

Short and Long-term Outcomes Associated with Large for Gestational Age Birth Weight

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Disclosure Statement: The author reports no conflicts of interest

Word Count: 4019

Keywords: Large for gestational age birth weight, macrosomia, diabetes, obesity, cardiovascular disease, birth trauma, shoulder dystocia, hypoglycemia

This is the author's manuscript of the article published in final edited form as:

Scifres, C. M. (2021). Short- and Long-Term Outcomes Associated with Large for Gestational Age Birth Weight. *Obstetrics and Gynecology Clinics of North America*, 48(2), 325–337. <https://doi.org/10.1016/j.ogc.2021.02.005>

Synopsis

Large for gestational age (LGA) birth weight is associated with multiple adverse short- and long-term outcomes. Infants born with LGA birth weight are at increased risk for NICU admission, respiratory distress, neonatal metabolic abnormalities including hypoglycemia, birth trauma, and even stillbirth or neonatal death. The risk for many of these complications increases with higher birth weights. Individuals with LGA birth weight also appear to be at subsequent increased risk for overweight/obesity, diabetes, cardiovascular disease, and even some childhood cancers. These data highlight the need for effective interventions to reduce risk across the lifespan.

Introduction

Large for gestational age (LGA) birth weight is associated with increased risk for perinatal morbidity and long-term metabolic complications, and this review will summarize the impact of LGA birth weight on both short- and long-term offspring outcomes. One challenge associated with evaluating risks associated with higher birth weight is that varying definitions have been used to describe excess fetal growth. In many studies, LGA is defined as a birth weight greater than the 90th percentile for gestational age.[1 2] However, others have suggested that the definition of LGA should be restricted to infants with birth weight greater than the 97th percentile (2 standard deviations above the mean), because it is this group of infants who are at highest risk for perinatal morbidity and mortality.[3 4] In this review, use of the term LGA will refer to a birth weight greater than the 90th percentile unless otherwise specified, as this is the most common definition utilized. Among singleton live births in the United States, infants born at 40 weeks' gestation at the 90th percentile had birth weight greater than 4000 grams, and those born at the 97th percentile had a birth weight greater than 4400 grams.[2] Another commonly used term to describe excess fetal growth is macrosomia, which implies growth beyond an absolute birth weight, typically 4000 or 4500 grams, regardless of gestational age. Regardless of the definition used, excess fetal growth is common. In 2018, data from the National Center for Health Statistics showed that 7.8% of all live-born infants in the United States weighed 4000 grams or more, 1% weighed more than 4500 grams, and 0.1% weighed more than 5000 grams.[5]

The short and long-term health outcomes associated with LGA birth weight may depend on the underlying etiology, but there is a paucity of data to provide clarity. Genetic causes of early excessive fetal growth include Beckwith-Wiedeman syndrome, Simpson-Golabi-

Behmel syndrome, Sotos syndrome, Weaver syndrome, and Berardinelli lipodystrophy. In these instances, the prognosis associated with the underlying syndrome is the most significant influence on outcomes. However, in most cases of LGA birth weight there is likely an interplay of fetal genetic growth potential and excess delivery of nutrients to the fetus, although the mechanisms that control fetal weight gain and growth are incompletely understood.

Risk Factors for LGA birth weight

Maternal factors associated with LGA birth weight include diabetes, overweight and obesity, and excess gestational weight gain. LGA birth weight is common in infants of mothers with diabetes, particularly in the setting of suboptimal glycemic control.[6] Excess delivery of glucose to the fetus results in fetal hyperglycemia, hyperinsulinemia, and increased growth.[7] This excess fetal growth is also associated with increased body fat and thicker skinfolds compared with offspring of women without diabetes.[8]. Recent data suggest that fetal genotype and maternal glucose levels have an additive effect on fetal growth.[9] Higher maternal triglycerides have also been associated with excess fetal growth.[10 11]

The risk of an LGA offspring increases in a linear fashion as the pre-pregnancy maternal weight rises, and obese women have the highest risk for delivery of an LGA birth weight infant.[12] This relationship between maternal BMI and fetal growth is independent of maternal glucose levels.[13] Finally, excess maternal weight gain during pregnancy is associated with LGA birth weight.[14] Women across the spectrum of pre-pregnancy BMI categories with excess gestational weight gain are 1.85 times more likely to deliver an infant with LGA birth weight than women with weight gain within recommendations.[14]

