Gonadotropin-releasing hormone agonist combined with hormone replacement therapy improves pregnancy outcome in intrauterine adhesion

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Abstract

Objective: This retrospective study aimed to explore the optimal endometrial preparation method in women with intrauterine adhesions (IUAs).

Method: A total of 882 frozen-thawed embryo transfer (FET) cycles were categorized into three groups based on endometrial preparation methods: hormone replacing therapy cycle (HRT, n=636), natural cycle (NC n=174), and HRT with GnRH-a pretreatment (HRT+GnRH-a, n=72. Logistic regression was performed to investigate the association between cycle regimens and pregnancy outcomes. Subgroup analysis of IUAs combined with thin endometrium (≤7mm) was also performed.

Results: HRT with GnRH-a pretreatment was associated with higher incidences of clinical pregnancy, ongoing pregnancy, and live birth, but lower early miscarriage compared with either HRT or NC. Logistic regression indicated that after controlling for potential confounders, the incidences of live birth (HRT+GnRH-a as reference; NC: aOR=0.577, 95%CI 0.304-1.093; HRT: aOR=0.434, 95%CI 0.247-0.765) and ongoing pregnancy (NC: aOR=0.614, 95%CI 0.324-1.165; HRT: aOR=0.470, 95%CI 0.267-0.829) remained significantly higher in HRT+GnRH-a compared to those in HRT, but comparable to those in NC. While there was no significant difference with respect to the clinical pregnancy rate (NC: aOR=0.695, 95%CI 0.374-1.291; HRT: aOR=0.650, 95%CI 0.374-1.127) and early miscarriage rate (NC: aOR=1.734, 95%CI 0.417-7.175; HRT: aOR=2.594, 95%CI 0.718-9.378) between groups. Subgroup analysis suggested there was no priority of endometrial preparation method in IUAs combined with thin endometrium.

Conclusion: HRT with GnRH-a pretreatment improves pregnancy outcomes in women with history of IUAs. GnRH-a may restore the endometrial receptivity in the FET cycles in IUAs.

Introduction

Intrauterine adhesions (IUAs) are filmy or dense fibrous adhesive bands found within the uterine cavity contributing to the adhesion of opposing endometrium. It usually occurs after dilation and curettage (D&C) of a gravid uterus. The pool prevalence of IUAs after miscarriage was about 19%. Women with a history of IUAs are at a reproductive disadvantage, and the pregnancy outcomes are inversely correlated with severity of disease [1]. Hysteroscopic surgery to remove IUAs followed by reproductive assistance technology is the most effective treatment to improve pregnancy prognosis, regardless, the reproductive outcomes in IUAs are much lower than those in general population, particularly when combined with thin endometrium [1, 2]. Although the real mechanism of IUAs resulting in poorer pregnancy outcomes remains unclear, evidence suggests that an altered biochemical or vascular environment is a possible explanation for impaired embryo implantation and adverse pregnancy results [3].

Frozen-thawed embryo transfer (FET) is being increasingly popular worldwide. This approach involves controlled ovarian stimulation (COS) followed by the cryopreservation of the viable embryos to be transferred in subsequent cycles in a possibly more physiological environment, thus avoiding the supra-physiologic hormonal levels observed during COS [4–6]. In women with IUAs, FET provides flexible timing

for embryo transfer (ET) in case hysteroscopic lysis or therapeutic treatment is needed before ET. Moreover, selective FET was reported to have better pregnancy outcomes than fresh ET in thin endometrium [7]. Proper endometrial preparation plays a key role to maximize IVF success rate and improve pregnancy results [8–10]. Therefore, we conducted a retrospective study to explore whether there is a best endometrial preparation protocol for IUAs.

Materials And Methods

This was a retrospective cohort study of 882 FET cycles with history of IUAs in our fertility center from January 2015 to June 2019. Excluding criteria were cycles with no viable embryos available for transfer or underwent Pre-implantation genetic diagnosis, cycles in which transferred embryos came from different ovarian stimulation cycles or sequential embryo transfer mixed with cleavage and blastocyst stage embryo, and cycles lost to follow up. The enrolled cycles were categorized into three groups according to the endometrial preparation protocols: natural cycle (NC), traditional hormone replacing therapy cycle (HRT, n = 636), and HRT with GnRH-a pretreatment (HRT + GnRH-a). This study was approved by the Institutional Review Board of the Shenzhen Zhongshan Urology Hospital. Informed consent was waived due to the retrospective nature of the study.

Standard regimens for COS were applied by clinicians in our center based on the individual ovarian reserve and response, including luteal phase gonadotrophin releasing hormone agonist protocol, antagonist protocol, and clomiphene-based mild stimulation protocol. Ovulation was triggered with either human chorionic gonadotropin (hCG, Livzon Pharmaceuticals, China) 6 500 – 10 000 IU or a single subcutaneous bolus of triptorelin (Diphereline; Ipsen, France) 0.2 mg when there were two leading follicles reached 18 mm. Transvaginal, ultrasound-guided oocyte retrieval was performed 34–36 hours after. Insemination of mature oocytes was performed by conventional IVF or ICSI according to the sperm parameters. Details on embryo culture, vitrification, thawing and transfer procedures have been described in our previous studies [11, 12]. Embryos on Day 3 were graded according to the morphology criteria [13]. Good and fair embryos were cryopreserved or underwent blastocyst culture. The Gardner grading system was used to evaluate the blastocyst quality [14]. Only blastocysts better than grade 3CC were selected for vitrification. The laboratory procedures were performed by well-trained embryologists, each with over 5 years of laboratory experience. There were no substantial changes of laboratory practices over the course of study.

The choice of endometrial preparation was dependent upon the experience of the clinician and patients' characteristic. NC was chosen if the patient had regular menses or refused to take medication, HRT with or without GnRH-a was selected in patient with irregular menses, or who lived at considerable distance and did not wish to be frequently monitored.

Natural cycle protocol. Follicle monitoring was started from day 8–10 of the cycle with vaginal ultrasound until the dominant follicle was ≥ 18 mm or the urine LH surge was detected. Ovulation was

spontaneous or triggered by 10 000 IU hCG (hCG, Livzon Pharmaceuticals, China). Oral administration of 20 mg progesterone twice daily was prescribed for 3–5 days before ET according to the embryo stage.

Hormone replacing therapy protocol. Endometrial preparation was started from day 2–3 of menstrual cycle, 4 mg of oral estradiol valerate (Progynova; Bayer, Germany) per day was started, and the dose was increased by 2 mg every 5 days. Estrogen was given for 15 days. Intramuscular administration of 60 mg progesterone daily (ZheJiang XianJu Pharmaceuticals, China) was prescribed for 4–6 days before ET according to the embryo stage.

Hormone replacing therapy with GnRH agonist. The injection of leuproreline acetate (Diphereline; Ipsen, France) 3.75 mg i.m., was administered during the mid-luteal phase of the menstrual cycle, twenty-nine days after the endometrial preparation was initiated, as described above for the HRT cycle.

In all three protocols, serum estradiol (E_2), progesterone (P) levels, and endometrium thickness (EMT) were measured on hCG day in NC or on progesterone day in the two HRT group. EMT was defined as the maximal distance from one interface of endometrial-myometrial to the other in the midsagittal plane, and was measured by highly trained physicians. One-two blastocysts or 1–3 cleavage stage embryos were transferred under ultrasound guidance. On the day of ET, common luteal support was prescribed with 20 mg progestin tablets (Duphaston; Abbott, Netherlands) orally twice daily and 90 mg progestin gel (Crinone; Merck, Germany) vaginally daily until a serum beta hCG assay was performed 11 (if blastocyst was transferred) or 13 days (if cleavage embryo was transferred) after FET. Luteal support was continued until the 12th gestational week in the case of pregnancy.

Clinical pregnancy was defined as the observation of at least one gestational sac on vaginal ultrasound at 6–7 weeks of gestation. Early miscarriage was defined as loss of clinical pregnancy before 12 weeks of gestation. Live birth was defined as the delivery of at least one live-born baby beyond 28 weeks of gestation. Ongoing pregnancy referred to a clinical pregnancy proceeding beyond 12 weeks of gestation.

