



The systematic error in the estimation of fetal weight and the underestimation of fetal growth restriction

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Background: the underdiagnosis of fetal growth restriction (FGR)

FGR, the failure of a fetus to reach its growth potential, is associated with an increased risk of perinatal morbidity (respiratory distress syndrome, seizures, sepsis, intraventricular hemorrhage, hypoxic ischemic encephalopathy, adverse neurodevelopmental outcomes) and mortality (stillbirth and neonatal death).¹⁻⁵ In addition, aberrations in fetal growth may have health implications across the lifespan of an individual, exemplified by the association of FGR with hypertension and other chronic medical disorders.^{6,7} Although FGR may not be preventable, identification and multivessel Doppler surveillance of fetuses with growth restriction has been demonstrated to decrease perinatal morbidity and mortality.⁸⁻¹⁰ As such, the identification of FGR remains an integral component of prenatal care internationally.

Guidelines for screening for FGR vary, with some countries using routine ultrasonography and others, such as the United States, adopting a risk-based approach.¹¹ Independent of approach, the overall antenatal diagnosis of FGR

Fetal growth restriction (FGR) is associated with an increased risk of perinatal morbidity and mortality and has lifetime implications for the risk of chronic medical conditions. Antenatal diagnosis of FGR remains poor, with the majority of cases remaining undiagnosed. Although several factors contribute to the underdiagnosis of FGR, the error in ultrasound estimation of fetal weight (EFW) generally is not considered in clinical practice. In this commentary, we suggest that the intrinsic, or systematic, error in ultrasound EFW is a significant factor contributing to the underestimation of fetuses predicted to have FGR and should be incorporated into screening and surveillance recommendations. To illustrate this point, we present an analytic model of published data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Fetal Growth Studies characterizing and quantifying the impact of the systematic error in ultrasound EFW on the underdiagnosis of FGR. Independent of the centile at which the risk of adverse outcome related to FGR begins, whether the 10th, 5th or 3rd percentile, our analysis suggests the need to modify to the current paradigm for identifying and responding to fetuses estimated to be at risk.

Key words: error in estimation, estimation fetal weight, fetal growth restriction, small for gestational age, underdiagnosis

remains poor, with the majority of cases remaining undiagnosed. Previous publications have demonstrated that 70–90% neonates with birth weight <10% (small-for-gestational age) are not identified as having FGR antenatally.¹²⁻¹⁵ Furthermore, there is evidence that perinatal morbidity and mortality is greater among undetected compared with detected cases of FGR.¹⁵⁻¹⁷ Therefore, improved diagnosis would allow more fetuses to benefit from antenatal surveillance and appropriately timed delivery, which may significantly impact perinatal outcome.

While several factors contribute to the underdiagnosis of FGR, including the poor reliability of clinical estimates of fetal size¹⁸⁻²⁰ and the use of risk-based screening approaches,²¹ the error in ultrasound estimation of fetal weight generally is not considered in clinical practice. For decades, sonographic measurements of fetal biometric variables (biparietal diameter, head

circumference, abdominal circumference, and femur length) have been used to predict EFW, and multiple estimation models have been published.²²⁻²⁶ However, a systematic review concluded that no single model was preferred given the substantial error in predicted EFW, with 95% confidence intervals exceeding 14% of birth weight for all methods.²⁶ This bidirectional, intrinsic, or systematic error in the estimation of fetal weight may have significant implications for clinical practice as a fetus with a normal EFW may in reality have FGR and be at risk for a poor outcome. The systematic error in the estimation of fetal weight is well-described in the literature; however, its impact on clinical practice and perinatal outcome remains poorly characterized.

We suggest that this systematic error in the estimation of fetal weight is a significant factor contributing to the underestimation of fetuses predicted to have FGR and should be incorporated into screening and surveillance

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recommendations. To illustrate this point, we present an analysis of published data to characterize and quantify the impact of the systematic error in ultrasound EFW on the underdiagnosis of FGR.

An analytic model of data from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies

Methods

We generated an analytic model using published data from the NICHD Fetal Growth Studies, a prospective cohort study that was conducted to develop contemporary fetal growth standards in a diverse US population.²⁷ In short, the NICHD Fetal Growth Studies recruited healthy women with low-risk singleton gestations from 12 clinical sites across the United States from 2009 to 2013 and collected detailed demographic, obstetric, and serial fetal ultrasound data. By the use of fetal anthropometric measurements, EFW centiles were developed for the study population by race/ethnicity. As per the original study methodology, 3 points (25th, 50th, 75th percentiles) were chosen at gestational ages that evenly split the distributions and the remaining percentiles were then estimated based on an assumed normal distribution of data. Estimated curves were then generated for the study population across gestation from the 15 to 40th week for each race/ethnic group.

For our analytic model, we used data from a single race/ethnicity population (White) within the NICHD Fetal Growth Studies dataset. Assuming a normal distribution and using EFW data from the NICHD Fetal Growth Studies publication, we calculated the standard deviation and raw EFW (in grams) at each centile by week of gestation from 30 to 40 weeks with the equation:

$$Z = \frac{X - \mu}{\sigma}$$

where Z is the z score, X is the raw score, μ is the population mean, and σ is the standard deviation of the population.

For example, at 30 weeks of gestation for white subjects, the mean and 10th percentile EFW were reported as 1555 and 1343 g, respectively. With a z score of -1.282 corresponding to the 10th percentile, the standard deviation was calculated to be 165.4 g. We then used mean, standard deviation, and centile z scores to calculate the EFW for all centiles at 30 weeks. Given that the mean and standard deviation vary by week of gestation, these calculations were repeated at each individual week of gestation from 30 to 40 weeks, which allowed for generation of EFW curves (10th, 50th, and 90th percentile).

We then sought to assess the impact of the error in ultrasound EFW on the diagnosis of FGR. Although the error in estimation of EFW varies by prediction model and publication, in a previous analysis, Lee et al²⁸ demonstrated that with a modified Hadlock model, 50% of fetuses have a birth weight within 5% of EFW, resulting in 50% of fetuses being either over- or underestimated. Assuming a proportional, bidirectional error that does not vary with gestational age, than 25% of fetuses have an EFW that is overestimated (half of total population with error $>5\%$). In the same analysis, Lee et al²⁸ demonstrated that with a modified Hadlock model 80% of fetuses have a birth weight within 10% of EFW, which results in 20% of fetuses being either over- or underestimated. As such, 10% of fetuses have an EFW that is overestimated (one half of population with error $>10\%$). We chose to define the systematic error in ultrasound EFW for our analytic model by using these parameters, which, as a conservative estimate of the error in EFW, would result in a cautious estimation of the actual impact.

We then applied this systemic error across centiles from at 30–40 weeks' gestation to calculate the EFW centile representing the point at which the error in estimation results in an actual EFW <10 th percentile (standard diagnostic criterion for FGR).¹ As an example, data calculated for the study population at 30 weeks' gestation are presented in Table 1. These calculations were repeated for each individual week of gestation, and

the centile intercepts were plotted by week of gestation to generate a curve. Quantification of the underdiagnosis of FGR was then performed. Lastly, to assess the distribution of potential FGR fetuses across EFW centiles, we calculated the likelihood of a fetus having FGR (EFW <10 th percentile) based on the initial EFW centile with incorporation of the described systematic error in estimation.

For this analysis, we assumed a proportional, bidirectional error in EFW that does not vary by gestational age. Given the clinical significance of underdiagnosing FGR, this analysis focused on only the lower half of the bidirectional error, resulting in an overestimation of fetal weight. For the purpose of this analysis, we specifically chose not to examine the relationship between altered fetal growth and adverse perinatal outcome. The EFW and/or anthropometric profile that constitutes FGR and the degree of altered growth that requires attention or obstetric intervention is the subject of significant debate, a comprehensive review of which is beyond the scope of this manuscript; however, independent of the centile at which the morbidity related to FGR begins, whether the 10th, 5th, or 3rd percentile, the systematic error in ultrasound EFW would contribute to the underestimation of fetuses predicted to have FGR at any specified diagnostic centile threshold.

