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ORIGINAL ARTICLE ***Gynaecology***

The density of endometrial glandular openings: a novel variable to predict the live birth rate in patients with intrauterine adhesions following hysteroscopic adhesiolysis

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STUDY QUESTION: Can the density of endometrial glandular openings (DEGO) be a reliable and simple new variable in the prediction of live birth after hysteroscopic adhesiolysis?

SUMMARY ANSWER: The DEGO grade at follow-up hysteroscopy outperforms American Fertility Society (AFS) score in predicting the live birth rate after hysteroscopic adhesiolysis for patients with intrauterine adhesions (IUAs).

WHAT IS KNOWN ALREADY: Several methods, such as endometrial thickness and AFS score, have been proposed for predicting the live birth rate in patients with IUAs who undergo hysteroscopic adhesiolysis.

STUDY DESIGN, SIZE, DURATION: A test cohort of 457 patients with IUAs who underwent hysteroscopic adhesiolysis and had satisfactory follow-up hysteroscopy videos were retrospectively enrolled between January 2016 and January 2017. A validation cohort comprising 285 IUA patients was prospectively enrolled from March 2018 to August 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS: An automated counting software tested the follow-up hysteroscopy videos to calculate the DEGO grade of all the 742 patients with IUAs after hysteroscopic adhesiolysis. The AFS score for each patient was also calculated at the same follow-up hysteroscopy. Logistic regression analysis was performed to develop prediction models to predict the live birth rate following hysteroscopic adhesiolysis. The performance of each of these prediction models was compared by calculating the AUC.

MAIN RESULTS AND THE ROLE OF CHANCE: In the test cohort ($n = 457$), 231 patients had a live birth, but 226 patients failed. In the validation cohort ($n = 285$), 117 patients had a live birth, while 168 patients did not. The logistic regression analysis revealed that both the DEGO grade and AFS score at follow-up hysteroscopy were closely correlated with the live birth rate in patients with IUAs ($P = 0$). The AUCs of AFS score and DEGO grade in the test cohort were 0.7112 and 0.8498, respectively ($P < 0.0001$). The AUCs of AFS score and DEGO grade in the prospective external validation cohort were 0.6937 and 0.8248, respectively ($P < 0.0001$).

LIMITATIONS, REASONS FOR CAUTION: Further well-designed prospective clinical studies with a multicentric larger sample size should be needed to confirm the feasibility and efficacy of DEGO.

WIDER IMPLICATIONS OF THE FINDINGS: The DEGO grade is an accurate predictor factor of live birth rate in patients with IUAs following hysteroscopic adhesiolysis and can represent in the future an important and promising tool for assessing obstetric outcomes in IUAs.

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Key words: density of endometrial glandular openings / AFS score / intrauterine adhesions / hysteroscopic adhesiolysis / live birth rate

Introduction

Intrauterine adhesions (IUAs) is an acquired uterine condition that occurs when scar tissue forms inside the uterine cavity or cervical canal, causing damage to the basal layer of the endometrium (Asherman, 1948; Sugimoto, 1978). IUAs can cause partial or total obliteration of the uterine cavity, reduce the implantation area, and diminish endometrial receptivity by impairing the blood supply (Schenker and Margalioth, 1982; Hooker et al., 2014). Diagnostic hysteroscopy is considered the gold standard among studies on IUAs, as it has higher accuracy in confirming the presence, extent, and morphological characteristics of adhesions, as well as the quality of the endometrium, than ultrasound and hysterosalpingography, and helps in the classification of IUAs (Valle and Sciarra, 1988; Capella-Allouc et al., 1999). Hysteroscopic adhesiolysis is a recommended and effective method to treat IUAs (Chen et al., 2017), which involves releasing the adhesions and restoring the shape of the cavity.

Our understanding of the complex physiology of the endometrium and implantation of the developing embryo is incomplete, although we know that steroid hormones, peptides, growth factors, and cytokines all play a part (Damario et al., 2001; Boomsma and Macklon, 2006; Edwards, 2006). Several methods have been proposed for predicting the live birth rate in patients with IUAs who undergo hysteroscopic adhesiolysis. These methods include using transvaginal ultrasound to evaluate endometrial thickness, as described by Baradwan et al. (2018), and utilizing the American Fertility Society (AFS) score (1988), which takes into account the adhesion area, the nature of the adhesions, and the patient's menstrual status.

An emerging area of investigation is the physiological importance of the expression of endometrial glandular openings (Masamoto et al., 2000). Hanada et al. (2012) showed that equine glandular density is strongly associated with endometrial function. Synthesis and release of Mucin 1 (MUC-1) and glycodelin-A by endometrial glands, are essential for the fetus in the early stages of pregnancy (Burton et al., 2002; Spencer, 2014). Software for automatic counting of endometrial glandular openings in image frames acquired during diagnostic hysteroscopy has been reported previously (Cunha-Filho et al., 2008). Endometrium can be evaluated by this software objectively in several situations (Hanada et al., 2012). In this study, we used this software to count and classify the endometrium of IUAs into four grades according to the density of endometrial glandular openings (DEGO) on follow-up hysteroscopy video. We then correlated the DEGO grade with the live birth rate following hysteroscopic adhesiolysis, as this relationship has yet to be reported in humans. From this evaluation, we propose using DEGO as a novel variable that is superior to existing methods as a predictor of live birth (Cunha-Filho et al., 2008).

Materials and methods

Patients

Four hundred fifty-seven patients with IUAs who underwent hysteroscopic adhesiolysis between January 2016 and January 2017 and had satisfactory follow-up hysteroscopy videos were retrospectively enrolled as the test cohort. From March 2018 to August 2018, 285 IUA patients were also prospectively enrolled for external validation of the prediction model. The ethics committee of the Third Xiangya Hospital of Central South University approved the study (IRB No. 2019-S465). The procedure was performed following the relevant guidelines and regulations. Informed consent was received after the procedure was fully explained to all participants. The surgeon scored IUAs according to the AFS classification scoring system as follows (1988): 1–4 (mild); 5–8 (moderate); and 9–12 (severe).

The inclusion criteria were: (i) IUAs confirmed by hysteroscopy; (ii) a desire for fertility; and (iii) normal hormone levels and ovulation. The exclusion criteria included: (i) Male infertility; (ii) primary infertility; (iii) tubercular IUAs; (iv) tubal factor infertility; (v) other lesions including endometrial polyps, atypical hyperplasia, or endometrial malignancy; and (vi) loss to follow-up.

After hysteroscopic adhesiolysis, patients were followed up by telephone for over 1 year. Pregnancy outcomes were tracked, including live birth or no live birth (abortion or infertility). The medical records, operative reports, and hysteroscopy videos of these patients were reviewed.

Surgical procedure and postoperative follow-up hysteroscopy

Hysteroscopic adhesiolysis and postoperative follow-up hysteroscopy were performed within 3–7 days following menstruation. Hysteroscopy was carried out using an operative hysteroscope with an outer sheath diameter of 5.4 mm and a working channel diameter of 1.67 mm (KARL STORZ SE & Co. KG–Tuttlingen, Baden-Württemberg, Germany).

When performing the hysteroscopic adhesiolysis, the hysteroscope was introduced into the cervical canal through the cervix with the aim of reaching the intrauterine cavity. The adhesions located in the central part of the uterine cavity were usually dissected first and then the lateral adhesions were cut out. First, the tubal ostia, which is the anatomical landmark during hysteroscopic adhesiolysis, needed to be retrieved. Then, upon its visualization, the adhesions could be easily dissected. In cases of intrauterine anatomy distortion caused by adhesions, 5-Fr double action forceps were used under transabdominal ultrasound monitoring, using a blunt spreading dissection technique (Zhang et al., 2015) to separate the adhesions and anatomically reveal the uterine cavity. If the intrauterine anatomy was clear, the IUAs were separated with 5-Fr single action sharp scissors and the scar tissue covering the intrauterine wall was treated with a 'cold scissors ploughing technique' (Zhao et al., 2020b) until the entire uterine cavity had been opened successfully with a clearly visible bilateral fallopian tube ostia.

After hysteroscopic adhesiolysis, a uterine-shaped stainless-steel intrauterine device (IUD) was inserted into the uterine cavity, and a double-channel, 12-Fr Foley catheter balloon, with the top catheter portion beyond the balloon removed, was inserted into the uterine cavity and distended using 2.5 ml of sterile saline, with the balloon in the center of the uterine-shaped IUD (Fig. 1). Hyaluronic acid gel (Pabuçcu *et al.*, 2019) (3 ml) was then injected into the uterine cavity through the catheter.

Postoperatively, a hysteroscopic follow-up strategy was conducted (3 months after the first surgery). During the follow-up procedure, the patients' hysteroscopy videos were recorded.

Method for calculating the DEGO

The software program for determining the DEGO in the follow-up hysteroscopy videos that is presented here comprises four steps. Step 1 is key frame selection; key frames are extracted from each video segment using a methodology from the singular value decomposition (Cunha-Filho *et al.*, 2008). This technique is used to retrieve a refined feature space in which visually similar feature vectors (i.e. frames) are more easily clustered, and their relative positions show their correlation and redundancy (Hanada *et al.*, 2012). Step 2 is grayscale imaging; after capturing the key frames in the original images, grayscale transformation is used to enhance the images. Step 3 is local histogram equalization; histogram equalization is a method in image processing that uses contrast adjustment from the image's histogram. In this study, images with low contrast were enhanced using a method called local histogram equalization, which spreads out the most frequent intensity values in an image. Step 4 is blob detection; in computer images, blobs are bright on dark or bright regions in an image. Laplacian of Gaussian is an operation in computer analysis of images that is used to smooth an image before processing. The program then computes the Laplacian of Gaussian for images with successive SDs and stacks them up in a cube. Blobs are the local maximum in this cube (Fig. 2). The method of classification for DEGO is as follows (see Fig. 3): G0 DEGO: The glands are abundant, and experts judge them to be normal DEGO, the mean $\pm$ SD of normal DEGO is 118 ± 25 (range, 92–146); G1 DEGO: less than G0 but over 2/3 G0; G2 DEGO: less than 2/3 G0 but over 1/3 G0; G3 DEGO: less than 1/3 G0.

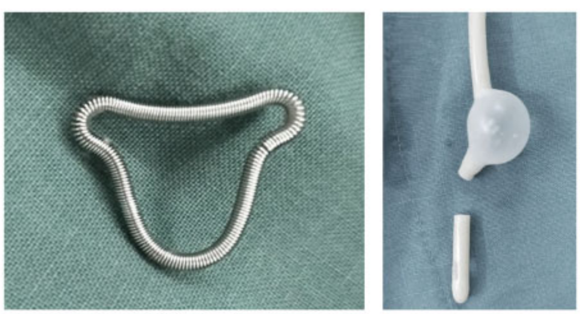

Figure 1. Uterine-shaped stainless-steel IUD and a double-channel, 12-Fr Foley catheter balloon. A uterine-shaped stainless-steel intrauterine device (IUD) was inserted into the uterine cavity, and a double-channel, 12-Fr Foley catheter balloon, with the top catheter portion beyond the balloon removed, was inserted into the uterine cavity and distended using 2.5 ml of sterile saline, with the balloon in the center of the uterine-shaped IUD after hysteroscopic adhesiolysis.

Other parameters, including the length of the uterine cavity, the number of visible uterine horns, and tubal ostia, were also measured and recorded. The AFS score of each patient was calculated. Two gynecologists confirmed all data of the above parameters.

Statistics

Statistical analysis was performed with the Statistical Analysis System 9.4 (SAS, USA). Differences between the live birth group and the no live birth group were tested using a χ^2 test or Fisher's exact test as appropriate. Logistic regression analysis was applied to decide which were the dominant variables as covariates combined with the AFS score or DEGO grade to establish the live birth rate prediction models. The AUCs of the models were compared to verify their prediction accuracy. A value of $P < 0.05$ was considered statistically significant.

Results

Telephone follow-up for 1-year post-hysteroscopic adhesiolysis in the test cohort showed that 231 patients had a live birth, and 226 patients did not have a live birth; in the validation cohort, 117 patients had a live birth, and 168 patients did not have a live birth. The automatic counting software showed the mean $\pm$ SD DEGO to be 61.7 ± 30 (range, 5–146), and the mean $\pm$ SD of normal DEGO to be 118 ± 25 (range, 92–146). Variables including age, recurrent IUAs, menstrual flow, uterine cavity length, number of visible cornu and tubal ostia, and especially AFS score and the DEGO were significantly related to the live birth rate post-hysteroscopic adhesiolysis ($P < 0.05$). Other variables, including gravidity history and IUA course, did not have any statistical significance in relation to the live birth rate after hysteroscopic adhesiolysis ($P > 0.05$) (Table I).

The risk factors for live birth rate were evaluated in univariate analysis. A multivariate logistical regression analysis was conducted for the meaningful variables ($P < 0.05$) identified by univariate logistical regression analysis. Compared with the live birth group, women in the no live birth group were older ($P = 0.0004$) and were more likely to have a higher AFS score ($P < 0.0001$). Women in the no live birth group were also significantly more likely to have DEGO grade of G1 ($P = 0.0114$), G2 ($P < 0.0001$) and G3 ($P < 0.0001$) (Table II).

Bivariate and binary logistic regression analysis revealed that AFS score and the DEGO grade were strictly related to the live birth rates in patients with IUAs (Tables III and IV). In the test cohort, the AUC of the prediction model of AFS score with other covariates (excluding the DEGO grade) was 0.7112. The AUC of the prediction model of DEGO grade with other covariates (excluding AFS score) was 0.8498 (Fig. 4). There was a significant statistical difference in the AUCs for DEGO grade and AFS score in the prediction of live birth rate in patients with IUAs ($P < 0.0001$) (Table V).

Bivariate and binary logistic regression analyses in the prospective external validation cohort revealed that DEGO grade performed well in predicting the live birth rate in patients with IUAs (Table VI). The AUCs for AFS score and DEGO grade in the validation cohort were 0.6937 and 0.8248, respectively (Fig. 5).

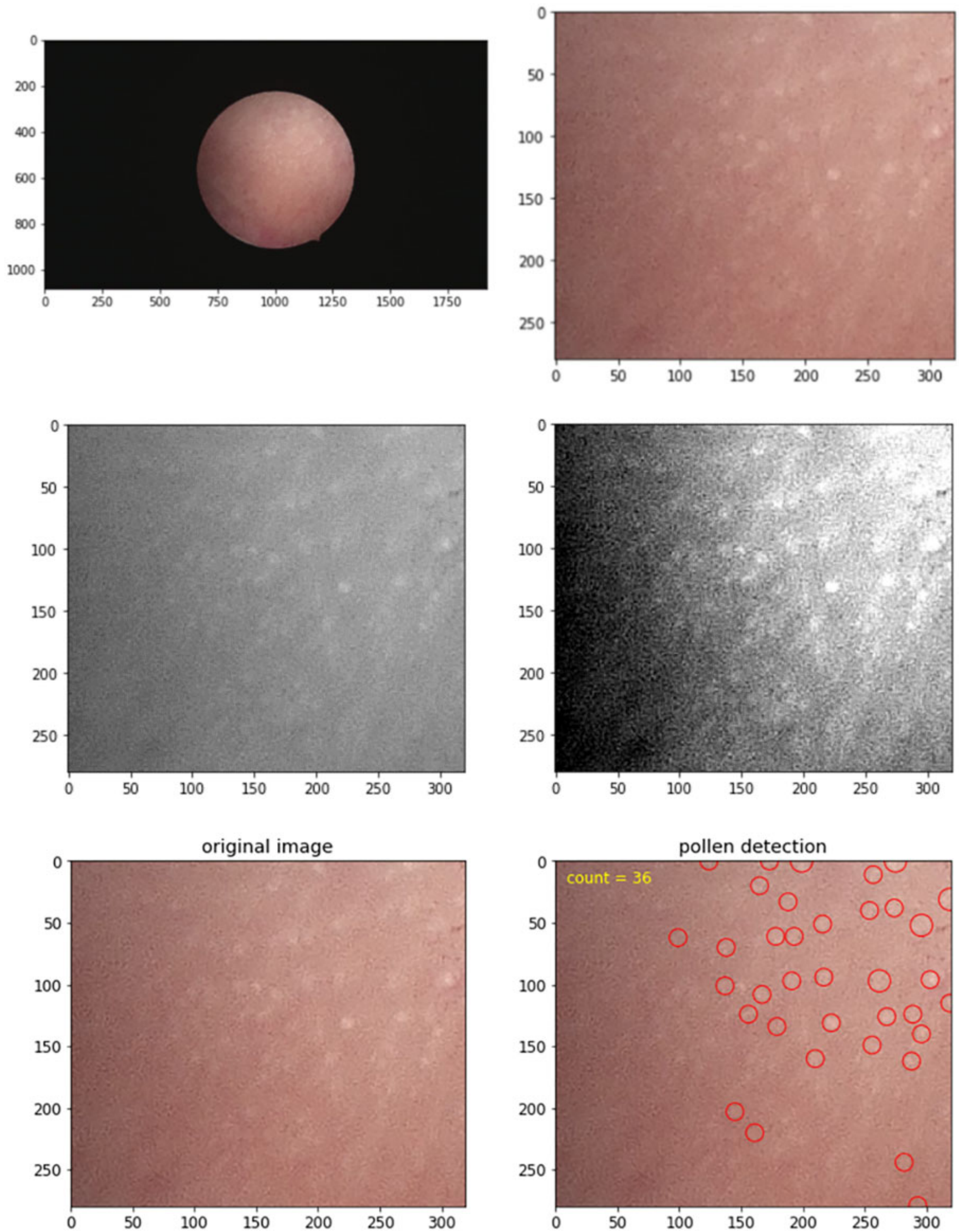

Figure 2. The software for determining the DEGO in the follow-up hysteroscopy videos. Step 1: Key frames were extracted from each video segment using a methodology based on the singular value decomposition. Step 2: Grayscale transformation is used to enhance the images. Step 3: The images with low contrast are enhanced using a method called local histogram equalization, which spreads out the most frequent intensity values in an image. Step 4: The program computes the Laplacian of Gaussian for images with successive SD and stacks them up in a cube. Finally, the DEGO in respond image were marked with small circles.

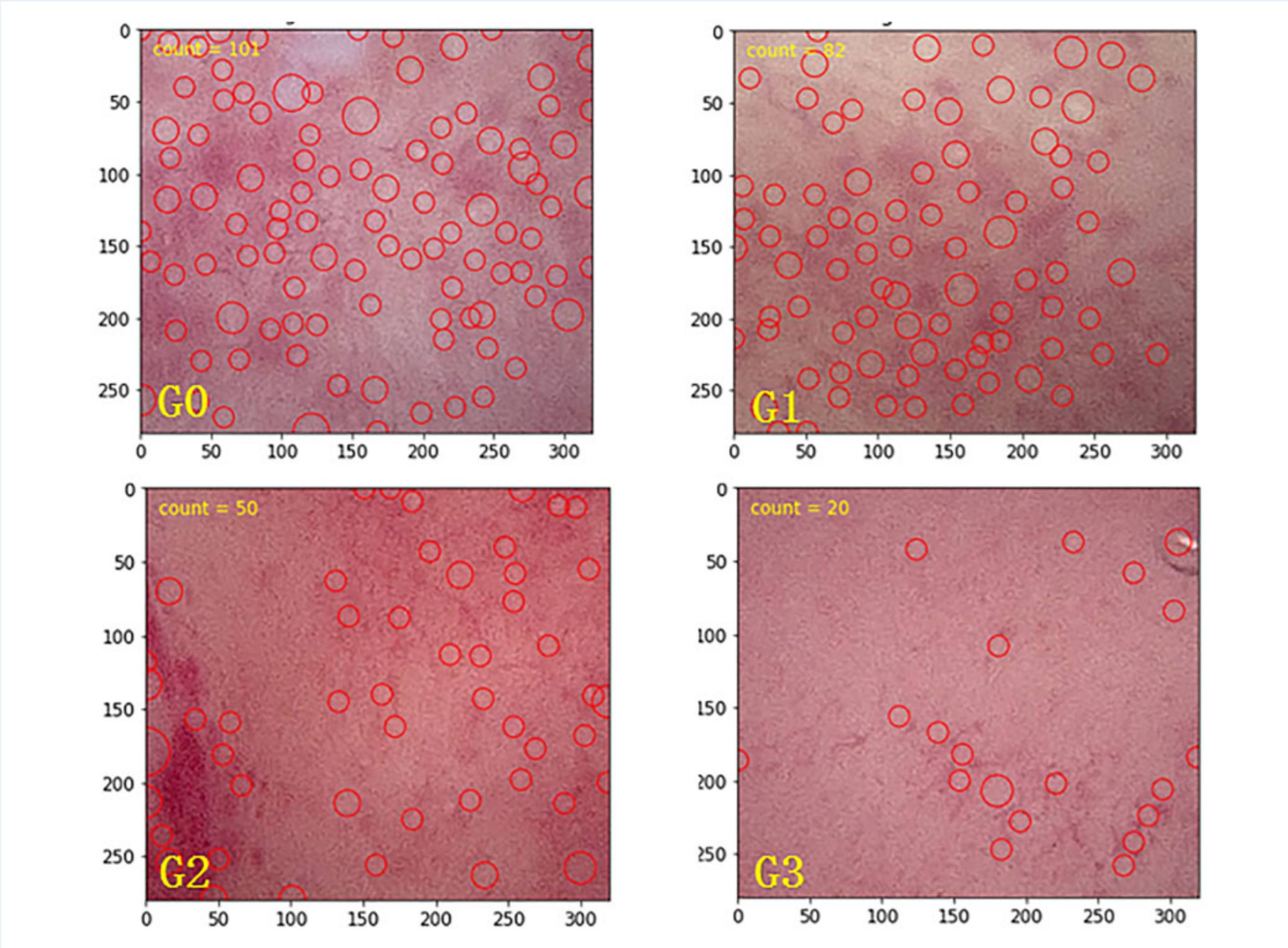

Figure 3. The method of classification for DEGO: G0 DEGO. The glands are abundant and experts judge them to be normal DEGO, the mean ± SD of normal DEGO was 118 ± 25 (range, 92–146); G1 DEGO: less than G0 but more than 2/3 G0; G2 DEGO: less than 2/3 G0 but more than 1/3 G0; G3 DEGO: less than 1/3 G0.

Discussion

Since hysteroscopy was introduced, the reported incidence and diagnosis of IUAs have increased considerably, especially in patients of childbearing age (Yu *et al.*, 2008a,b). The most common risk factor for IUAs is pregnancy-associated dilation and curettage (March, 2011; Takai *et al.*, 2015). As earlier studies have shown, dilation and curettage after abortion accounts for over 80% of IUAs (Deans and Abbott, 2010; Xiao *et al.*, 2014). In our study, 77.9% of patients had a history of dilation and curettage in early pregnancy, and 5.0% had a history of hysteroscopic diagnostic curettage. This finding was consistent with those of earlier studies (Xiao *et al.*, 2014).

The primary concern for patients with IUAs is their chance to have a live birth following hysteroscopic adhesiolysis. The AFS scoring system was developed for the clinical evaluation of the severity of IUAs and to help predict pregnancy outcomes. The variables of the AFS scoring system include the adhesion area, the nature of the adhesions, and the patient's menstrual status. Menstrual status is used to test endometrial function; however, this variable is extremely subjective and may not accurately reflect the patient's endometrial function.

Endometrial biopsy is another commonly used method for assessing endometrial status. However, the utility of endometrial biopsy for evaluating the endometrium has been the primary question of some well-designed studies (Coutifaris *et al.*, 2004). One reason for this is that the prevalence of out-of-phase endometrial biopsies was not found to be different between fertile or infertile populations (Coutifaris *et al.*, 2004). The accuracy of histologic endometrial dating for the detection of endometrial defects is uncertain (Young, 2017). Another reason is that a single biopsy is not necessarily representative of the entire endometrium (Schlafer, 2007). Thus, the assessment of the DEGO from a single biopsy could lead to an inaccurate diagnosis and prognosis (Hanada *et al.*, 2012). Measurement of endometrial thickness by ultrasound is also suboptimal, as it varies along with the menstrual cycle and cannot determine the status of endometrial glands. DEGO is a

Table 1 Clinical characteristics of the patients with intrauterine adhesions in the test cohort and validation cohort.

Clinical characteristic	Category	Test cohort: Live birth group	Test cohort: No live birth group	P1	Validation cohort: Live birth group	Validation cohort: No live birth group	P2	Total
Age	N (N missing)	231 (0)	226 (0)	$P = 0.0003$	117 (0)	168 (0)	$P = 0.0061$	742 (0)
	Mean (SD)	30.3 (4.30)	31.9 (4.94)		30.5 (4.48)	32.1 (4.84)		31.2 (4.71)
Gravidity	1	47 (20.3%)	53 (23.5%)	$P = 0.0038$	28 (23.9%)	40 (23.8%)	$P = 0.4333$	168 (22.6%)
	2	73 (31.6%)	41 (18.1%)		39 (33.3%)	45 (26.8%)		198 (26.7%)
	≥ 3	111 (48.1%)	132 (58.4%)		50 (42.7%)	83 (49.4%)		376 (50.7%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Parity	1	228 (98.7%)	218 (96.5%)	$P = 0.1390$	113 (96.6%)	161 (95.8%)	$P = 0.8744$	720 (97.0%)
	2	2 (0.9%)	7 (3.1%)		3 (2.6%)	6 (3.6%)		18 (2.4%)
	≥ 3	1 (0.4%)	1 (0.4%)		1 (0.9%)	1 (0.6%)		4 (0.5%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Abortion	1	75 (32.5%)	75 (33.2%)	$P = 0.0692$	48 (41.0%)	62 (36.9%)	$P = 0.7866$	260 (35.0%)
	2	75 (32.5%)	53 (23.5%)		34 (29.1%)	52 (31.0%)		214 (28.8%)
	≥ 3	81 (35.1%)	98 (43.4%)		35 (29.9%)	54 (32.1%)		268 (36.1%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Recurrent IUA	Yes	42 (18.2%)	75 (33.2%)	$P = 0.0003$	27 (23.1%)	56 (33.3%)	$P = 0.0648$	200 (27.0%)
	No	189 (81.8%)	151 (66.8%)		90 (76.9%)	112 (66.7%)		542 (73.0%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Menstruation	NA	1 (0.4%)	1 (0.4%)	$P = 0.0168$	0 (0.0%)	0 (0.0%)	$P = 0.0445$	2 (0.3%)
	Eumenorrhea	29 (12.6%)	26 (11.5%)		3 (2.6%)	0 (0.0%)		58 (7.8%)
	Oligomenorrhea	189 (81.8%)	170 (75.2%)		110 (94.0%)	156 (92.9%)		625 (84.2%)
	Amenorrhea	12 (5.2%)	29 (12.8%)		4 (3.4%)	12 (7.1%)		57 (7.7%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
IUA course	NA	36 (15.6%)	43 (19.0%)	$P = 1.0000$	0 (0.0%)	0 (0.0%)	$P = 1.0000$	79 (10.6%)
	≤ 6 months	52 (22.5%)	49 (21.7%)		46 (39.3%)	65 (38.7%)		212 (28.6%)
	>6 months	143 (61.9%)	134 (59.3%)		71 (60.7%)	103 (61.3%)		451 (60.8%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Uterine cavity length	N (N miss)	227 (4)	221 (5)	$P = 0.0114$	117 (0)	168 (0)	$P = 0.1502$	733 (9)
	Mean (SD)	7.2 (0.52)	7.0 (0.68)		7.3 (0.61)	7.2 (0.74)		7.1 (0.64)
Uterine horn adhesion	Bilateral adhesion	4 (1.7%)	10 (4.4%)	$P = 0.0869$	4 (3.4%)	18 (10.7%)	$P = 0.0446$	36 (4.9%)
	Unilateral adhesion	2 (0.9%)	6 (2.7%)		2 (1.7%)	6 (3.6%)		16 (2.2%)
	None adhesion	225 (97.4%)	210 (92.9%)		111 (94.9%)	144 (85.7%)		690 (93.0%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
Visibility of fallopian tube ostia	Bilateral invisible	5 (2.2%)	22 (9.7%)	$P = 0.0000$	7 (6.0%)	24 (14.3%)	$P = 0.0104$	58 (7.8%)
	Unilateral invisible	5 (2.2%)	23 (10.2%)		5 (4.3%)	17 (10.1%)		50 (6.7%)
	Bilateral visible	221 (95.7%)	181 (80.1%)		105 (89.7%)	127 (75.6%)		634 (85.4%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
DEGO degree	NA	1 (0.4%)	14 (6.2%)	$P = 0.0000$	0 (0.0%)	0 (0.0%)	$P = 0.0000$	15 (2.0%)
	G0	39 (16.9%)	3 (1.3%)		24 (20.5%)	3 (1.8%)		69 (9.3%)
	G1	152 (65.8%)	56 (24.8%)		70 (59.8%)	38 (22.6%)		316 (42.6%)
	G2	35 (15.2%)	109 (48.2%)		19 (16.2%)	86 (51.2%)		249 (33.6%)
	G3	4 (1.7%)	44 (19.5%)		4 (3.4%)	41 (24.4%)		93 (12.5%)
	Total	231 (100.0%)	226 (100.0%)		117 (100.0%)	168 (100.0%)		742 (100.0%)
AFS score	N (N miss)	230 (1)	226 (0)	$P = 0.0000$	117 (0)	168 (0)	$P = 0.0000$	741 (1)
	Mean (SD)	2.7 (1.01)	3.5 (2.03)		2.8 (1.52)	3.8 (2.28)		3.2 (1.83)

IUA, Intrauterine adhesion; AFS, American Fertility Society; DEGO, the density of endometrial glandular openings; P1, *P*-value for Test cohort; P2, *P*-value for Validation cohort; NA, no answer; G1, grade 1 of DEGO; G2, grade 2 of DEGO; G3, grade 3 of DEGO.

Table II Univariate analysis of the risk factors for live birth rate.

Variables	Category	Estimate	SE	χ^2*	*P*-value	Odds ratio	95% confidence interval
Age		−0.0733	0.0206	12.6355	0.0004	0.929	0.893–0.968
Gravidity	1	Reference					
	2	0.697	0.2797	6.2097	0.0127	2.008	1.16–3.474
	≥3	−0.0531	0.2382	0.0498	0.8235	0.948	0.595–1.512
Parity	1	Reference					
	2	−1.2976	0.8074	2.5832	0.108	0.273	0.056–1.329
	≥3	−0.0449	1.4174	0.001	0.9748	0.956	0.059–15.382
Abortion	1	Reference					
	2	0.3472	0.2426	2.0477	0.1524	1.415	0.88–2.277
	≥3	−0.1905	0.2218	0.7375	0.3905	0.827	0.535–1.277
Recurrent IUA	Yes	Reference					
	No	0.8043	0.2215	13.1854	0.0003	2.235	1.448–3.45
Menstruation	Eumenorrhea	Reference					
	Oligomenorrhea	−0.00325	0.29	0.0001	0.9911	0.997	0.565–1.76
	Amenorrhea	−0.991	0.4367	5.1493	0.0233	0.371	0.158–0.874
IUA course	≤6 months	Reference					
	>6 months	0.00558	0.2326	0.0006	0.9809	1.006	0.637–1.586
Uterine cavity length		0.4033	0.1609	6.2813	0.0122	1.497	1.092–2.052
Uterine horn adhesion	Bilateral adhesion	reference					
	unilateral adhesion	−0.1823	1.0083	0.0327	0.8565	0.833	0.115–6.013
	None adhesion	0.9853	0.5993	2.7026	0.1002	2.679	0.827–8.671
Visibility of fallopian tube ostia	Bilateral invisible	reference					
	Unilateral invisible	−0.0444	0.6992	0.004	0.9493	0.957	0.243–3.766
	Bilateral visible	1.6812	0.5055	11.0627	0.0009	5.372	1.995–14.467
DEGO degree	G0	reference					
	G1	−1.5663	0.6192	6.3991	0.0114	0.209	0.062–0.703
	G2	−3.7008	0.6298	34.527	<0.0001	0.025	0.007–0.085
	G3	−4.9626	0.7948	38.9901	<0.0001	0.007	0.001–0.033
AFS scores		−0.3684	0.0752	23.997	<0.0001	0.692	0.597–0.802

*χ^2 test for entire group.

more reliable marker of endometrial function as the number of glandular openings is constant throughout the menstrual cycle (Lüdicke *et al.*, 2001). However, the appearance of the glandular openings does change during the menstrual cycle (from dot and punctate-type to ring-type) and is related to reproductive status and live birth rate (Li *et al.*, 2010). More awareness of these changes and further study will yield more information for the future assessment of endometrial health.

In our study, the AUC of the prediction model of DEGO grade with other covariates (excluding AFS score) was 0.8498, which was significantly higher than the AUC of the prediction model of AFS score with other covariates (excluding DEGO grade) (AUC = 0.7112). The same performance was observed in the prospectively enrolled external validation cohort. Therefore, DEGO grade can be used to predict the live birth rate of IUA patients with more accuracy than the AFS scoring system.

Additionally, several other variables were found to be related to endometrial regeneration and, consequently, the implantation rates of IUA patients, including age (Maheshwari *et al.*, 2008), pre-hysteroscopic adhesiolysis history (Zhao *et al.*, 2020a), and the length of the uterine cavity (from the fundus to the external cervical os) (Revelli *et al.*, 2016; Gao *et al.*, 2019). These variables were included in our prediction models as covariates. Out of all these variables, however, the DEGO was the most relevant to the endometrium condition and was most closely related to the live birth rate post-hysteroscopic adhesiolysis. With this in mind, surgeons need to do their best to protect the endometrium during hysteroscopic adhesiolysis; for instance, they should use regular scissors instead of electrical instruments, which may cause thermal injury to the endometrium (Malhotra *et al.*, 2012, 2017), applying a ploughing technique to provide a surface with a fresh, rich blood supply on which the endometrium may grow and cover post-hysteroscopic adhesiolysis (Zhang *et al.*, 2015; Zhao *et al.*, 2020b).

An important innovation of this study is to highlight the utility of DEGO grade as a variable in predicting live birth rates for patients with IUAs who undergo hysteroscopic adhesiolysis and have hopes for

Table III Multivariate logistical regression analysis of DEGO degree and other covariates (excluding AFS score).

Variables	Category	Estimate	SE	χ^2*	*P*-value	Odds ratio	95% confidence interval
Test cohort							
Intercept		3.3705	1.2008	7.8786	0.005	/	/
Age		−0.0849	0.0278	9.3622	0.0022	0.919	0.87–0.97
Gravidity	2	0.7324	0.354	4.2788	0.0386	2.08	1.039–4.163
	≥3	0.6298	0.3135	4.0345	0.0446	1.877	1.015–3.471
Visibility of fallopian tube ostia	Unilateral invisible	0.2791	0.86	0.1053	0.7456	1.322	0.245–7.133
	Bilateral visible	1.3508	0.654	4.266	0.0389	3.86	1.071–13.909
DEGO	G1	−1.4932	0.6273	5.6653	0.0173	0.225	0.066–0.768
	G2	−3.5891	0.6403	31.4194	<0.0001	0.028	0.008–0.097
	G3	−4.7467	0.8143	33.9816	<0.0001	0.009	0.002–0.043
Validation cohort							
Intercept		2.7356	1.3021	4.4141	0.0356	/	/
Age		−0.0441	0.0339	1.695	0.1929	0.957	0.895–1.023
Gravidity	2	0.4683	0.4219	1.2319	0.267	1.597	0.699–3.652
	≥3	0.2055	0.394	0.272	0.602	1.228	0.567–2.658
Visibility of fallopian tube ostia	Unilateral invisible	0.5001	0.808	0.3831	0.5359	1.649	0.338–8.034
	Bilateral visible	0.401	0.5634	0.5066	0.4766	1.493	0.495–4.506
DEGO degree	G1	−1.3449	0.6652	4.0872	0.0432	0.261	0.071–0.96
	G2	−3.441	0.6819	25.4664	<0.0001	0.032	0.008–0.122
	G3	−4.3012	0.8331	26.6538	<0.0001	0.014	0.003–0.069

*χ^2 test for entire group.

Table IV Multivariate logistical regression analysis of AFS score and other covariates (excluding DEGO degree).

Variables	Category	Estimate	SE	χ^2*	*P*-value	Odds ratio	95% confidence interval
Test cohort							
Intercept		−0.14	1.7925	0.0061	0.9377	.	
Age		−0.0904	0.0226	15.9919	<0.0001	0.914	0.874–0.955
Recurrent IUA	No	0.6711	0.2459	7.4449	0.0064	1.956	1.208–3.168
Uterine cavity length		0.1093	0.1831	0.3562	0.5506	1.115	0.779–1.597
Visibility of fallopian tube ostia	Unilateral invisible	1.3826	1.1928	1.3435	0.2464	3.985	0.385–41.281
	Bilateral visible	2.6334	1.087	5.8689	0.0154	13.92	1.653–117.196
AFS score		−0.275	0.0946	8.4571	0.0036	0.76	0.631–0.914
Validation cohort							
Intercept		0.9246	1.6803	0.3028	0.5821	/	
Age		−0.0739	0.028	6.9504	0.0084	0.929	0.879–0.981
Recurrent IUA	No	0.3485	0.291	1.4342	0.2311	1.417	0.801–2.507
Uterine cavity length		0.1499	0.1934	0.6012	0.4381	1.162	0.795–1.697
Visibility of fallopian tube ostia	Unilateral invisible	0.0642	0.6983	0.0084	0.9268	1.066	0.271–4.191
	Bilateral visible	0.5908	0.4834	1.4941	0.2216	1.805	0.7–4.656
AFS score		−0.2482	0.0832	8.8974	0.0029	0.78	0.663–0.918

*χ^2 test for entire group.

future fertility. To our knowledge, this is the first study to test DEGO measured by hysteroscopy as a potential predictor of the live birth rate post-hysteroscopic adhesiolysis. Our study revealed that the DEGO grade in follow-up hysteroscopy videos was significantly correlated with the live birth rate. When the AUCs were compared to verify prediction accuracy, DEGO showed a closer correlation with the live birth rate post-hysteroscopic adhesiolysis than other traditional methods, and the strengths of the study lie in its statistical design with external validation of the results.

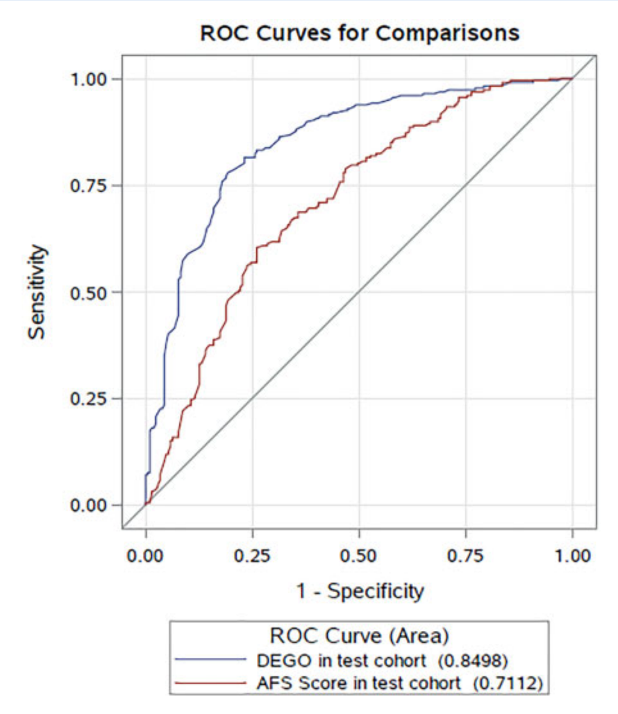

Figure 4. The ROCs (receiver operating characteristic curves) of the prediction models in the test cohort. The AUCs of the prediction models of AFS score with other covariates (excluding DEGO degree) and DEGO degree with other covariates (excluding AFS score).

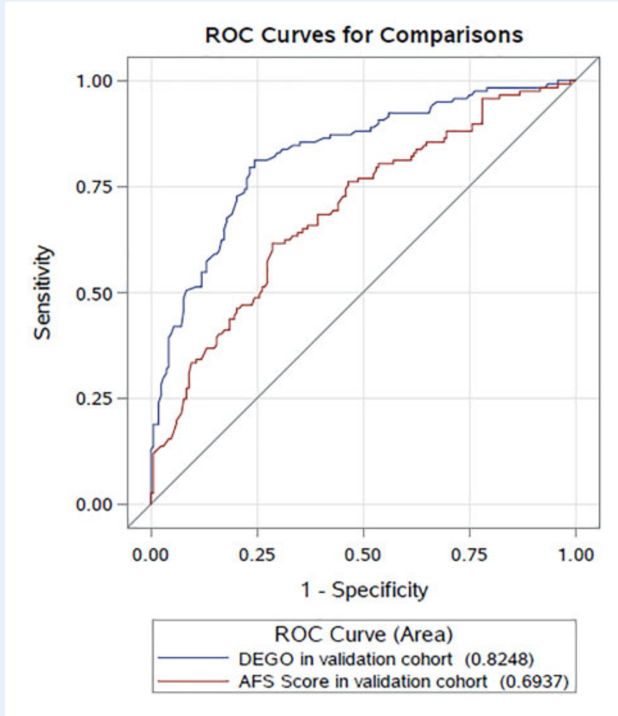

Figure 5. The ROCs of the prediction models in the validation cohort: The AUCs of the prediction models of AFS score with other covariates (excluding DEGO degree) and DEGO degree with other covariates (excluding AFS score).

Table V Comparison of the area under the curves of the prediction models in the test cohort.

Comparison of AUCs	Estimate	SE	95% CI	χ^{2}*	Pr > χ^{2}*
DEGO degree—AFS score	0.1386	0.0246	0.0905–0.1868	31.8172	<0.0001

*χ^2 test for entire group; Pr, *P*-value.

Table VI Comparison of the area under the curves of the prediction models in the different cohorts.

Model	Cohort	AUC	SE	95% CI	*P*
AFS score	Validation cohort	0.6937	0.0317	0.6317–0.7557	$P < 0.0001$
	Test cohort	0.7112	0.0248	0.6626–0.7599	
DEGO degree	Validation cohort	0.8248	0.0253	0.7753–0.8743	$P < 0.0001$
	Test cohort	0.8498	0.0187	0.8132–0.8865	

As with any study, our investigation has limitations. The discussion of DEGO as new technology is limited to what we observed and is germane to the general obstetrics and gynecology. Additionally, endometrial thickness, as monitored by transvaginal ultrasound, was not reported. However, we believe our findings could supply some valuable information for the prediction of live birth rates in IUA patients. Further well-designed prospective clinical studies with a multicentric larger sample size will be needed to confirm the feasibility and efficacy of DEGO.

In conclusion, with DEGO, we propose a new and accurate method for the hysteroscopic evaluation of the endometrium in IUA patients. This alternative method provides a more accurate prediction of live birth rate for patients with IUAs following hysteroscopic adhesiolysis.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Authors' roles

(i) Conception and design: D.X.; (ii) Collection and assembly of data: X.Z.; (iii) Data analysis and interpretation: B.G., X.Y., and A.Z.; (iv) Manuscript writing: All authors; (v) Final approval of manuscript: all authors.

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Conflict of interest

The authors have no conflicts of interest to declare.

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