Statistical Analysis

The demographic characteristics and clinical outcomes were described as mean ± SD for continuous variables and as frequency with proportion for categorical variables. The differences between groups were tested using the ANOVA test for continuous variables and the Pearson's chi-square test for categorical variables. Logistic regression was applied to examine the associations between replacement regimens and pregnancy outcomes after controlling for potential confounders, which included maternal age, BMI, parity, duration of infertility, indication of treatment, fertilization method, endometrium preparation protocol, embryo stage, number of embryos transferred, number of top embryos and endometrium thickness. Endometrial preparation protocol was included as a categorical variable, and HRT + GnRH-a group was selected as the reference. The results were reported as adjusted odds ratios (aORs) with 95% confidential intervals (CIs). Subgroup analysis was performed to access the optimal cycle regimen in IUAs combined with thin endometrium (≤ 7mm). *P*-values (two-tailed) less than 0.05

were considered statistically significant. SPSS version 19.0 (IBM SPSS, Chicago, IL) was applied to made statistical analysis in our study.

Results

The study comprised of 882 eligible FET cycles, including 636 AC cycles, 174 NC cycles, and 72 HRT + GnRH-a cycles. The demographic data are shown in Table 1. NC group was associated with older maternal age, AC group had and a lower maternal BMI, and more blastocyst stage embryo transfer. HRT + GnRH-a group was associated with higher nulliparous rate and longer duration of infertility.

HRT with GnRH-a pretreatment was observed with higher incidences of clinical pregnancy, ongoing pregnancy, and live birth, but lower early miscarriage compared with either conventional HRT or NC (Fig. 1). Logistic regression indicated that after controlling for potential confounders, the incidence of live birth (HRT + GnRH-a as reference; NC: aOR = 0.577, 95%CI 0.304–1.093; HRT: aOR = 0.434, 95%CI 0.247–0.765) and ongoing pregnancy (NC: aOR = 0.614, 95%CI 0.324–1.165; HRT: aOR = 0.470, 95%CI 0.267–0.829) were significantly higher in HRT + GnRH-a compared to those in HRT, but comparable to those in NC. While there was no significant difference with respect to the clinical pregnancy rate (NC: aOR = 0.695, 95%CI 0.374–1.291; HRT: aOR = 0.650, 95%CI 0.374–1.127) and early miscarriage rate (NC: aOR = 1.734, 95%CI 0.417–7.175; HRT: aOR = 2.594, 95%CI 0.718–9.378) between groups (Table 2). There were 203 cycles with thin endometrium in this study, and subgroup analysis suggested there was no priority of endometrial preparation method in IUAs combined with thin endometrium (Table 3).

Discussion

Intrauterine adhesions (IUAs) or Asherman syndrome refer to the formation of filmy or dense fibrous bands within the uterine cavity. These are frequently occurred after mechanical or infectious injury to the basal layer of endometrium [15, 16]. IUAs were first described by Heinrich Fritsch in 1894 [17]. The pool prevalence of IUAs was reported to be 19% in a meta-analysis, however, it varies between different populations and by the injury types [16, 18]. The exact mechanism of IUAs remains elusive, possibly involves hypoxia, impaired neovascularization, and abnormal expression of adhesion-associated cytokines [15]. IUAs can be asymptomatic but often lead to menstrual and fertility disfunctions, and the pregnancy results are inversely correlated with the severity of disease [18].

It is generally accepted that moderate to severe IUAs are usually associated with poor fecundability and adverse obstetric and neonatal outcomes. Schenker and Margalioth reported a 41% prevalence of infertility and only 45.5% spontaneous conception rate in a large cohort with untreated IUAs. Of those, 40% suffered spontaneous miscarriage, 23% preterm delivery, 13% placenta accrete, and 12% ectopic pregnancy [19]. In our study, the overall clinical pregnancy rate of IUAs was 43.88%, the live birth rate was 31.75%, and the early miscarriage rate was 20.67%. However, in those combined with thin endometrium, the clinical pregnancy rate was 25.62%, live birth rate was 13.30%, and early miscarriage rate was 36.54%. Our results were in line with the previous studies [1, 20].