Neonatal Complications associated with LGA birth weight

Severity of fetal overgrowth and the risk for neonatal complications

Multiple studies have demonstrated that neonatal morbidity for term infants is greater in infants with birth weight greater than 4000 grams compared to those with birth weight between 2500 and 3999 grams.[4 15] The risk for both infant and maternal morbidity is increased when birth weight is either LGA or between 4000 and 4500 grams, and it increases sharply when the birth weight is more than 4500 grams.[4 16-18] Because of this, macrosomia is commonly divided into three categories, each with differing types and levels of risk: 1) 4000-4499 grams, 2) 4500-4999 grams, and 3) more than 5000 grams.[19]

The risk for morbidity based on increasing levels of macrosomia was highlighted using data that included all singleton live births in the United States from 1995-1997 with a gestational age between 37- and 44-weeks' gestation. The authors clearly demonstrated progressively increasing morbidity that occurs as the birth weight increases above 4000 grams.[4] As shown in the Table, the risk for adverse outcomes including birth injury, Apgar score ≤ 3 at 5 minutes of life, assisted ventilation greater than 30 minutes, and meconium aspiration increased progressively from normal weight (birth weight 3000-3999 g) to grade 1 (birth weight 4000-4499 g), grade 2 (4500-4999 g) and grade 3 (birth weight ≥ 5000 g) macrosomia. Both neonatal and infant mortality were increased only in those infants with grade 3 macrosomia. Not all data are consistent, as a large cohort study of more than 6 million birth and infant death records from the United States demonstrated that infants with birth weights from 4000 to 4499 grams were not at increased risk of morbidity or mortality compared to those with a birth weight of 3500-3999 grams. However, infants with birth weights of 4500-

4999 grams were at significantly increased risk of stillbirth, neonatal mortality (especially because of birth asphyxia), birth injury, neonatal asphyxia, meconium aspiration, and cesarean delivery. A birth weight of 5000 grams or greater was associated with even higher risks, including an elevated risk of sudden infant death syndrome.[17]

While much of these data focused on infants with a birth weight >4000 grams, a retrospective cohort study using U.S. Vital Statistics from 2011 to 2013 found that infants delivered between 37-39 weeks' gestation who were LGA (>90th percentile) but less than 4000 grams were at increased risk for composite neonatal morbidity that included any of the following: Apgar score less than 5 at 5 minutes, assisted ventilation for more than 6 hours, seizure or serious neurologic dysfunction, significant birth injury, or neonatal mortality. In this same cohort, composite maternal mortality, including maternal transfusion, ruptured uterus, unplanned hysterectomy, admission to the intensive care unit, or unplanned procedures was also higher in pregnancies complicated by LGA birth weight.[18] King, et al. also found that an ultrasound estimated fetal weight greater than 4000 or 4500 grams in laboring women at term was associated with a higher risk for composite perinatal morbidity that included shoulder dystocia, third or fourth degree perineal laceration, postpartum hemorrhage, maternal hospitalization ≥ 5 days, neonatal birth trauma, meconium aspiration syndrome, perinatal infection, and neonatal length of stay ≥ 5 days.[20]

LGA birth weight and preterm birth

LGA birth weight (birth weight >97th percentile) may be associated with an increased risk of preterm birth. Using a Dutch perinatal registry of singleton births in nulliparous women from 1999 to 2010, van Zijl, et al. found that the risk of preterm birth between 25 and <37 weeks

gestation was greater in LGA (birth weight >97th percentile for age) birth weight infants compared with those with an AGA birth weight (11.3 versus 7.3 percent, odds ratio [OR] 1.8, 95% CI 1.7-1.9).[21]

Unlike term LGA infants who are at increased risk for morbidity, there are some data to suggest that among infants born preterm, LGA birth weight is associated with lower morbidity and mortality when compared to AGA birth weight infants matched for gestational age. These findings were illustrated by a retrospective review of data from the Vermont Oxford Network of preterm infants at 22 to 29 weeks' gestation born between 2006 and 2014.[22] Compared with AGA infants, LGA preterm infants had decreased risks of mortality, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, late-onset sepsis, severe retinopathy of prematurity, and chronic lung disease. LGA infants were more likely to have early-onset sepsis and severe intraventricular hemorrhage, but these findings were not consistent across gestational ages. These data suggest that for preterm infants, larger birth weight may be a protective factor resulting in better outcomes. However, these findings are limited by a lack of information regarding maternal medical comorbidities such as diabetes that may impact neonatal outcomes. These results were unchanged when the authors excluded infants born above the 97th percentile of birth weight for gestational age, but it is still possible that these findings may have been impacted by misdating of LGA infants.