Results

The curves for EFW that include the 10th, 50th, and 90th percentiles across gestation from 30–40 weeks for the study population are presented in Figure 1. Applying the systematic error to this dataset, assuming that 50% of fetuses have a birth weight within 5% of EFW, then 25% of all fetuses with an EFW at the 20th percentile are actually <10 th percentile. In addition, 25% of fetuses with an EFW at the 15th and 12th percentiles have an EFW <8 th and <6 th percentiles, respectively (Figure 1, orange-shaded region and description in legend). Assuming that 80% of fetuses have a birth weight within 10% of EFW, then 10% of all fetuses with an EFW at

TABLE 1
Application of systematic error in EFW at 30 weeks' gestation

Raw EFW	Centile _{raw}	5% error adjustment		10% error adjustment	
		EFW _{5% error}	Centile _{5% error}	EFW _{10% error}	Centile _{10% error}
1170	1	1112	<1	1053	<1
1215	2	1155	<1	1094	<1
1244	3	1182	1	1119	<1
1265	4	1202	2	1139	<1
1283	5	1219	2	1155	<1
1298	6	1233	3	1168	<1
1311	7	1245	3	1180	1
1323	8	1256	4	1190	1
1333	9	1267	4	1200	2
1343	10	1276	5	1209	2
1352	11	1284	5	1217	2
1361	12	1293	6	1225	2
1369	13	1300	6	1232	3
1376	14	1308	7	1239	3
1384	15	1314	7	1245	3
1391	16	1321	8	1252	3
1397	17	1327	8	1257	4
1404	18	1333	9	1263	4
1410	19	1339	10	1269	4
1416	20	1345	10	1274	4
1422	21	1351	11	1280	5
1427	22	1356	11	1285	5
1433	23	1361	12	1289	5
1438	24	1366	12	1294	6
1444	25	1371	13	1299	6
1449	26	1376	14	1304	6
1454	27	1381	15	1308	7
1459	28	1386	15	1313	7
1464	29	1390	16	1317	7
1468	30	1395	17	1321	8
1473	31	1399	17	1326	8
1478	32	1404	18	1330	9
1482	33	1408	19	1334	9
1487	34	1413	19	1338	9
1491	35	1417	20	1342	10
1496	36	1421	21	1346	10
1500	37	1425	22	1350	11
1505	38	1429	22	1354	11

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(continued)

TABLE 1
Application of systematic error in EFW at 30 weeks' gestation (continued)

Raw EFW	Centile _{raw}	5% error adjustment		10% error adjustment	
		EFW _{5% error}	Centile _{5% error}	EFW _{10% error}	Centile _{10% error}
1509	39	1433	23	1358	12
1513	40	1437	24	1362	12
1517	41	1441	24	1366	13
1522	42	1446	25	1369	13
1526	43	1450	26	1373	14
1530	44	1454	27	1377	14
1534	45	1457	28	1381	15
1538	46	1462	29	1385	15
1543	47	1465	29	1388	16
1547	48	1469	30	1392	16
1551	49	1473	21	1396	17
1555	50	1477	32	1400	17

This table represents an example of the calculations for one individual week of gestation applying the systematic error in ultrasound EFW (lower half of the bidirectional error resulting in the underestimation of fetal weight). Calculations were performed for assumptions of both a 5% and 10% systematic error in EFW across centiles, which represent 25% and 10% of the fetal population, respectively. Calculations were repeated at each week of gestation from 30 to 40 weeks (data not shown). As seen in the Table 1, of all fetuses with an EFW at the 20th percentile at 30 weeks' gestation, 25% have an actual EFW at the 10th percentile, and 10% are at the 4th percentile. In addition, of all fetuses with an EFW at the 36th percentile, 25% have an actual EFW at the 21st percentile, and 10% are at the 10th percentile.

EFW, estimation of fetal weight.

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the 30th percentile are actually <10th percentile. In addition, 10% of fetuses with an EFW at the 25th and 15th percentile are actually <9th and <5th percentiles, respectively (Figure 1, yellow-shaded region).