Hysteroscopic surgery to remove IUAs followed by reproductive assistance technology has become the most effective treatment for good pregnancy outcomes [21]. It is well recognized that successful implantation relies on a properly developed blastocyst, a receptive endometrium, and synchrony of these factors. Evidence works out that the expression of certain membrane-bound, soluble, and secretory factors transforms the endometrium from the nonreceptive to the receptive state and supports embryo attachment. Factors expressed during this temporal window are considered as receptivity biomarkers, including pinopodes, integrin b3, leukemia inhibitory factor (LIF), expression of homeobox genes HOXA 10 and HOXA 11 [22, 23]. Most of these molecules are regulated by a hormonal and paracrine manner. In IUAs, the impaired endometrium may loss responses to the ovarian steroids and fail to produce these protective molecules, therefore present as defective endometrial receptivity.

In FET, endometrium receptivity is achieved by dedicated endometrial preparation protocols, which can largely be divided into natural and hormone replacing cycles. In NC, the sequential estrogen and P required for endometrial maturation are derived from the developing follicle, and the timing of embryo transfer depends on the identification of spontaneous luteinizing hormone (LH) surge or hCG triggering. NC provides a more physiologic milieu for embryo implantation. However, premature ovulation may occur with elevated P levels, resulting in deleterious effect on endometrial receptivity [24]. In HRT, exogenous estrogen and P are sequentially administered to mimic natural endometrial growth and achieve an appropriate implantation window. HRT with GnRH-a pretreatment is performed to minimize the risk the spontaneous follicle development and offers the most control over the timing, though the cycle is much more prolonged and expensive.

An optimal protocol of endometrial preparation may improve pregnancy outcomes in FET. To date, there is insufficient evidence to support the superiority of one approach over another in general population [25, 26]. An adequate thickness of endometrium is indispensable for a successful pregnancy, especially in IUAs. Utilization of exogenous estrogen is effective to increase endometrial thickness during the hyperplasia period [27], HRT cycles to prepare the endometrium is therefore recommended as the preference of choice in IUAs. Our study demonstrated that endometrial preparation by HRT with GnRH-a pretreatment is superior to NC and conventional HRT protocols in IUAs. Indeed, one prospective randomized trial conducted by El-Toukhy T and coworkers found that compared to conventional HRT, pretreatment with GnRH-a achieved significantly higher clinical pregnancy (24% vs 11.3%, OR 2.5, 95%CI 1.2−5.5) and live birth rates (20% vs 8.5%, OR 2.9, 95%CI 1.2-8) [28]. Recently, a multicenter retrospective cohort study also revealed that HRT with GnRH-a pretreatment appears to be superior to HRT without GnRH-a, regarding the live birth rate and miscarriage rate [29]. Animal study suggests that GnRH-a, but not GnRH antagonist, may restore uterine expression levels of key receptivity markers including Hoxa10, Hoxa11, Lif and integrin b3 mRNA and protein, as well as increase the abundance and development of pinopodes, hence improve endometrial receptivity in adenomyosis [30, 31]. All these findings finding strengthen the evidence of GnRH-a pretreatment in improving intrauterine receptivity. Moreover, GnRH-a therapy was reported to suppress inflammation in endometriosis, adenomyosis and uterine myoma [32]. It is plausible that IUAs may be associated with chronic endometritis, and HRT with GnRH-a pretreatment may improve reproductive outcomes by curbing potential inflammatory reactions in IUAs.

IUAs combined with thin endometrium (< 7 or 8 mm) has been demonstrated to significantly decrease implantation and pregnancy rate [1, 33]. Guo Z and coworkers suggested that for women with a thin endometrium and were undergoing IVF, FET was associated with significantly higher incidences of live birth, clinical pregnancy, and biochemical pregnancy than in the fresh ET group [7]. Besides, it was showed that in ovarian stimulation cycles, GnRH-a prolonged protocol (one depot of 3.75 mg GnRH-a), instead of short GnRH-a long protocol (0.1mg of GnRH-a per day) was an effective treatment to improve endometrial receptivity in patients with medium (7 < EMT < 14mm), particularly thin endometrium (≤ 7 mm) [34, 35]. Unfortunately, there has been no similar analysis in FET cycles. In our study, subgroup analysis revealed that the pregnancy results were not significantly differ between groups, which may due to the small sample size of the subgroup. On the other hand, it is also possible that the receptivity state in IUAs combined with thin endometrial may no more be restored by GnRH-a.

Our study was mainly limited by its respective nature. There was no grading of IUA severity in this study as most intrauterine adhesiolyises were not performed in our hospital, hence the medical history was not available. However, we restricted the enrolled patients to whose uterine cavities in the last hysteroscopic views were normal and there were no significantly differences of the endometrial thickness between groups. Additionally, the sample of IUAs combined with thin endometrium was relatively small. Further study is warranted to verify our findings.

Conclusions

To sum up, our study indicates that cycle regimen of HRT with GnRH-a pretreatment improves pregnancy outcomes in women with history of IUAs. GnRH-a may restore the uterine receptivity rather than EMT in the FET cycles in IUAs.

Declarations

Authors' contributions

MML designed the study. ZQZ completed the data analysis, and wrote the article. ZHZ and XSR revised the article and approved the final version. XF and WY took part in acquisition and analysis of data. MML and ZY supervised the entire study and approved the final article.

(SZSM201502035). The funding body have not participated in the design of the study and collection, analysis, interpretation of data or in writing the manuscript.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Shenzhen Zhongshan Urology Hospital (approval SZZSECHU-F-2020043).

Conflict of Interest

The authors declare no conflict of interest.

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Tables

nal and treatment characteristics between different endometrial preparation protocols in women with
on.

	HRT	NC	HRT+GnRH-a	*P*
	636	174	72	
e (y)	34.21±4.78	36.02±4.20	34.99±4.80	0.000
l)	1.78±1.19	2.02±1.50	1.85±1.20	0.086
	21.66±3.22	21.22±2.94	22.64±3.32	0.006
%)	151(23.74)	53(30.46)	25(34.72)	0.042
nfertility (y)	3.07±2.42	2.91±2.47	4.34±3.90	0.000
treatment, n (%)				0.000
	264(41.51)	72(41.38)	34(47.22)	
lisorder	59(9.28)	1(0.57)	3(4.17)	
riosis	63(9.91)	19(10.92)	16(22.22)	
y	21(3.30)	9(5.71)	0(0.00)	
	28(4.40)	16(9.20)	2(2.78)	
	91(14.31)	28(16.09)	13(18.06)	
	110(17.30)	29(16.67)	4(5.56)	
method, n (%)				0.789
	485(76.26)	127(72.99)	52(72.22)	
	149(23.43)	46(26.44)	20(27.78)	
	2(0.31)	1(0.57)	0(0.00)	
e, n (%)				0.001
	213(33.49)	84(48.28)	33(45.83)	
	423(66.51)	90(51.72)	39(54.17)	
mbryos transferred (n)	1.73±0.65	1.82±0.70	1.92±0.69	0.027
op embryos (n)	1.34±0.93	1.49±0.95	1.56±0.96	0.056
n thickness (mm)	8.50±1.73	8.75±1.82	8.89±1.94	0.071
nancy rate (%)	43.55	41.95	51.39	0.379
gnancy rate (%)	32.39	34.48	47.22	0.042
te (%)	29.87	32.76	45.83	0.021
riage rate (%)	22.74	19.18	8.11	0.112

al cycle; AC, artificial cycle; GnRH-a, gonadotropin releasing hormone agonist; BMI, body mass

, in vitro fertilization; ICSI, intracytoplasmic sperm injection; E2, estrogen; P, progesterone

as considered as statistically significant

ble II. Crude and adjusted ORs of different endometrial preparation protocol.

	HRT+GnRH-a	NC	P_1	HRT	P_2
nical egnancy rate					
rude					
(95%CI)	reference	0.684(0.394,1.187)	0.177	0.730(0.448,1.189)	0.206
ljusted					
(95%CI)	reference	0.695(0.374,1.291)	0.250	0.650(0.374,1.127)	0.125
going egnancy rate					
rude					
(95%CI)	reference	0.588(0.337,1.028)	0.063	0.535(0.327,0.875)	0.013[*]
ljusted					
(95%CI)	reference	0.614(0.324,1.165)	0.136	0.470(0.267,0.829)	0.009[*]
e birth rate					
rude					
(95%CI)	reference	0.576(0.328,1.009)	0.054	0.503(0.307,0.825)	0.006[*]
ljusted					
(95%CI)	reference	0.577(0.304,1.093)	0.091	0.434(0.247,0.765)	0.004[*]
rly scarriage rate					
rude					
(95%CI)	reference	2.689(0.721,10.031)	0.141	3.336(0.992,11.227)	0.052
ljusted					
(95%CI)	reference	1.734(0.417,7.175)	0.450	2.594(0.718,9.378)	0. 146

natural cycle; AC, artificial cycle; GnRH-a, gonadotropin releasing hormone agonist

: AC vs. NC, P_2: AC+GnRH-a vs. NC

<0.05 was considered as statistically significant

:ernal and treatment characteristics between different endometrial preparation protocols in uterine bined with thin endometrium.

	HRT	NC	HRT+GnRH-a	P
	147	43	13	
e (y)	35.78±5.05	37.65±3.48	37.46±5.56	0.054
)	1.98±1.53	2.37±2.34	2.46±1.61	0.316
	21.63±2.88	21.42±2.63	21.30±2.17	0.864
%)	19(12.93)	6(13.95)	2(15.38)	0.959
nfertility (y)	2.63±2.14	2.27±1.66	3.50±2.74	0.174
treatment, n (%)				0.360
	46(31.29)	17(39.53)	6(46.15)	
lisorder	4(2.72)	0(0.00)	0(0.00)	
riosis	9(6.12)	4(9.30)	1(7.69)	
y	8(5.44)	6(13.95)	0(0.00)	
	7(4.76)	3(6.98)	0(0.00)	
	30(20.41)	5(11.63)	4(30.77)	
	43(29.25)	8(18.60)	2(15.38)	
method, n (%)				0.101
	101(68.71)	35(81.40)	8(61.54)	
	46(31.29(	7(16.28)	5(38.46)	
	0(0.00)	1(2.33)	0(0.00)	
e, n (%)				0.011
	41(27.89)	21(48.84)	7(53.85)	
	106(72.11)	22(51.16)	6(46.15)	
mbryos transferred (n)	1.67±0.68	1.86±0.60	1.85±0.80	0.225
op embryos (n)	1.21±0.99	1.44±0.88	1.31±1.11	0.389
n thickness (mm)	6.37±0.74	6.49±0.63	6.15±1.07	0.324
nancy rate (%)	23.26	27.21	15.38	0.596
gnancy rate (%)	18.6	13.61	15.38	0.717
te (%)	18.6	11.56	15.38	0.477
riage rate (%)	20	42.5	0	0.229

al cycle; AC, artificial cycle; GnRH-a, gonadotropin releasing hormone agonist; BMI, body mass

, in vitro fertilization; ICSI, intracytoplasmic sperm injection; E2, estrogen; P, progesterone

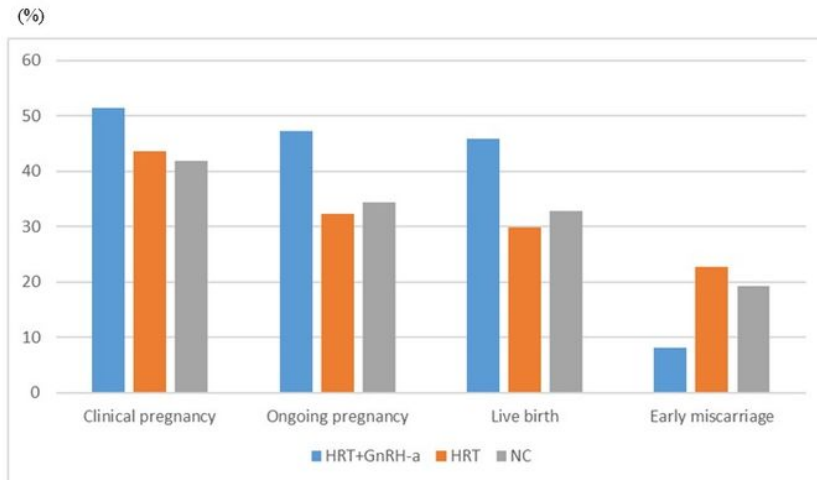as considered as statistically significant

Figures

Figure 1. Pregnancy outcomes of different endometrial preparation protocols in all women with history of IUA.

Figure 1

Pregnancy outcomes of different endometrial preparation protocols in all women with history of IUA.

Supplementary Files

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