Median # of labs drawn	0 (0,2)	5 (4, 8)	p<0.001

Mean difference of oocytes retrieved (Adjusted)	Cardinal – HI = +0.73		95% CI (-1.94, 3.4)
Mean difference of MIIs (Adjusted)	Cardinal – HI = +1.3		95% CI (-1.0, 3.6)
Premature ovulation	0	0	--
OHSS	2 (3.5%)	14 (23%)	p=0.002
Mean difference in total charges	Cardinal – HI = -$5040		p<0.001