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ARTICLE

Prediction of IVF/ICSI outcome based on the follicular output rate

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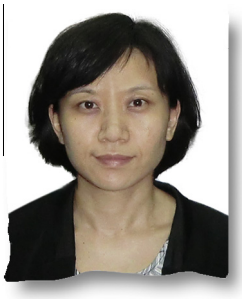

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Abstract This study assessed the true accuracy of follicular output rate (FORT) as a prognostic indicator of response to FSH and reproductive competence after IVF/intracytoplasmic sperm injection. A total of 1643 cycles, including 140 polycystic ovary syndrome (PCOS) patients who underwent ovarian stimulation, were studied. FORT was calculated as the ratio of preovulatory follicle count on the day of stimulation × 100/small antral follicle count (3–10 mm in diameter) at baseline. Low, medium and high FORT groups were defined according to tertile values. Among 1503 non-PCOS cycles, numbers of retrieved oocytes and of all embryos that could be transferred, as well as rates of good-quality embryos, embryo implantations and clinical pregnancies, progressively increased with FORT. In PCOS patients, FORT were significantly lower in patients who achieved clinical pregnancy compared with those who did not (0.56 ± 0.21 versus 0.66 ± 0.29, $P = 0.031$). Fertilization and good-quality embryo rates were significantly higher with medium FORT than low and high FORT ($P = 0.001$ and $P = 0.047$, respectively). Medium FORT in PCOS patients and high FORT in non-PCOS patients may predict better outcomes for IVF/ICSI.

KEYWORDS: embryo transfer, follicular output rate, IVF, ICSI, ovarian stimulation, polycystic ovary syndrome

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Introduction

Ovarian stimulation is a key procedure in assisted reproduction technology. This stimulation is achieved by the administration of exogenous gonadotrophin to increase follicular recruitment and oocyte yields. Although the regulatory mechanisms determining the extent of the sensitivity of individual antral follicles to FSH remains to be elucidated, the appropriate response of antral follicles to FSH and a high quality of oocytes may result in a good outcome after IVF/intracytoplasmic sperm injection (ICSI).

There is no marker that can predict both ovarian response and oocyte competence. The antral follicular count (AFC) comprises the number of follicles of 3—10 mm diameter measured in ovaries at the start of the menstrual cycle (Chang et al., 1998; de Carvalho et al., 2008). The AFC may reflect the size of the remaining primordial pool in women with proven natural fertility (Kline et al., 2005; Scheffer et al., 1999) and is highly correlated to the number of oocytes retrieved (Bancsi et al., 2002; Broer et al., 2009). Otherwise, AFC can be used in the prediction of ovarian response but not of oocyte/embryo quality or IVF outcome (Melo et al., 2009). The number of preovulatory follicles obtained at the end of ovarian stimulation is not a reliable reflection of antral follicle sensitivity to FSH, as it is greatly influenced by the number of small antral follicles available before treatment. To evaluate follicular responsiveness to exogenous FSH, the use of the follicular output rate (FORT) as an innovative measure has been suggested (Genro et al., 2011). FORT is assessed by the ratio of the preovulatory follicle count (PFC; 16—22 mm) obtained in response to FSH administration on the day of human chorionic gonadotrophin (HCG) to the small antral follicle count (3—10 mm) observed after the complete suppression of endogenous gonadotrophins by gonadotrophin-releasing hormone agonist (GnRHa) (FORT = PFC × 100/AFC) (Gallot et al., 2012; Genro et al., 2011, 2012). Gallot et al. (2012) found that FORT may be a qualitative reflector of ovarian follicular competence only in patients with regular menstrual cycles. The values of FORT as a predictor of IVF/ICSI outcome in polycystic ovary syndrome (PCOS) and non-PCOS patients were unknown. The aim of the present investigation was to assess the true accuracy of FORT as a prognostic indicator of the response to FSH and the reproductive competence reflected by the outcomes of oocytes and embryos after IVF/ICSI treatment.