We then calculated the likelihood of a fetus having FGR based on their EFW percentile with incorporation of the systematic error, which is presented in Figure 2. Notably, the effect of the systematic error is continuous across EFW centiles, with a clinically meaningful increase in FGR underestimation beginning at an EFW in the 20–25th percentile. As demonstrated in Figure 2, the risk of FGR remains as high as 10% as EFW approaches the 50th percentile. Similarly, given the chance of EFW underestimation, not all fetuses with EFW < 10th percentile will have FGR. Figure 2 was generated with the use of data from the study population at 39 weeks' gestation with the assumption of 50% of fetuses having a birth weight within 5% of EFW. Graphs using data from different gestational weeks or alternative

assumptions regarding the systematic error in ultrasound EFW are similar (data not shown).

Summary/conclusion

The systematic error in the estimation of fetal weight is a significant factor contributing to the underestimation of fetuses predicted to have FGR, resulting in an increased likelihood of missed diagnoses as percentile EFW decreases. As such, the error in EFW should be incorporated into current screening and surveillance recommendations for the detection and management of FGR.

Several factors contribute to the underdiagnosis of FGR, including the poor reliability of clinical estimates of fetal size,^{18–20} risk-based compared with universal ultrasound screening approaches,²¹ and the limited accuracy of ultrasound in the estimation of fetal weight or prediction of birth weight.²⁶ Although recent academic efforts and trials have focused on the impact of routine third-trimester ultrasound assessment for FGR,^{21,29} a paucity of

attention has been directed toward the accuracy of ultrasound EFW and its clinical impact on the detection of FGR. Our analytic model demonstrates that the inherent, or systematic error in ultrasound EFW can significantly impact the detection of FGR, as many fetuses with “normal” EFW centiles are actually <10th percentile. The effect of this systematic error is continuous across centiles with a greater likelihood of FGR as EFW centile decreases. The risk of FGR, however, remains as high as 10% even as EFW approaches the 50th percentile (Figure 2).

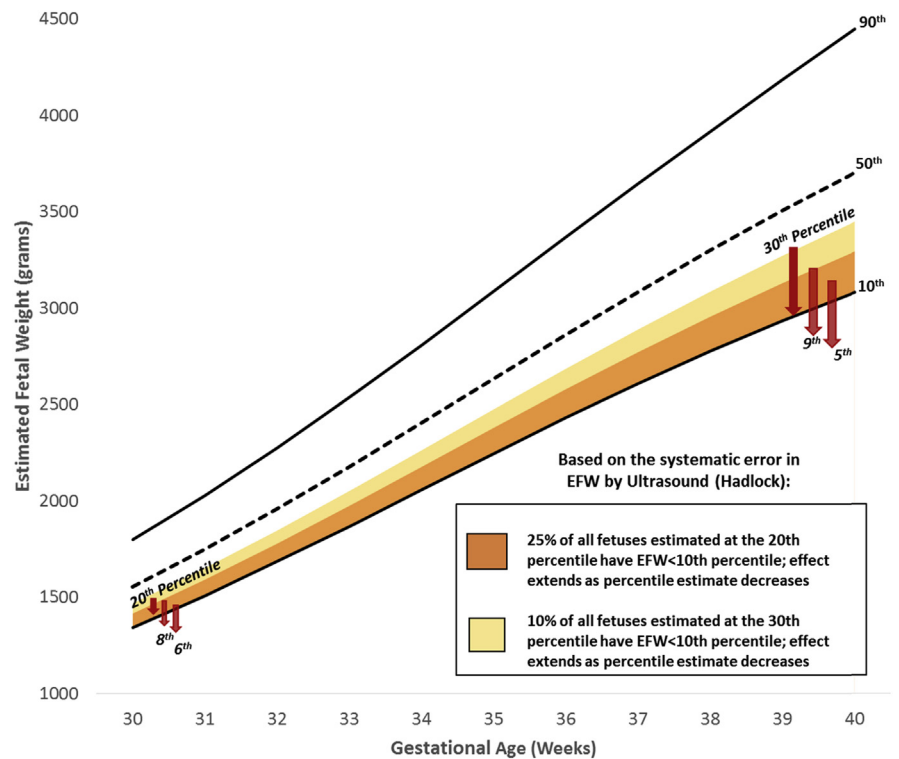
Importantly, the systemic error in ultrasound EFW represents a limitation of the technology and cannot be eliminated by altering the EFW prediction model, method of assessment (population reference, population standard, or individualized growth curve), or number of ultrasound examinations (single vs serial), because each individual ultrasound assessment has an independent margin of error. As such, a strategy to improve the sensitivity of ultrasound for