LGA birth weight and birth defects

Fetal overgrowth may be associated with increased risk for minor congenital anomalies. A retrospective case-control study of more than two million births in Latin America found that .

after adjusting for covariates including maternal diabetes, LGA was associated with the following anomalies: talipes calcaneovalgus (OR 4.82), hip subluxation caused by intrauterine deformation (OR 1.63), hydrocephaly (OR 3.1), combined angiomas (OR 2.77), and non-brown pigmented nevi (OR 1.46).[23] The authors of a separate report from the Texas Birth Defects Monitoring Division found that infants with congenital anomalies were more likely than infants without birth defects to have a birth weight ≥ 4500 grams (OR 1.65, 95% CI 1.39-1.96).[24]

LGA birth weight and neonatal metabolic abnormalities

LGA infants may have increased intrauterine exposure to excessive nutrients, especially glucose, which may result in hyperinsulinemia, increased utilization of oxygen and glucose, and oxidative stress.[25 26] Compared to their AGA counterparts, infants with LGA birth weight may also have increased levels of cord blood leptin and insulin as well as decreased levels of adiponectin and soluble leptin receptor.[27 28] Ahlsson, et al. also found that infants with LGA birth weight demonstrate increased lipolysis and a propensity for decreased insulin sensitivity at birth.[26] Although the mechanisms are incompletely understood, metabolic abnormalities seen in LGA infants may lead to complications including hypoglycemia, polycythemia, and asphyxia.

Hypoglycemia can occur in LGA infants when the placental supply of glucose is interrupted at birth, even in the absence of maternal diabetes. Groenendaal, et al. used the Netherlands Perinatal Registry data from 1997 to 2002 to evaluate the relationship between LGA birth weight ($>90^{\text{th}}$ percentile) and neonatal hypoglycemia in infants without other risk factors for hypoglycemia. Among LGA infants of women without diabetes, hypoglycemia occurred in

10.5% and seizures possibly related to hypoglycemia occurred in 0.2% of these infants. In another large case series of 887 LGA infants (birth weight >90th percentile) born to women without diabetes, 16 percent had hypoglycemia (blood glucose level <40 mg/dL) during the first 24 hours of life.[30] These data highlight the importance of routine post-delivery glucose monitoring in infants with LGA birth weight.

Polycythemia also occurs more frequently in LGA infants born to women both with and without diabetes when compared to AGA infants.[31 32] While the precise mechanism of LGA-associated polycythemia is unknown, it is thought to be due to increased production of erythropoietin which results from fetal hypoxia caused by the increased oxidative demands associated with hyperglycemia and hyperinsulinemia.

LGA birth weight and neonatal intensive care admission

LGA infants are often admitted to the neonatal intensive care unit (NICU) for indications beyond hypoglycemia. This was demonstrated by a study from the Arizona Neonatal Intensive Care Program (NICP) for infants born between 1994-1998.[33] In this study, the characteristics of infants with a birth weight >4000 grams who were enrolled in the NICP (criteria included prolonged NICU stay [>72 hours], readmission to a NICU, or transport to a NICU) were described. The four most common diagnoses in LGA infants (accounting for 53 percent of the admission diagnoses) were respiratory distress (19 percent), transient tachypnea of the newborn (16 percent), hypoglycemia (9 percent), and meconium aspiration (9 percent).[33] In a separate analysis, Tolosa et al. found that 11.7 percent of infants with a birth weight >4000 grams were admitted to the NICU.[34] The most common diagnoses leading to NICU admission included respiratory distress, suspected sepsis, hypoglycemia,

and perinatal depression. The average length of stay for all macrocosmic infants admitted to the NICU was 8 ± 6 days, and this was increased to 22 ± 13 days for infants with grade 3 macrosomia.