Materials and methods

Subjects

In total, 1643 cycles of IVF/ICSI treatment from January 2010 to December 2011 were included in the present study. Women from 23 to 44 years of age were included if they fulfilled the following criteria: (i) both ovaries present; (ii) FSH <12 IU/l, oestradiol <80 pg/ml and prolactin in the normal range before ovarian stimulation; (iii) presence of a normal uterine cavity; (iv) normal thyroid-stimulating hormone concentration or euthyroid as determined by the investigator; and (v) no current or past diseases affecting the administration of gonadotrophin. Indications for IVF/ICSI were: (i) female factors, 1063 cycles (64.7%), such as tubal factor, endometriosis or ovulation dysfunction; (ii) male factors, 176 cycles (10.7%); and (iii) both factors, 404 cycles (24.6%).

Among all patients, 1503 cases were non-PCOS and 140 cases were diagnosed as PCOS based on the presence of two out of three criteria of The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group (2004), including oligo- and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovaries. Other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumours and Cushing's syndrome) were excluded. The median age was 32 in both the PCOS and non-PCOS groups. Among the patients with PCOS, there were 79 cases (56.43%) with oligo- and/or anovulation + hyperandrogenism + polycystic ovaries, 46 cases (32.86%) with oligo- and/or anovulation + polycystic ovaries, 11 cases (7.86%) with oligo- and/or anovulation + hyperandrogenism and four cases (2.86%) with hyperandrogenism + polycystic ovaries.

Treatment protocol

All patients underwent standard pituitary down-regulation protocol with GnRHa (triptorelin, Diphereline; Ipsen Pharma Biotech, France) 0.05 mg between day 5—7 after ovulation or on day 21 of the oral contraceptive cycles. Fourteen days later, complete pituitary desensitization was confirmed by the detection of serum oestradiol concentrations <50 pg/ml, LH <3 IU/l, no follicles >10 mm in diameter and endometrial thickness <7 mm by ultrasound examination. Gonadotrophin was administered with recombinant FSH (Gonal F; Merck Serono, Switzerland) 150—300 IU/day until the day of HCG administration (250 μg, Ovidrel; Merck Serono, Switzerland).

On the day of recombinant FSH and HCG administration, ovarian ultrasound scans were performed using a transvaginal probe (Aloka Medical, Japan). FORT was calculated as PFC on the day of HCG × 100/AFC at baseline (the first day of FSH).

Transvaginal oocyte retrieval was performed 34—36 h after the administration of HCG. Oocytes were fertilized either via conventional insemination or ICSI based on the couple's history. Fertilization was assessed 16—18 h after IVF or ICSI. Embryo transfers were performed 3 days after oocyte retrieval. No more than three embryos per patient were transferred; surplus embryos were cryopreserved. Progesterone vaginal tablets (Besins, Iscovesco, France) were administered 600 mg/day as luteal support from the day of the oocyte retrieval. Clinical pregnancy was defined as the presence of a gestational sac confirmed 5 weeks after embryo transfer by ultrasonography.

Informed consent was received from all subjects. The study were approved by the local ethics committee of Yantai Yuhuangding Hospital (YYH 2011-12-19, granted 19 December 2011).

Statistical analysis

Data were statistically described in terms of means ± SD. The data were analysed using a two-tailed Student's t-test, ANOVA and Turkey's post-hoc test for independent data. For comparing categorical data, the Pearson chi-squared test

was performed. Spearman correlation analysis was used to test the correlation between FORT and clinical features. Multiple linear regression analysis was performed to find the possible independent determinants of test variables and their contributions. *P*-values of <0.05 were considered statistically significant. All statistical analyses were performed with Statistical Package for Social Sciences version 13.0 (SPSS, Chicago, IL, USA).

Results

FORT, characteristics and IVF/ICSI outcomes in non-PCOS patients

Among the 1503 non-PCOS cases, the clinical pregnancy rate was 52.43% (788/1503). The patient characteristics, ovarian stimulation data and IVF outcomes in the clinically pregnant (788 cycles) and non-pregnant groups (715 cycles) are shown in **Table 1**. FORT was similar in patients who were pregnant and who were not pregnant (0.66 ± 0.25 versus 0.63 ± 0.26). Age, duration of infertility, FSH/LH ratio, serum basal oestradiol concentration, AFC, PFC, FSH starting dose, duration of gonadotrophin, total gonadotrophin dose and numbers of retrieved oocytes, total embryos and transferred embryos were similar between these two groups. Only the rates of 2PN fertilization (69.20% versus 64.79%, $P < 0.001$) and good-quality embryos (75.77% versus 55.90%, $P < 0.001$) were significantly higher in patients who achieved clinical pregnancy.