detection of FGR must include “casting a wider net” and having a heightened suspicion for FGR at a broader range of EFW centiles, including those traditionally defined as “normal.” We recognize that adopting this approach also increases the risk of a normally grown fetus being misclassified as FGR, which may have consequences, such as increased surveillance, interventions, or health care costs. In the recently published Pregnancy Outcome Prediction (POP) study, which assessed the impact of routine third-trimester ultrasonography, researchers estimated that for each additional FGR diagnosis, 2 false-positive diagnoses were made, which may result in unnecessary intervention.²¹ Therefore, any change in screening must balance the benefits of increased detection with the potential for harm from false positive diagnoses.

For example, at MetroHealth Medical Center, in response to our analysis and the underdiagnosis of FGR in our population, we recently adopted a new approach for the detection and management of FGR. At our institution, any fetus with an EFW between then 10th and 20th percentile for gestational age by a modified Hadlock model has a fractional thigh volume determined, which has been demonstrated to improve the accuracy of fetal weight estimation when compared with conventional estimation models.^{28,30} The EFW incorporating this volumetric assessment is compared with the EFW by conventional biometry. If fractional thigh volume suggests an EFW < 10th percentile, antenatal surveillance is initiated with serial multi-vessel Doppler assessment. If the EFW by fractional thigh volume and conventional biometry are both 10–20th percentile, then short-interval follow-up growth is recommended and antenatal testing may be initiated based on additional clinical parameters (ie, previous history of intrauterine growth restriction, history of medical comorbidities, temporal trend in growth velocity, etc). We anticipate having data on the impact of this practice change on FGR detection and perinatal outcomes in the near future. Importantly, our practice change represents only one example by which

FIGURE 1

Systematic error in EFW and the underdiagnosis of FGR



Example at 30 weeks' gestation and using 5% systematic error: 20th percentile EFW is 1416 g. Applying a 5% error (71 g) leading to underestimation results in EFW of $1416 - 71 = 1345$ g, which corresponds to <10th percentile. 15th percentile EFW is 1384 g. Applying a 5% error (69 g) leading to underestimation results in EFW of $1384 - 69 = 1315$ g, which corresponds to <8th percentile. 12th percentile EFW is 1361 g. Applying a 5% error (68 g) leading to underestimation results in EFW of $1361 - 68 = 1293$ g, which corresponds to <6th percentile.

EFW, estimation of fetal weight; FGR, fetal growth restriction.

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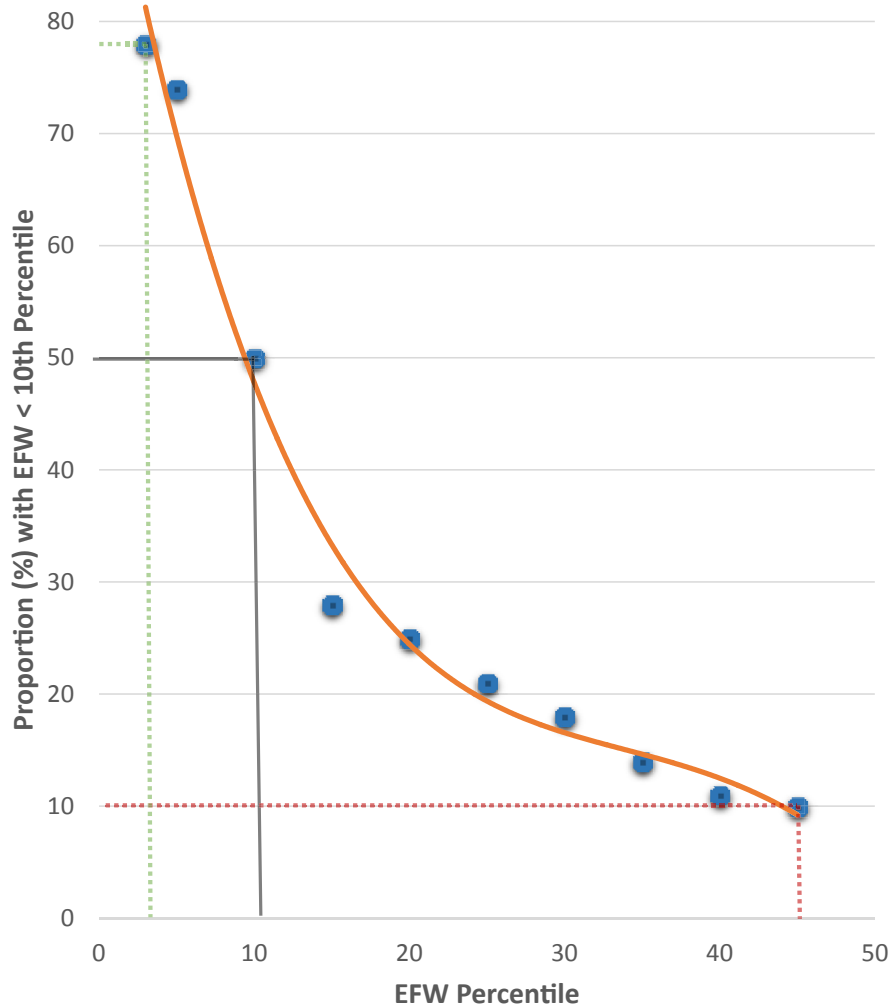
the impact of the systematic error in ultrasound EFW on FGR detection can be addressed. Rather than adopting any specific protocol, we recommend acknowledgement and incorporation of this systematic error into antenatal screening programs with the individualization of management guidelines based on patient and population risks as well as institutional care delivery models and resources.

In this analytic model, we used an EFW < 10th percentile to define FGR, which is the standard definition adopted by the American Congress of Obstetricians and Gynecologists.¹ We recognize that not all fetuses with EFW < 10th percentile have pathologic FGR, because

some may be constitutionally small or may be misclassified due to EFW underestimation, which is highlighted in Figure 2. A clear distinction between pathologic FGR and other causes of EFW < 10th percentile, however, cannot always be determined during antenatal care. As such, we felt that using standard diagnosis of FGR, a broadly accepted criterion to identify fetuses at risk and initiate surveillance, would be appropriate to illustrate the impact of the systematic error in EFW on the diagnosis of FGR, which occurs independent of the centile threshold used as a diagnostic cut point.

Our analytic model has other limitations, including the fact that choosing a

FIGURE 2
Likelihood of FGR by EFW centile



Likelihood of FGR diagnosis at each centile with polynomial regression line. Calculation based on assumption that 50% of fetuses have a birth weight within 5% of EFW using data at 39 weeks' gestation. At the 10th percentile, 50% of all fetuses will be over- or underestimated (*solid gray solid line*). The systemic error in EFW results in underestimation, where not all fetuses with EFW < 10th have FGR (*green dotted line*) and overestimation, where FGR may be present in 10% of all fetuses with an EFW as high as the 50th percentile (*red dotted line*).

EFW, estimation of fetal weight; FGR, fetal growth restriction.

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specific percentile threshold to define FGR precludes the identification of fetuses with pathologic growth that manifests as decreasing growth velocity or trajectory at normal EFW centiles. By not meeting their growth potential, these fetuses are at risk for adverse perinatal outcomes,^{31,32} may remain undiagnosed and would not be captured comprehensively by our analytic model.

Therefore, a multimodal effort to improve FGR detection is needed to further minimize underdiagnosis.

We acknowledge that the literature is rife with debate regarding the parameters used to define FGR (EFW centiles, abdominal circumference centiles, umbilical artery Doppler abnormalities, cerebral placental ratio) as well as the EFW centiles, at which the risk of fetal

and neonatal morbidity and mortality begin to increase.^{1,33-36} Notably, the effect of the systematic error of ultrasound EFW is continuous across EFW centiles, thereby placing a fetus with an EFW considered to be "normal" at risk of adverse outcome. Therefore, independent of the centile at which the morbidity related to FGR begins, whether the 10th, 5th, or 3rd percentile, this analysis suggests modifying the current paradigm for identifying and responding to fetuses estimated to be at risk of FGR. ■

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