LGA infants are more likely to develop respiratory distress than appropriate for gestational age infants.[4 33] There are several potential causes for the increased risk for respiratory complications. Some data have suggested that there is an increased risk for respiratory distress syndrome (RDS) in newborns of women with diabetes.[35] The higher incidence of cesarean deliveries in LGA infants likely also increases the risk of respiratory complications in the newborn.[36] In addition, meconium aspiration may be more common in LGA infants.[4]

LGA birth weight and shoulder dystocia

Larger infants, especially with macrosomia, are at increased risk for shoulder dystocia, brachial plexus injury and clavicular fracture,[4 37 38] and the risk of birth injury increases with the severity of macrosomia.[4] Shoulder dystocia occurs in 0.2-3.0% of all vaginal deliveries,[39] but this risk increases to 9-14% when birth weight is more than 4500 grams.[16 40 41] Maternal diabetes further increases the risk for shoulder dystocia. Among pregnancies complicated by diabetes, a birth weight of 4500 grams or more has been associated with a 20-50% risk for shoulder dystocia.[16 40]

Shoulder dystocia is associated with increased risk for birth injury, and the risk for birth injury among LGA infants is higher for vaginal compared to cesarean delivery. In one large case series, birth injury was three times more likely when LGA infants (birth weight 4500 to 5000 grams) were delivered vaginally compared with cesarean delivery (9.3 vs 2.6%,

p<0.003).[37] Macrosomic newborns also have a 10-fold increased risk for clavicular fracture.[33] In addition to fractures, brachial plexus injuries are more common in macrosomic infants. In the United States, transient and persistent neonatal brachial plexus injuries complicate 1.5 per 1,000 total births.[42] A meta-analysis found that the odds for brachial plexus injury was increased 11-fold among infants who weigh more than 4000 grams and 20-fold among infants weighing more than 4500 grams, although mode of delivery was not accounted for.[43] Case-control studies demonstrate that the odds of brachial plexus palsy among newborns delivered vaginally is 18-fold to 21-fold higher when birth weights exceed 4500 grams,[44-46] with absolute rates between 2.6% and 7%.[47 48] Brachial plexus palsy also can occur in the absence of shoulder dystocia or with cesarean birth.[42] Large case series confirm that 80-90% of brachial plexus palsy will resolve by 1 year of age,[49 50] indicating that most cases of brachial plexus palsy will resolve without permanent disability. However, birth weights greater than 4500 grams are associated with a higher risk for persistent injury.[51 52]

LGA birth weight and stillbirth or neonatal death

Macrosomic infants are at increased risk for perinatal asphyxia, and this risk may be highest in offspring of women with diabetes.[3 4 37 53] The higher frequency of low Apgar scores in LGA compared with AGA infants provides indirect evidence of the increased risk for perinatal asphyxia in LGA infants. Contributing factors are thought to include increased oxygen utilization due to fetal hyperglycemia and hyperinsulinemia, and complications of delivery related to shoulder dystocia.

Although neonatal mortality is higher in LGA than in AGA term infants, it is only substantially higher in only the most severe grade of macrosomia. In a study of all singleton, term live births between 1995 and 1997, the neonatal mortality rate was only higher in infants born with grade 3 macrosomia (BW >5000 g) compared with normal birth weight (<4000g) infants (adjusted OR 2.69, 95% CI 1.91-3.8).[4] Similar results were noted in a Canadian study that reported more than a twofold increased risk of deaths in term infants with BW greater than the 97th percentile compared with AGA term infants.[53] Recent data also indicate that the risk for stillbirth may be increased in the setting of fetal macrosomia when the birth weight exceeds 4500 grams (OR 1.27, 95% CI 1.22-1.32) or 5000 grams (OR 5.69, 95% CI 5.69-6.22).[54]

Long-term outcomes associated with LGA birth weight

Childhood development and outcomes associated with LGA birth weight

It is of utmost importance to understand how LGA birth weight affects long-term growth and development. Data increasingly show that the origins of obesity begin very early in life, with multiple risk factors present before 2 years of age.[55] Multiple studies have found an association between birth weight and BMI or overweight/obesity in childhood and young adulthood.[56-58] Traditionally it was thought that LGA birth weight was followed by a decreasing growth trajectory in infancy.[59] However, more recent data suggests that this may not be the case. Hediger, et al. utilized data from the Third National Health and Nutrition Examination Survey (NHANES III) to compare early childhood growth patterns of LGA compared to AGA newborns.[60] They found that infants with LGA birth weight were heavier, taller, and had a larger head circumference through 47 months of age. These same

investigators also used the NHANES III data to assess the impact of LGA birth weight on muscularity and “fatness” in childhood.[61] They found that from ages of 2 to 47 months, infants with LGA birth weight had higher levels of muscularity and less excess fatness. This was particularly true at the youngest gestational ages. Hediger, et al. also found that children born LGA remain longer and heavier from 36-83 months of age, and that children born LGA may be prone to increasing accumulation of fat in early childhood.[62] However, they were unable to account for maternal characteristics such as diabetes in their analyses. Kapral, et al. found that infants who either had a birth weight at term greater than 4,500 grams or those who were born preterm with a birth weight z-score greater than the 90th percentile for gestational age subsequently had higher BMI z-scores from kindergarten to second grade when compared to normal birthweight controls.[63] Data from the Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in Children and Infants Study demonstrated that a birth weight >90th percentile in the absence of maternal diabetes was associated with increased odds of overweight/obesity in both boys (OR 1.7, 95% CI 1.3-2.2) and girls (OR 1.6, 95% CI 1.3-2.0), while birth weight >90th percentile in the setting of maternal diabetes demonstrated a significant association with childhood weight only in girls (OR 2.6, 95% CI 1.1-6.4).[64]

Several studies have examined infant and early childhood factors that are associated with growth in infancy. In a Norwegian cohort, Lande, et al. compared feeding practices between infants of high ponderal index (PI – calculated using the formula mass (kg)/height (m³)) at birth (PI above the 90th percentile) and normal PI at birth (PI between 10th and 90th percentiles) and examined how birth size and infant feeding practices were related to BMI at 12 months.[65] They found that infants with a higher PI at birth had a shorter duration of

exclusive breastfeeding. In addition, both high PI at birth and short-term exclusive breastfeeding were associated with a higher BMI at 12 months, highlighting the complex interplay between birth weight and infant feeding practices on infant growth. Although prior cross-sectional work found that compared to normal-weight infants, larger infants have similar parent-reported eating behaviors and feeding practices, infants with a birth weight >4000 grams who maintained a high weight-for-length at 7 to 8 months of age had lower maternal-reported satiety responsiveness and maternal social interactions during feeding.[66] Sleep may also play an important role in the growth and development of infants who are macrosomic at birth. Goetz, et al. examined sleep practices during infancy and toddlerhood among children with a birth weight >4000 grams.[67] They found that longer sleep duration in the first several years of life is associated with development of normal BMI among macrosomic infants. However, there is a paucity of interventional trials designed to improve health outcomes specifically targeting infants with LGA birth weight.

Data suggest that LGA birth weight may also be associated with metabolic disturbances in childhood that portend the development of later diabetes and insulin resistance. A cross sectional study of prepubertal children found that LGA birth weight was associated with increased insulin resistance and oxidative stress, even in normal weight children.[68] Several additional studies show that a history of LGA birth weight is associated with increased insulin resistance among prepubertal children. However, data are conflicting regarding the magnitude and direction of alterations in adiponectin that accompany these changes in insulin resistance.[69 70] Both heavier birth weight and higher weight gain after birth are associated with increased risk for hypertension during childhood.[71]

There is also strong interest in the impact of fetal overgrowth on long-term neurodevelopmental outcomes, but the available data are limited. In a study of 2930 children from the Early Childhood Longitudinal Study, Birth Cohort (ECLS-B), the cognitive function of 271 children with birth weights greater than or equal to the 90th percentile did not differ from that of children with normal birth weight (defined as a birth weight between the 5th and 89th percentile) at 9 months, and 2, 3.5, and 5.5 years of age.[72] While these data are reassuring, observational studies have suggested that maternal GDM and type 2 diabetes (both of which are associated with increased risk for fetal overgrowth) may be associated with an increased risk for autism and other adverse neurodevelopmental outcomes.[73] [74]

Fetal overgrowth has also been associated with several additional adverse outcomes that may be less intuitive but warrant mention. Although the mechanism is uncertain, LGA birth weight has been associated with an increased risk for dental caries in early childhood.[75] Fetal overgrowth has also been linked to several childhood leukemias as well as tumors of the central nervous system, renal tumors, soft tissue sarcomas, neuroblastoma, lymphoma, and germ cell tumors.[76 77] [78] Further work is needed to clarify the nature of these relationships.