FORT was correlated with AFC ($r = -0.162$, $P < 0.001$), PFC ($r = 0.607$, $P < 0.001$), serum basal FSH concentration ($r = -0.123$, $P < 0.001$), total number of embryos that could be transferred ($r = 0.259$, $P < 0.001$) and the number of good-quality embryos ($r = 0.197$, $P < 0.001$). Multiple linear regression analysis was performed to study the major independent factors for the number of good-quality embryos, which was used as the dependent variable. Among all of the independent variables, FORT ($t = 1.982$, $P < 0.05$) and number of retrieved oocytes ($t = 17.246$, $P < 0.01$) were influential factors, but not AFC or PFC.

The mean value of FORT was 0.65. To interpret the relationship between follicular sensitivity to FSH and the IVF/ICSI outcome, patients were divided into three groups according to FORT. Low FORT ($n = 402$), medium FORT ($n = 632$) and high FORT ($n = 469$) referred to FORT values below the 33rd percentile (FORT <0.5), between the 33rd and 67th percentiles (FORT 0.5∼0.73) and above the 67th percentile (FORT >0.73), respectively. The clinical characteristics and ovarian stimulation data of the patients, such as age, serum basal oestradiol concentration and starting dose of FSH, were similar in the low, medium and high FORT groups (**Table 2**). However, the FSH/LH ratio (1.73 ± 1.87 versus 1.52 ± 0.82 versus 1.49 ± 0.82, respectively; $P = 0.007$) and AFC (14.51 ± 6.33 versus 14.00 ± 5.37 versus 12.32 ± 4.28, respectively; $P < 0.001$) were highest in the low FORT group. PFC (5.49 ± 2.85 versus 8.41 ± 3.27 versus 11.54 ± 4.33, respectively; $P < 0.001$), the number of retrieved oocytes (8.45 ± 5.64 versus 11.52 ± 6.37 versus 13.30 ± 6.34, respectively; $P < 0.001$) and the total number of embryos available (4.94 ± 3.22 versus 6.37 ± 3.69 versus 7.33 ± 3.89, respectively; $P < 0.001$) increased progressively from the low to high FORT groups. Meanwhile, the rates of good-quality embryos, embryo implantation and clinical pregnancy increased dramatically in accordance with FORT ($P < 0.05$); the fertilization rate remained steady.

FORT, characteristics and IVF/ICSI outcomes in PCOS patients

As shown in **Table 3**, women with PCOS who achieved clinical pregnancy exhibited significantly lower FORT values (0.56 ± 0.21 versus 0.66 ± 0.29, respectively; $P < 0.05$) than those without clinical pregnancy. In PCOS patients, there

Table 1 Characteristics, ovarian stimulation data and IVF/ICSI outcomes of non-PCOS patients according to pregnancy.

	Clinical pregnancy (n = 788)	*Non-pregnancy* (n = 715)	P-*value*
Age (years)	33 ± 4	33 ± 4	NS
Duration of infertility (years)	5 ± 3	5 ± 4	NS
FSH/LH ratio	1.56 ± 1.41	1.58 ± 0.91	NS
Serum basal oestradiol (pg/ml)	40.89 ± 31.56	43.04 ± 55.52	NS
AFC	13.86 ± 5.36	13.34 ± 5.48	NS
Dose of starting FSH (IU)	235.93 ± 53.18	246.96 ± 57.11	NS
Duration of gonadotrophin (days)	9.15 ± 1.27	9.10 ± 1.35	NS
Total gonadotrophin dose (IU)	2147.39 ± 600.90	2222.24 ± 617.19	NS
PFC	8.42 ± 3.90	8.37 ± 4.54	NS
FORT	0.66 ± 0.25	0.63 ± 0.26	NS
Retrieved oocytes	11.71 ± 6.29	10.74 ± 6.56	NS
Total embryos	6.85 ± 3.65	5.66 ± 3.76	NS
Embryos transferred	2.22 ± 0.49	2.21 ± 0.60	NS
2PN fertilization rate	69.20 (6385/9227)	64.79 (4979/7685)	<0.001
Good-quality embryo rate	75.77 (4091/5399)	55.90 (2263/4048)	<0.001

Values are mean ± SD or % (*n*/total).
AFC = antral follicle count; NS = not statistically significant; PFC = preovulatory follicle count.

