COMPARATIVE OUTCOMES OF NEW BCL6-GUIDED TREATMENT STRATEGIES IN WOMEN WITH UNEXPLAINED INFERTILITY: A MULTICENTER RETROSPECTIVE ANALYSIS OF 2,451 PATIENTS

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INTRODUCTION AND BACKGROUND

Endometriosis and progesterone resistance are recognized contributors to implantation failure, recurrent pregnancy loss (RPL), and unexplained infertility (UI).[1] B-cell lymphoma 6 (BCL6) is an inflammatory biomarker associated with endometriosis and impaired endometrial receptivity. Previous studies have demonstrated that BCL6-positive patients experience significantly reduced reproductive outcomes when left untreated. Published untreated cohorts report pregnancy rates of approximately 18% and live birth rates at an average 14%.[4,5,9]

While GnRH agonists and laparoscopy are currently the most established interventions, less is known regarding outcomes associated with alternative BCL6-guided treatment approaches including letrozole, norethindrone, and GnRH antagonists such as Elagolix.

OBJECTIVE

To compare reproductive outcomes among BCL6-positive patients receiving different targeted treatment modalities prior to embryo transfer and to contextualize these outcomes relative to published untreated cohorts.

MATERIAL AND METHODS

Study Design
Retrospective multicenter cohort study.

Study Population
2,451 patients from 18 IVF centers
All underwent BCL6 testing prior to embryo transfer
Presenting symptoms included unexplained infertility (UI), recurrent pregnancy loss (RPL) and/or recurrent implantation failure (RIF)

Clinical Characteristics
Mean prior failed cycles: 1.8
PGT-A testing ; 85% of patients
Patients receiving combination therapies were excluded
Patients with incomplete clinical records were excluded

Treatment Groups
BCL6-positive patients received one of the following:

- GnRH Agonist -Lupron
- GnRH Antagonist - Elagolix
- Aromatase Inhibitor- Letrozole
- Progestins- Norethindrone
- Surgery- Laparoscopy

Primary Outcomes
Clinical Pregnancy Rate (PR)
Live Birth Rate (LBR)

Statistical analyses were performed using Chi-Square and Two-Proportion Z Testing.

RESULTS

Group	N
Total Patients	2,451
BCL6 Positive	1,346
BCL6 Negative	1,105

BCL6 Positive Patients (1,346)

Treatment	Dosage	Total Patients	Pregnancies	PR %	Live Births	LBR %
GnRH Agonists (Lupron)	3.75 x 2 60 days	867	644	74%	478	55%
Laparoscopy	NA	76	60	78%	48	63%
Letrozole	5mg 60 days	169	112	66%	83	49%
Norethindrone	5 mg 60 days	38	22	58%	20	53%
Elagolix* Interpret cautiously due to limited sample size	200 mg BID 60 days	9	7	78%	7	78%
NO TREATMENT From published prospective studies[2,3,8]	NA	120	22	18%	13	11%

BCL6 Negative Patients (1,105)

Success Rates for negative BCL6 patients were 72% PR and 53% LBR, consistent with previous published studies[6.,7.,9]

CONCLUSIONS

Previous publications have focused on the use of GnRH agonists as the primary hormone treatment modality for BCL6 positive patients. This retrospective analysis is the first study reporting the success rates using a variety of treatment options among various centers. While GnRH pathways continue to provide the best results, other methods are still significantly better than no treatment at all. The cumulative outcomes provides statistical power for alternative options and supports earlier published data on the value of BCL6 testing in women with UI undertaking IVF. In those studies, results showed positive BCL6 expression (histologic score, >1.4) was highly associated with endometriosis[1,2,5] . In addition, positive BCL6 expression, untreated was strongly associated with poor reproductive outcomes compared to negative BCL6 expression (12% vs 52%, respectively)[3,4,8]. Follow-up independent studies continued to show the success of treatment on BCL6-positive patients [2,6,7,8]..

Treatment	Pregnancy Improvement	Live Birth Improvement
GnRH Agonist	4.1×	5.0×
Letrozole	3.7×	4.5×
Norethindrone	3.2×	4.8×
Laparoscopy	4.3×	5.7×
GnRH Antagonist	4.3×	7.1×

All BCL6-Guided Treatments Outperformed Untreated Controls

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LIMITATIONS

Retrospective design, treatment selection not randomized, unequal treatment group sizes, small GnRH antagonist cohort, and potential center-specific practice variation

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