Longer-term outcomes associated with LGA birth weight

LGA birth weight has also been linked to obesity in later life. Studies from both the Netherlands and Israel found that higher birth weight was associated with an increased risk for overweight and obesity at 17-26 years of age.[79 80] In a study from Sweden, mothers born LGA were more likely to be overweight or obese than their AGA counterparts. Those overweight women were also more likely to give birth to LGA infants, propagating a vicious

cycle.[81] LGA birth weight has also been linked to later medical comorbidities including type 2 diabetes[82 83] and cardiovascular disease.[84]

Conclusions

Fetal overgrowth is associated with multiple adverse short- and long-term adverse outcomes, and we still have much to learn regarding how to optimize outcomes for these infants. Birth weight is distinct from body composition, and more robust studies are needed to clarify the pattern of fat and lean body mass distribution of infants with LGA birth weight to assess whether we can accurately identify babies at highest risk for later-life metabolic complications. We know that treating maternal diabetes can reduce the risk for LGA birth weight. However, the majority of LGA infants are born to women without diabetes, and there are few consistently successful interventions targeting maternal obesity and excess gestational weight gain. Nutrition before conception and during pregnancy plays a fundamental role in influencing maternal weight gain, fetal growth, and neonatal outcomes,[85 86] but there is a paucity of data regarding optimal maternal nutrition in pregnancies complicated by LGA fetal growth. Once an LGA infant is born, there is also much to learn about how to optimize health and alter the trajectory towards obesity and metabolic disease. The early postnatal nutritional environment, and in particular breastfeeding, may modulate the long-term risks of obesity.[87] However, many available epidemiologic studies do not report information on infant feeding practices. Detailed information on pregnancy factors associated with excess fetal growth and infancy/early childhood factors associated with later obesity will be critical to develop evidence-based interventions to improve the health of infants with LGA birth weight.

Table 1: Neonatal Outcomes by Macrosomia Class

	Control (3000-3999 g) % with outcome aOR (95% CI)	Grade 1 (4000-4499 g) % with outcome aOR (95% CI)	Grade 2 (4500-4999 g) % with outcome aOR (95% CI)	Grade 3 (≥5000 g) % with outcome aOR (95% CI)
Birth Injury	0.3 Ref	0.5 1.99 (1.92-2.05)	0.8 3.14 (2.96-3.32)	1.3 4.53 (3.95-5.19)
Apgar score ≤3 (5 min)	0.1 Ref	0.1 1.30 (1.21-1.39)	0.2 2.01 (1.76-2.29)	0.5 5.20 (4.09-6.62)
Assisted ventilation ≥30 min	0.3 Ref	0.3 1.19 (1.14-1.23)	0.5 1.85 (1.73-1.99)	1.3 3.96 (3.45-4.55)
Meconium aspiration	0.2 Ref	0.3 1.28 (1.23-1.34)	0.4 1.65 (1.52-1.79)	0.6 2.61 (2.15-3.16)
Neonatal mortality rate (<28 days)	0.07 Ref	0.06 0.87 (0.80-0.96)	0.07 1.0 (0.83-1.21)	.19 2.69 (1.91-3.80)
Infant mortality rate (<1 yr)	0.22 Ref	0.16 0.82 (0.78-0.86)	0.18 0.91 (0.80-1.02)	0.40 2.01 (1.58-2.55)

All logistic regression models include measures of maternal race, age, education, marital status, prenatal care use, parity, previous macrosomic birth, previous pregnancy loss, maternal diabetes

mellitus, hypertension, smoking, alcohol use, and gestational age; the reference group was 3000-3999 g. (Data adapted from Boulet SL, Alexander GR, Salihu HM, Pass M. Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol* 2003; 188:1372-8.)

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