Table 2 Characteristics, ovarian stimulation data and IVF/ICSI— outcomes of non-PCOS patients according to FORT.

	Low FORT (<0.5; n = 402)	*Medium FORT* (0.5—0.73; n = 632)	*High FORT* (>0.73; n = 469)	P-*value*
Age (years)	33 ± 4	33 ± 4	33 ± 4	NS
Duration of infertility (years)	5 ± 3	5 ± 4	5 ± 3	NS
FSH/LH ratio	1.73 ± 1.87	1.52 ± 0.82	1.49 ± 0.82	0.007
Serum basal oestradiol (pg/ml)	45.38 ± 64.76	39.92 ± 33.45	41.66 ± 36.23	NS
AFC	14.51 ± 6.33	14.00 ± 5.37	12.32 ± 4.28	<0.001
Dose of starting FSH (IU)	241.45 ± 59.23	242.05 ± 55.28	239.82 ± 51.64	NS
Duration of FSH (days)	9.23 ± 1.66	9.22 ± 1.08	9.20 ± 1.24	NS
Total gonadotrophin dose (IU)	2221.04 ± 680.35	2168.74 ± 572.81	2170.06 ± 594.70	NS
PFC	5.49 ± 2.85	8.41 ± 3.27	11.54 ± 4.33	<0.001
Retrieved oocytes	8.45 ± 5.64	11.52 ± 6.37	13.30 ± 6.34	<0.001
Total embryos	4.94 ± 3.22	6.37 ± 3.69	7.33 ± 3.89	<0.001
Embryos transferred	2.27 ± 0.58	2.28 ± 0.53	2.28 ± 0.52	NS
2PN fertilization rate	67.84 (2303/3395)	66.95 (4874/7280)	67.13 (4187/6237)	NS
Good-quality embryo rate	65.98 (1311/1987)	66.48 (2678/4028)	68.91 (2365/3432)	0.033
Implantation rate	29.71 (271/912)	33.80 (488/1444)	35.08 (375/1069)	0.031
Clinical pregnancy rate	46.27 (186/402)	53.80 (340/632)	55.86 (262/469)	0.012

Values are mean ± SD or % (*n*/total).
AFC = antral follicle count; NS = not statistically significant; PFC = preovulatory follicle count.

Table 3 Characteristics, ovarian stimulation data and IVF/ICSI outcomes of PCOS patients according to pregnancy.

	Clinical pregnancy (n = 66)	*Non-pregnancy* (n = 74)
Age (years)	32 ± 4	32 ± 3
Duration of infertility (years)	5 ± 3	6 ± 3
Body mass index (kg/m^2)	25.14 ± 3.56	25.42 ± 3.76
FSH/LH ratio	0.93 ± 0.57	0.87 ± 0.53
Serum testosterone (ng/ml)	0.41 ± 0.17	0.40 ± 0.20
Serum basal oestradiol (pg/ml)	39.37 ± 17.60	42.06 ± 25.79
AFC	19.67 ± 5.98	19.74 ± 6.01
Dose of starting FSH (IU)	212.69 ± 500.83	229.90 ± 66.72
Duration of gonadotrophin (days)	9.21 ± 1.53	9.01 ± 1.46
Total gonadotrophin dose (IU)	1966.86 ± 574.60	2017.40 ± 740.06
PFC	10.56 ± 4.07	12.28 ± 4.93
FORT[a]	0.56 ± 0.21	0.66 ± 0.29
Retrieved oocytes	14.42 ± 7.18	15.35 ± 7.66
Total embryos	8.47 ± 4.28	8.39 ± 4.55
Embryos transferred	2.24 ± 0.43	2.15 ± 0.52
2PN fertilization rate	67.33 (641/952)	63.20 (718/1136)
Good-quality embryo rate	70.30 (393/559)	68.12 (423/621)

Values are mean ± SD or % (*n*/total).
[a]$P = 0.031$.
AFC = antral follicle count; NS = not statistically significant; PFC = preovulatory follicle count.

were no differences in embryo implantation or clinical pregnancy rates in the low, medium and high FORT groups (**Table 4**). Interestingly, although the number of retrieved oocytes was highest in the high FORT group (12.04 ± 7.54 versus 15.63 ± 7.08 versus 17.21 ± 7.66, respectively; $P < 0.05$), the rates of fertilization (63.47% versus 69.49% versus 60.66%, respectively; $P < 0.05$) and good-quality embryos (68.06% versus 72.71% versus 64.99%, respectively; $P < 0.05$) were significantly higher in the medium FORT group. Furthermore, a better IVF/ICSI outcome was achieved in PCOS patients with medium FORT values.

Discussion

In IVF treatment, basal FSH, AFC and serum anti-Müllerian hormone (AMH) concentrations are used to assess the basal ovarian reserves and to predict ovarian response and IVF outcome. However, these indicators have several

Table 4 Characteristics, ovarian stimulation data and IVF/ICSI outcomes of PCOS patients according to FORT.

	Low FORT (<0.5; n = 45)	*Medium FORT* (0.5–0.73; n = 56)	*High FORT* (>0.73; n = 39)	P-*value*
Age (years)	32 ± 4	32 ± 3	33 ± 4	NS
Duration of infertility (years)	5 ± 3	6 ± 3	5 ± 4	NS
Body mass index (kg/m^2)	25.72 ± 3.70	25.60 ± 3.87	24.34 ± 3.17	NS
FSH/LH ratio	1.04 ± 0.58	0.84 ± 0.53	0.82 ± 0.52	NS
Serum testosterone (ng/ml)	0.38 ± 0.16	0.37 ± 0.20	0.36 ± 0.19	NS
Serum basal oestradiol (pg/ml)	39.73 ± 19.66	39.53 ± 21.32	43.89 ± 26.38	NS
AFC	22.36 ± 5.86	19.86 ± 5.72	16.44 ± 4.94	<0.001
Dose of starting FSH (IU)	208.61 ± 59.10	228.57 ± 64.08	227.24 ± 54.33	NS
Duration of gonadotrophin (days)	10.04 ± 1.94	8.68 ± 0.96	8.64 ± 0.96	<0.001
Total gonadotrophin dose (IU)	2116.67 ± 802.68	1974.33 ± 651.38	1879.17 ± 476.65	NS
PFC	7.93 ± 2.92	11.79 ± 3.27	15.10 ± 4.89	<0.001
Retrieved oocytes	12.04 ± 7.54	15.63 ± 7.08	17.21 ± 7.66	0.005
2PN fertilization rate	63.47 (344/542)	69.49 (608/875)	60.66 (407/671)	0.001
Good-quality embryo rate	68.06 (211/310)	72.71 (373/513)	64.99 (232/357)	0.047
Implantation rate	25.51 (25/98)	31.67 (38/120)	27.59 (24/87)	NS
Clinical pregnancy rate	46.67 (21/45)	53.57 (30/56)	38.46 (15/39)	NS

Values are mean ± SD or % (*n*/total). AFC = antral follicle count; NS = not statistically significant; PFC = preovulatory follicle count.

limitations. For example, previous research has demonstrated that lower baseline concentrations of FSH were correlated with improved ovarian responses and pregnancy rates in IVF cycles using GnRHa (Jurema et al., 2003). However, meta-analysis has concluded that basal FSH should not be regarded as a useful routine test for the prediction of IVF outcomes (Bancsi et al., 2003), possibly due to intercycle variability (Bancsi et al., 2004). AFC may well represent the actual functional ovarian reserves and is highly correlated to the number of oocytes retrieved (Broer et al., 2009). However, it cannot predict the oocyte/embryo quality or the IVF outcome in an egg donation programme (Melo et al., 2009). The present data also show that AFC is not independent of the number of good-quality embryos. Studies have shown that AMH could be a predictor of ovarian reserve and of IVF success (Barad et al., 2009; Lekamge et al., 2007; Wunder et al., 2008). However, conflicting research could not attribute predictive power of pregnancy outcomes to AMH (Lee et al., 2008; Smeenk et al., 2007). Similarly to most studies assessing the accuracy of predicting antral follicle sensitivity to FSH, PCOS cases were not excluded from the current analyses. In fact, patients with PCOS have clearly elevated AFC and AMH concentrations (Broekmans et al., 2008; La Marca et al., 2009). In the studies conducted on PCOS cases only, serum AMH concentrations on day 3 of the stimulation cycle could be used as a marker for ovarian response, as well as for reproductive outcomes in assisted reproduction cycles (Kaya et al., 2010). For AMH as a laboratory test, the measurement stability should be dealt with according to routine procedures, but routine assays may not yet be readily available. Therefore, standardization of these assays is urgently needed.

FORT as an innovative measure is calculated as the ratio of PFC to AFC, and it is independent of the preexisting antral follicle number. FORT is considered a new objective look at the ovarian response and a useful tool for studying the regulation of follicle responsiveness. The observed relationship between IVF/ICSI outcomes and the percentage of antral follicles that effectively respond to FSH administration reaching preovulatory maturation suggests that FORT may be a qualitative reflector of ovarian follicular competence only in patients with regular menstrual cycles (Gallot et al., 2012). To evaluate the value of FORT as a predictor of IVF/ICSI outcomes further, the present study calculated FORT in a large cohort of PCOS and non-PCOS patients.

The results show no difference in FORT between the pregnancy and non-pregnancy groups of non-PCOS patients. The rates of good-quality embryos, embryo implantations and clinical pregnancies increased dramatically in accordance with FORT values. The correlation analysis indicated that FORT was correlated with the numbers of embryos suitable for the transfer of good-quality embryos. In non-PCOS patients, FORT may be an indicator of response to FSH and of reproductive competence, as reflected by the outcome of oocytes and embryos after IVF/ICSI treatment. A better IVF/ICSI outcome was achieved in non-PCOS patients with high FORT values.

In PCOS patients, the data are noteworthy in indicating a lower FORT in the pregnancy group and a better IVF/ICSI outcome among patients with medium FORT values. Normal ovaries have fewer antral follicles and the saturation of the FSH receptor population may have limited oestradiol production. In contrast, the PCOS ovary contains two- or three-times the number of antral follicles in a normal ovary. Women with PCOS exhibit significantly greater capacity for oestradiol production in response to gonadotrophin stimulation as the result of a larger number of stimulated granulosa cells. These patients appear to have an increased risk of ovarian hyperstimulation syndrome. Furthermore, oestradiol production was relatively transient in PCOS patients because a marked decline was detected after peak concentrations; this effect differed from normal women who exhibited persistent elevations of oestradiol for up to 24 h (Coffler et al., 2003). Previous studies have demonstrated

the abnormalities of folliculogenesis and granulosa cell function in patients with PCOS (Franks et al., 2003). High oestradiol concentrations on the day of HCG administration could potentially affect oocyte maturity (Fábregues et al., 2004) and quality (Aboulghar et al., 1997). Given the diverse clinical characteristics of infertile women with PCOS and their hyperresponsiveness to FSH, it is important to moderate the dose of FSH to achieve a medium FORT value and thereby to improve the outcomes of IVF/ICSI in PCOS patients.

Antral follicle responsiveness to FSH, as far as it is measurable by FORT, was negatively correlated with the circulating AMH concentrations in normo-cycling women. This result is consistent with the theory that AMH inhibits the sensitivity of antral follicles to FSH (Genro et al., 2011). Further clinical and basic research is needed to understand the relationship between FORT and AMH.

In conclusion, the present findings indicate that medium FORT values in PCOS patients and higher FORT values in non-PCOS patients may predict better outcomes for IVF/ICSI. FORT, as a clinical measure of antral follicle responsiveness to FSH, is related to overall follicular health and provides new insight into the definition of 'poor responders' and the criteria for cycle cancellation, which has been based on the output of antral follicle response to FSH, rather than the absolute number of follicles recruited. To improve the outcomes of IVF/ICSI, FORT should be modulated according to the heterogeneity of follicle competence by adopting these individualized ovarian stimulation protocols.

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