## OBSTETRICS

# Congenital diaphragmatic hernia: does gestational age at diagnosis matter when evaluating morbidity and mortality?

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**OBJECTIVE:** The objective of the investigation was to study the relationship between gestational age at diagnosis and mortality and morbidity in fetuses with an isolated congenital diaphragmatic hernia.

**STUDY DESIGN:** Between January 2008 and November 2013, 377 live births with isolated congenital diaphragmatic hernia diagnosed antenatally at a known gestational age were recorded in the database of the French National Center for Rare Diseases. The primary outcome studied was mortality estimated at 28 days and at 6 months. The secondary outcome was morbidity evaluated by pulmonary arterial hypertension at 48 hours, oxygen therapy dependence at 28 days, oral disorders, enteral feeding, and prosthetic patch repair. Analyses were adjusted for the main factors of congenital diaphragmatic hernia severity (side of the hernia, thoracic herniation of the liver, gestational age at birth, lung-to-head ratio, and prenatal treatment by tracheal occlusion.

**RESULTS:** Mortality rates at 28 days decreased significantly ($P < .001$) when gestational age at diagnosis increased: 61.1%,

39.2%, and 10.4% for a diagnosis in the first, second, and third trimester, respectively. Adjusted odds ratios were 3.12 [95% confidence interval, 1.86–5.25] and 0.35 [95% confidence interval, 0.18–0.66] for a diagnosis in the first and third trimesters, respectively, compared with a diagnosis in the second trimester. Similarly, morbidity decreased significantly when gestational age at diagnosis increased, and the trend remained significant after adjustment for the main factors of congenital diaphragmatic hernia severity ($P < .001$).

**CONCLUSION:** Gestational age at diagnosis is an independent predictor of postnatal prognosis for children presenting an isolated congenital diaphragmatic hernia and should be taken into account when estimating postnatal morbidity and mortality.

**Key words:** congenital diaphragmatic hernia, first trimester, morbidity, mortality, prognosis

Congenital diaphragmatic hernia (CDH) is a severe congenital anomaly that occurs in 2–5 in 10,000 births.[1-3] Over the past 20 years, prenatal detection of CDH has improved worldwide, reaching 60% in Europe.[4-6] Newborn outcome has improved over the years, especially when birth of

affected fetuses takes place in a center with an optimal neonatal intensive care unit and pediatric surgery. Survival rates may reach 80% in centers with a high case load of CDH per year.[7,8]

Prenatal management of fetuses with CDH (for instance, fetal surgery by endoscopic tracheal occlusion) as well as postnatal management requires proper evaluation of the prognosis. Pulmonary hypoplasia and persistent pulmonary hypertension are the 2 main determinants of neonatal mortality and morbidity, and new tools have been focused on their evaluation.[9] Few ultrasound markers are available. The prognosis is established on the basis of the side of the hernia, the position of the liver, the amniotic fluid volume, and lung parameters such as lung to head circumference ratio

**Flowchart of the French congenital diaphragmatic hernia database**
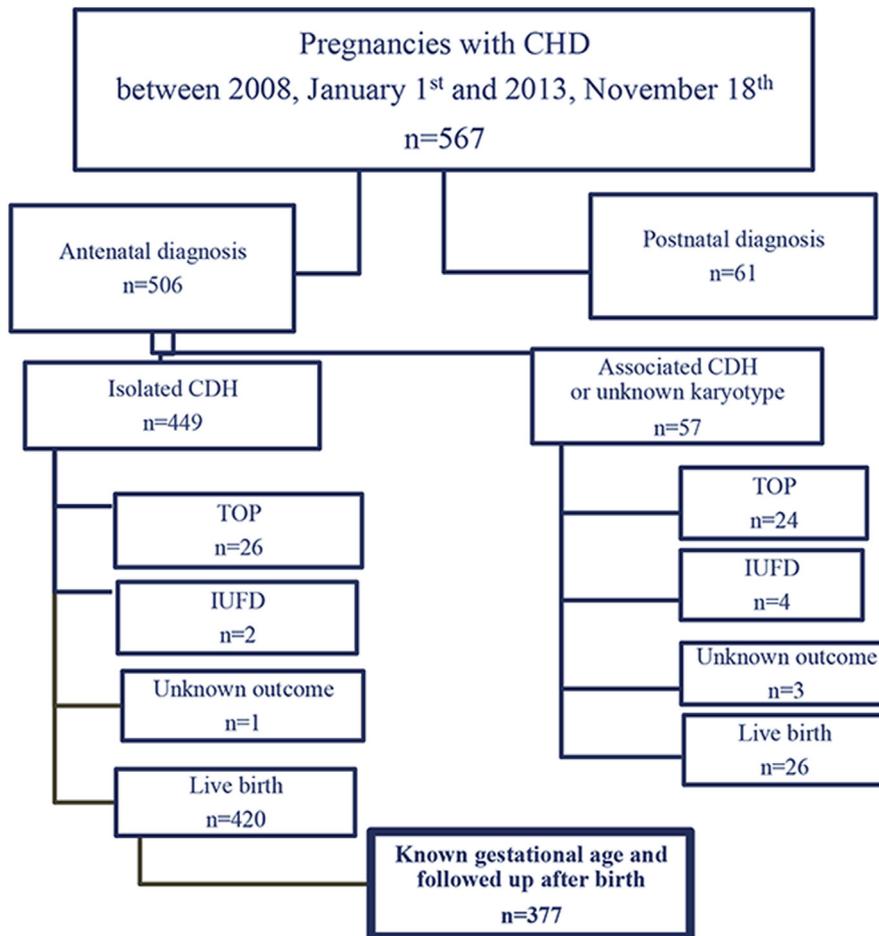


CDH, congenital diaphragmatic hernia; IUFD, intrauterine fetal death; TOP, termination of pregnancy.

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(LHR),[10-13] with a relatively low predictive value.

Gestational age at the time of diagnosis has been advocated as a potential prognostic factor, but it remains a matter of debate. Some studies have found that fetuses with CDH diagnosed after 25 weeks of gestation (WG) have lower mortality rates,[11,14-16] whereas others, including a recent one, found no difference in mortality rate between early (<25 WG) and late prenatal (>25 WG) diagnosis.[9,17]

Although the diagnosis of CDH is more often made in the second trimester, it is possible as early as the first trimester if the following exist: (1) the technical examination conditions are optimal; (2) attention is paid to the diaphragm, to the position of the stomach, and the situs of the heart when performing the scan; and (3) the viscera have already migrated into the chest.

First-trimester diagnosis of CDH is more frequent in cases of nuchal translucency or when CDH is associated with other malformations.[18,19] In France, women have an average of 5 ultrasound scans during their pregnancy, and 86.5% of pregnant women have first-trimester ultrasound with nuchal translucency measurement.[20]

The prognosis of fetuses with isolated CDH diagnosed early in pregnancy remains unknown. Although it is logical to think that the early occurrence of pulmonary hypoplasia worsens the prognosis

in comparison with later diagnosis, this has not been established or studied in a large enough sample.

The aim of the present study was to investigate the relationship between gestational age at diagnosis and morbidity and mortality in fetuses with isolated CDH.

## MATERIALS AND METHODS

A CDH database was established in France in 2007 by the National Center for Rare Diseases. At an annual national meeting, participating perinatal centers are encouraged to enter CDH cases in the database. Diagnosis, management, and delivery in CDH cases were standardized in the network. Pregnancies were managed in a fetal medicine unit, and deliveries occurred in a tertiary care center. In all cases amniocentesis and ultrasound was offered to rule out chromosomal abnormality and associated malformations. Microarrays were not performed on a routine basis at this time. Confirmation of diagnosis and LHR measurement were done by a referring physician.

Isolated left CDH was defined as CDH with a normal karyotype and no other malformation detected at ultrasound. The newborns were followed up until 6 months. All babies were treated following a standardized protocol established by the members of the Center for Rare Diseases.[21,22] Neonates were intubated in the delivery room and admitted to a neonatal intensive care unit. Ventilatory support was initiated in all cases, with high-frequency oscillation ventilation when necessary.

Extracorporeal membrane oxygenation (ECMO) was not used because its usefulness is still debated because of the risk of long-term complications. Indeed, the use of ECMO is associated with a higher risk of neurological impairment.[23,24] Whether the increased incidence of adverse outcome associated with ECMO indicates a more severe form of CDH or reflects ECMO-associated complications is still a matter of debate. In general, ECMO is reserved for the sickest newborns.[25]

Surgical repair (with or without a prosthetic patch) was done in all cases as

### TABLE 1
### Ultrasound examination of liveborns with isolated CDH diagnosed antenatally (n = 377)

| n (%) or median [IQR] | Total | First trimester (n = 18) | Second trimester (n = 263) | Third trimester (n = 96) |
|---|---|---|---|---|
| Left-sided CDH | 319 (0.85) | 17 (0.94) | 223 (0.85) | 79 (0.82) |
| Thoracic herniation of the liver | 152 (0.41) | 7 (0.42) | 125 (0.48) | 20 (0.22) |
| $LHR_{o/e}$ | 0.42 [0.33–0.54] | 0.41 [0.34–0.44] | 0.40 [0.33–0.52] | 0.50 [0.37–0.68] |

*CDH*, congenital diaphragmatic hernia; *IQR*, interquartile range; $LHR_{o/e}$, ratio of the observed over the expected lung-to-head circumference ratio.

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soon as the neonate was hemodynamically stable, usually within 24–48 hours.

Data were recorded through a web-based questionnaire accessible by password. They concerned gestational age established at diagnosis, the side of the hernia, the position of the liver, LHR, associated anomalies, and postnatal follow-up data such as mortality, persistent pulmonary hypertension of the newborn (PPHN), and oxygen therapy dependence. Gestational age was established in all cases by ultrasound measurement of crown-rump length between 11 and 14 WG.

The LHR was computed by multiplying the 2 longest perpendicular diameters of the contralateral lung at the level of the 4-chamber view of the heart and dividing this by the head circumference.[14] LHR was routinely measured at the second-trimester ultrasound scan between 22 and 24 weeks. However, it could be measured later in pregnancy if CDH was diagnosed later. In practice, ratio of the observed over the expected lung-to-head circumference ratio ($LHR_{o/e}$) was used because it is independent of gestational age.[26] It is computed by dividing the observed LHR by the expected value for gestational age on 2-dimensional ultrasound.

The study was limited to isolated CDH (ie, normal fetal karyotype, absence of other structural anomalies), and terminations of pregnancy and intrauterine fetal deaths were excluded.

The primary outcome was neonatal mortality, which was evaluated at 28 days and at 6 months. The secondary outcome was postnatal morbidity, defined

### TABLE 2
### Outcome of the newborns with an isolated CDH according to the trimester of diagnosis

| Outcome | Total (n = 377) | Trimester of CDH diagnosis | | | P value[a] |
|---|---|---|---|---|---|
| | | First (n = 18) | Second (n = 263) | Third (n = 96) | |
| **Mortality** | | | | | |
| At 28 d | 32.9% (28.2–37.9) | 61.1% (35.7–82.7) | 39.2% (33.2–45.3) | 10.4% (0.05–18.3) | < .001 |
| At 6 mo[b] | 39.0% (34.0–44.2) | 82.3% (56.6–96.2) | 44.5% (38.3–50.8) | 16.1% (0.09–25.2) | < .001 |
| **Respiratory morbidity** | | | | | |
| PPHN at 48 h[c] | 61.6% (56.0–66.9) | 100% (78.2–100) | 70.0% (63.3–76.0) | 35.9% (26.1–46.5) | < .001 |
| Oxygen dependence at 28 d[d] | 37.7% (31.7–44.0) | 100% (59.0–100) | 46.5% (38.6–54.6) | 16.3% (9.2–25.8) | < .001 |
| **Gastrointestinal morbidity[e]** | | | | | |
| Oral disorders | 19.3% (14.3–25.1) | 33.3% (0.84–90.6) | 24.6% (17.7–32.7) | 9.1% (3.7–17.8) | .006 |
| Enteral feeding | 15.0% (10.6–20.4) | 0.0% (0–70.8) | 20.1% (13.8–27.8) | 6.4% (2.1–14.3) | .011 |
| **Surgery[c]** | | | | | |
| Prosthetic patch repair | 27.1% (22.0–32.8) | 55.6% (21.2–86.3) | 32.6% (25.9–39.9) | 12.6% (6.5–21.5) | < .001 |

*CDH*, congenital diaphragmatic hernia; *PPHN*, persistent pulmonary hypertension of the newborn.

[a] *P* value for the association between outcome and gestational age at diagnosis was modeled by fractional polynomials; [b] Among newborns not lost to follow-up at 6 months (n = 364); [c] Among children who were alive at 48 hours of life (n = 323); [d] Among children who were alive at 28 days of life (n = 253); [e] Among children who were alive at 6 months (n = 222).

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## FIGURE 2
### Mortality rate at 28 days according to gestational age at diagnosis of CDH
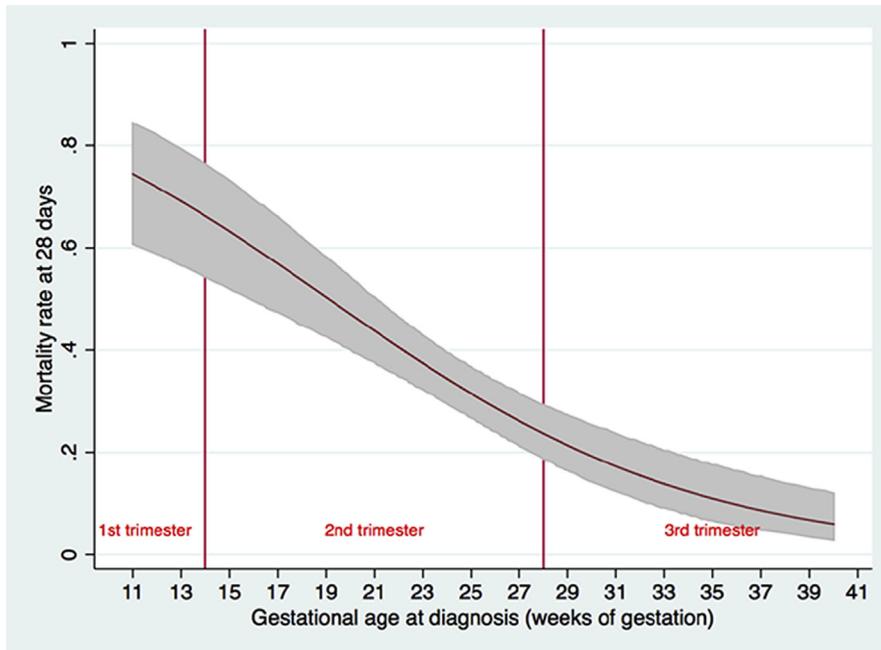


The association between gestational age at diagnosis and mortality was modeled with fractional polynomials and is statistically significant ($P < .001$). The sample size was 377. The *gray band* indicates the confidence interval of the curve.

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by respiratory and gastrointestinal morbidity. Respiratory morbidity was characterized by PPHN at 48 hours and oxygen therapy dependence at 28 days. PPHN (assessed by echocardiography at 48 hours of life) was defined by pulmonary artery systolic pressure above 40 mm Hg. It was assessed among children who were alive at 48 hours.

Oxygen therapy dependence at 28 days was assessed among children who were alive at 28 days. Gastrointestinal morbidity was characterized by oral disorders (defined by gastroesophageal reflux disease and/or swallowing disorders) and enteral feeding. It was studied among children who were alive at 6 months.

We also studied prosthetic patch repair during surgery as a marker of a more severe defect and worse prognosis.[27]

To take into account a potential effect of the center, we adjusted for the size of the center, defined by the number of CDH cases per year: fewer than 5 cases per year; between 6 and 15 cases per year; more than 16 cases per year.

This study received the approval of the Scientific Committee of the National Center for Rare Diseases and the Institutional Review Board of the southern Paris area (referent Comité de Protection des Personnes 14−044).

### Statistical analysis
Descriptive results are displayed as a percentage or median and interquartile range. The relationships between gestational age at diagnosis and outcome (mortality or morbidity) were modeled with a logistic regression using fractional polynomials that give an optimal data fit.[28] This method provides curves and their 95% confidence intervals and allows calculation of odds ratios for mortality and morbidity after having divided gestational age into the usual 3 trimesters ($\leq$14 WG, 15−28 WG, and $\geq$29 WG).[29,30] Univariate analyses were first conducted, and then adjustments were

made for the factors associated with CDH severity: side of the hernia, thoracic herniation of the liver, gestational age at birth, $LHR_{o/e}$, and treatment by fetal tracheal occlusion.

The statistical analyses were performed with Stata 12 (StataCorp, College Station, TX).

### RESULTS
Between January 2008 and November 2013, 567 pregnancies with CDH were recorded in 30 fetal medicine units. Of these, 506 (89.2%) were diagnosed antenatally and 449 with isolated CDH (Figure 1). Of these 449 pregnancies, 420 ended in a live birth after exclusion of 26 terminations of pregnancy, 2 intrauterine fetal deaths, and 1 of unknown outcome. Among those 420 live births, gestational age at diagnosis was unknown for 26 and follow-up at 28 days after birth was not complete in the database for 17, leaving 377 cases for the sample analyzed.

In this sample, the median birthweight was 2950 g (interquartile range, 2500−3300). The median gestational age at diagnosis was 23 + 5 WG (interquartile range, 22−29); 18 cases were diagnosed in the first trimester, 263 in the second, and 96 in the third. Table 1 shows the results of the prenatal ultrasound examination. In these 377 cases, 364 children (96.6%) were followed up until 6 months.

The mortality rate was 32.9% at 28 days and 39.0% at 6 months (Table 2). Among neonates who died before 28 days of life, 18% died immediately on the first day of life in the delivery room.

There was a statistically significant relationship between gestational age at diagnosis and mortality at 28 days, as shown by Figure 2, in which the mortality rate decreases steadily with the date of diagnosis. Mortality rates at 28 days according to the trimester of diagnosis were 61.1%, 39.2%, and 10.4% in the first, second, and third trimesters, respectively ($P < .001$) (Table 2). Similarly, mortality rate at 6 months decreased significantly with the trimester of diagnosis ($P < .001$): 82.3%, 45.5%, and 16.1% for cases diagnosed in the

first, second, and third trimesters, respectively.

After adjustment for the main factors of severity of CDH (see *Statistical analysis* section), the relationship between gestational age at diagnosis and mortality at 28 days remained significant ($P < .001$, Table 3). Adjusted odds ratios and 95% confidence intervals were 3.10 (1.85−5.21) and 0.35 (0.18−0.66) for the first and third trimesters, respectively, compared with the second trimester.

Results were similar for respiratory morbidity characteristics. For instance, the rate of PPHN at 48 hours was significantly greater when diagnosis was made earlier in the pregnancy (Figure 3 and Table 2). This relationship remained significant after adjustment for the main factors of CDH severity (Table 3).

Prosthetic patch repair at surgery was significantly more common for CDH diagnosed earlier in pregnancy, with a rate of 55.6% for children diagnosed in the first trimester, 32.8% for those diagnosed in the second trimester, and 12.6% for those diagnosed in the third trimester.

All the results remained similar after adjustment for size of center.

## COMMENT

Our results show a significant relationship between gestational age at CDH diagnosis and morbidity and mortality, even after adjustment for factors of severity of CDH. This suggests that gestational age at diagnosis is an independent predictor of the morbidity and mortality of isolated CDH.

Gestational age at diagnosis as a prognostic factor is a subject of debate in the literature. Some authors have concluded that a diagnosis before 25 WG is associated with higher mortality than diagnosis after 25 WG.[14-16] Other studies showed that gestational age at diagnosis has no effect on postnatal prognosis.[2,9,31,32] However, these results need to be interpreted with caution: the number of patients was always small and the studies were not specifically designed or powered to evaluate gestational age at diagnosis as a potential prognostic factor. Moreover, gestational age at diagnosis has never been considered as a continuous variable but as

a categorical variable, and this contributes to a lack of statistical power in these studies.[33]

Our findings suggest that CDH forms diagnosed early are characterized by a larger opening and a need for patch repair. They are therefore more severe.[34] However, adjustment for liver position and LHR$_{o/e}$, which reflects the degree of pulmonary hypoplasia and correlates not only with neonatal mortality but also with morbidity,[27,32] did not change the relation between gestational age at diagnosis and severity of outcome. Thus, the early diagnosis of CDH appears to be a prognostic factor by itself.

The disturbance of embryological mechanisms leading to CDH is not fully understood, and this has led to a variety of interpretations. In the nitrofen model of CDH, because of the early nitrofen interference with lung development

before diaphragm development, a dual mechanism was postulated, which may explain pulmonary hypoplasia in CDH by 2 insults: a primary pulmonary abnormality affecting both lungs before diaphragm development and compression occurring secondarily and affecting the ipsilateral lung after defective diaphragm development by mechanical forces.[35] However, it is now clearly established that the diaphragmatic malformation is not a consequence of the impaired development of the adjacent lung tissue.[36]

The opening in the diaphragm is present from the embryological period, but it is impossible to tell precisely when the viscera migrate into the thorax. However, it is logical to hypothesize that the earlier the insult during lung development, the more severe the disturbance in lung parenchyma and vascularization development will be, leading to severe

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**TABLE 3**
**Adjusted odds ratios and 95% confidence intervals for trimester of CDH diagnosis**

| Variable | Trimester of CDH diagnosis | | | |
| | First (n = 18) | Second (n = 263) (reference) | Third (n = 96) | P value[a] |
|---|---|---|---|---|
| **Mortality** | | | | |
| At 28 d | 3.12 [1.86−5.25] | 1 | 0.35 [0.18−0.66] | < .001 |
| At 6 mo[b] | 3.09 [1.86−5.11] | 1 | 0.38 [0.21−0.70] | < .001 |
| **Respiratory morbidity** | | | | |
| PPHN at 48 h[c] | 2.85 [1.76−4.64] | 1 | 0.27 [0.15−0.49] | < .001 |
| Oxygen dependence at 28 d[d] | 3.22 [1.52−6.81] | 1 | 0.18 [0.08−0.39] | < .001 |
| **Gastrointestinal morbidity[e]** | | | | |
| Oral disorders | 1.65 [0.73−3.75] | 1 | 0.66 [0.28−1.52] | .014 |
| Enteral feeding | 4.56 [1.58−13.2] | 1 | 0.58 [0.21−1.59] | .002 |
| **Surgery[c]** | | | | |
| Prosthetic patch repair | 1.47 [0.85−2.53] | 1 | 0.57 [0.29−1.10] | < .001 |

Adjustment for side of the hernia, thoracic herniation of the liver, gestational age at birth, LHR$_{o/e}$, and a treatment by fetal therapy occlusion.

*CDH*, congenital diaphragmatic hernia; *LHR$_{o/e}$*, ratio of the observed over the expected lung-to-head circumference ratio; *PPHN*, persistent pulmonary hypertension of the newborn.

[a] *P* value for the association between outcome and gestational age at diagnosis modeled by fractional polynomials; [b] Among newborns not lost to follow-up at 6 months (n = 364); [c] Among children who were alive at 48 hours (n = 323); [d] Among children who were alive at 28 days (n = 253); [e] Among children who were alive at 6 months (n = 222).

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**Pulmonary hypertension rate at 48 hours of life according to gestational age at diagnosis of CDH**
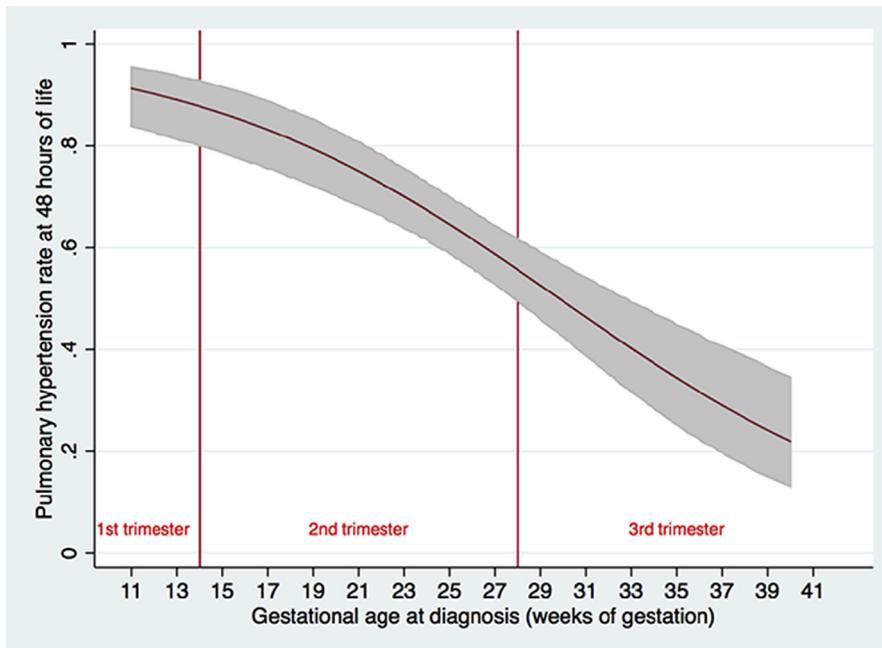


The association between gestational age at diagnosis and pulmonary hypertension rate was modeled with fractional polynomials and is statistically significant ($P < .001$). The sample size was 323. The *gray band* indicates the confidence interval of the curve.

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lung hypoplasia and persistent pulmonary hypertension, although this has never been demonstrated. Our results confirm this hypothesis because early diagnosis was a prognostic factor for morbidity and mortality.

Moreover, because an early diagnosis remained a prognostic factor independent of the severity of CDH (and especially of the degree of lung compression as measured by LHR$_{o/e}$), this argues in favor of a specific role of CDH forms occurring early. Beyond the later lung compression that happens whatever the earliness of the start of CDH, the primary pulmonary abnormality because of a very early insult to the growing lung should play a role.

Our sample of CDH cases is not exhaustive because only cases referred to tertiary centers with fetal medicine units were recorded and because termination of pregnancy and intrauterine fetal death and associated forms are underrepresented, compared with published rates.[4,37] However, our study focuses on the prognosis of live children with CDH, so this does not alter our results because these cases have been excluded from the study sample.

Magnetic resonance imaging was not routinely used in our sample. It would allow better quantification of total fetal lung volume or herniation of the liver. However, it is very unlikely that it would modify the results on the relationship between gestational age at diagnosis and magnetic resonance imaging markers because these parameters will not be much modified in severe cases because the ipsilateral lung is small and most of the liver in the thorax.

Moreover, in France, women have access to induced abortion before 14 WG and may resort to this if an anomaly is diagnosed at the first-trimester ultrasound examination, possibly before

seeking appropriate prenatal counseling. However, such a decision is taken at a time when the severity of the disease is unknown. Furthermore, we verified that the characteristics of the recorded CDH remain steady over time. Therefore, it is unlikely that the selection of the sample introduced a bias because our study is devoted to the relationship between prenatal factors and morbidity and mortality.

Most results on prenatal predictive factors have been reported from a few large centers.[26,27,38,39] It is therefore difficult to generalize them to a larger category of centers. The strength of our study is that it is a national multicenter study including 30 tertiary centers with a large sample of patients with CDH, especially those diagnosed between 11 and 14 WG, with few lost to follow-up. We verified that adjustment for the category of center did not modify the results. