The Impact of Menopausal Status on Idiopathic Subglottic Stenosis

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BACKGROUND

Idiopathic subglottic stenosis (iSGS) occurs almost exclusively in females (99%), which suggests a hormonal link. Although this association has been largely observed, there exists little research to establish the impact of estrogen or progesterone on disease manifestation. Our study is the first to analyze iSGS median time to recurrence with respect to menopausal status in a surgery naïve cohort following their first procedure. Additionally, our study examines the effect of birth control and hormone replacement therapy on disease recurrence.

OBJECTIVES

> **Assess the impact of menopausal status on time to recurrence**

> **Assess the effect of hormone replacement therapy and birth control on disease recurrence**

METHODS

Patients that underwent their first laser wedge excision at Mayo Clinic were retrospectively reviewed and grouped based on their response to questions about their menopausal status at time of surgery, as well as age of first period, number of full-term pregnancies, and usage of exogenous hormones. Crucially, our study controlled for prior airway surgery by only enrolling patients who underwent laser wedge excision at index and subsequently. 85 patients met this criteria and were enrolled. Statistics included univariable and multivariable analyses with hazard ratios.

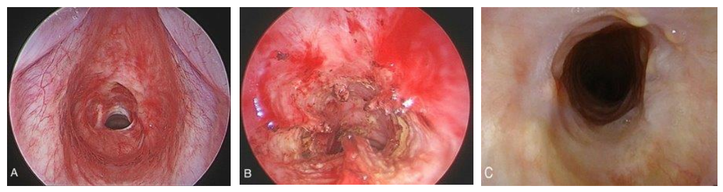


Figure 1: iSGS disease pre- and post-Laser Wedge Excision (LWE) surgery. All patients included were treated primarily with LWE.

RESULTS

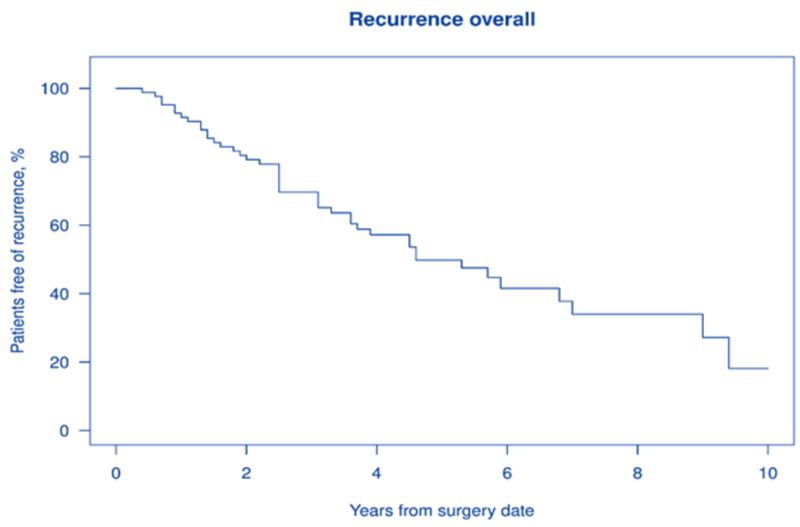


Figure 2 (above): Plot of recurrence and age.

Figures 3-6 (right): Plots of recurrence with respect to menstrual status, hormone replacement therapy, birth control, and triple therapy compliance.

	Recurrence		
	No (N=42)	Yes (N=43)	Total (N=85)
Age			
N	42	43	85
Less than 35 years	5 (12%)	7 (16%)	12 (14%)
35 to 45 years	6 (14%)	4 (9%)	10 (12%)
45 to 55 years	14 (33%)	18 (42%)	32 (38%)
55 to 65 years	9 (21%)	10 (23%)	19 (22%)
Older than 65 years	8 (19%)	4 (9%)	12 (14%)
Current menopausal status, n (%)			
Premenopausal	10 (24%)	9 (21%)	19 (22%)
Perimenopausal	4 (10%)	4 (9%)	8 (9%)
Postmenopausal	28 (67%)	30 (70%)	58 (68%)
Age at first period, n (%)			
Less than 12	3 (8%)	5 (13%)	8 (10%)
12-14	35 (88%)	29 (75%)	64 (81%)
15 or older	2 (5%)	5 (13%)	7 (9%)
Missing	2	4	6
Full-term pregnancies, n (%)			
0	9 (22%)	6 (14%)	15 (18%)
1	1 (2%)	3 (7%)	4 (5%)
>1	31 (76%)	33 (78%)	64 (77%)
Missing	1	1	2

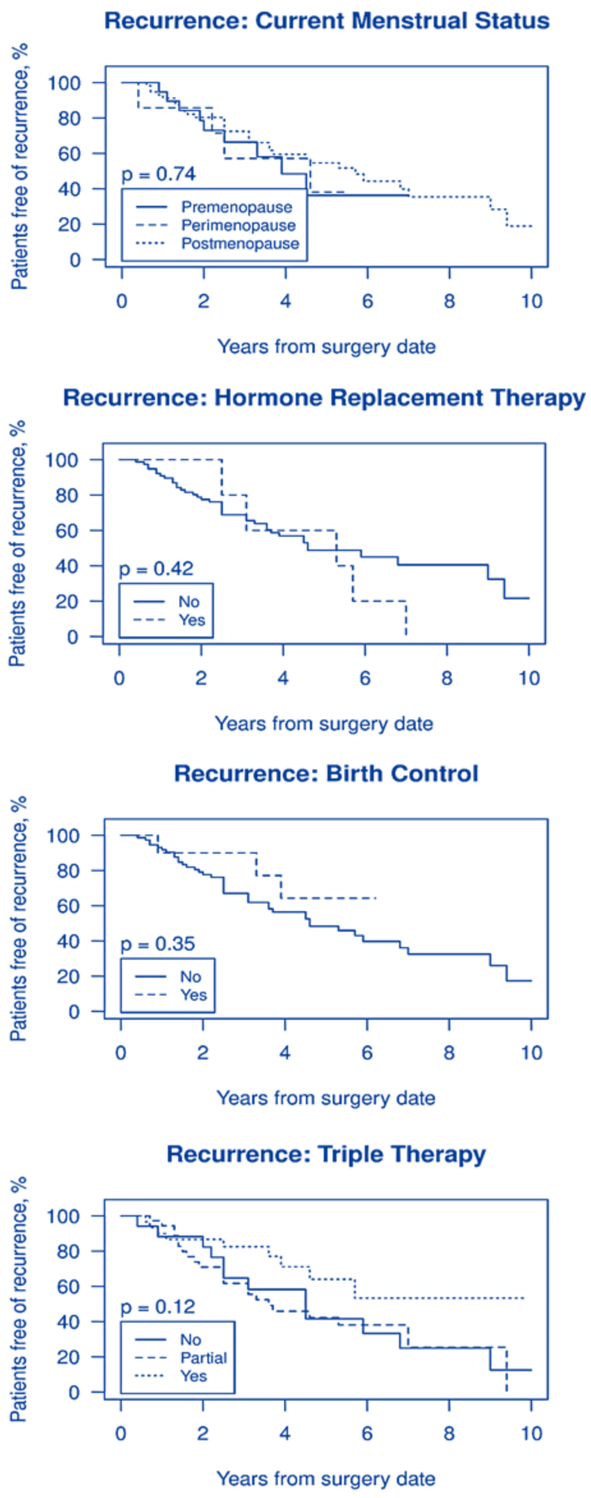
Table 1 (L): Study demographics.

	Only significant	
Parameter	HR (95% CI)	p-value
Age (continuous)	0.95 (0.92, 0.97)	**<.0001**
Birth Control		
No	Ref	
Yes	0.26 (0.08, 0.91)	**0.04**
Triple Therapy Compliant		
No	1.89 (0.79, 4.53)	0.15
Partial	2.59 (1.18, 5.67)	**0.02**
Yes	Ref	

Table 2 (upper R): Summary of multivariable analysis of risk of recurrence.

Pre- and Peri-Menopausal	# of Patients
Patients on birth control	10
Recurred	3
Did not recur	7

Table 3 (lower R): Recurrence respective to birth control for pre- and peri-menopausal groups.



DISCUSSION

Estrogen levels in women peak in the second decade of life. This level declines to around 50% by menopause and continues to significantly decline afterwards[1]. In our study, each additional year of age was associated with an average **reduction in risk of recurrence of around 3%** (Figure 2). Interestingly, **women aged less than 35 years old were approximately ten times more likely to recur than those older than 65 years**. This effect may suggest the propensity of estrogen to mediate disease recurrence in young women who naturally have high levels of the hormone. Estrogen has been shown to promote fibroblast migration and increase collagen deposition[2,3]. ISGS is a disease of excessive fibrosis which may be aggravated by estrogen.

Our univariable analysis shown in Figures 3-6 did not demonstrate significance in time to recurrence with respect to menstrual status, hormone replacement therapy, birth control, or triple therapy compliance. However, after control for other variables in the multivariable analysis (Table 2), birth control was found to be significant. Compared to patients not on birth control, **those on birth control have a 74% decrease in the risk of recurrence**. In other words, birth control was shown to play a protective role by decreasing the risk of recurrence. Mishell and colleagues measured serum estrogen in premenopausal women taking oral contraceptives and found lower than usual levels of estradiol[4]. Other researchers measured significantly lower levels of estradiol, as well as luteinizing and follicular hormones, in women taking birth control[5]. Our study consisted of 10 pre- and peri-menopausal patients on oral contraceptives. Of those, 3 recurred and 7 did not recur (Table 3). The significant reduction in serum estradiol may explain the relative reduction in risk of recurrence in pre-menopausal women taking oral contraceptives.

CONCLUSIONS

- Estrogen is presumed to play a role in iSGS disease due to its high prevalence in women
- Our study used strict inclusion criteria by only enrolling patients who were assessed at first surgical intervention and were only treated with LWE
- Our study showed decreased risk of recurrence in older women with decreased estrogen
- Pre- and peri-menopausal women on oral contraceptives were at significantly lower risk of recurrence when compared to their counterparts not on birth control

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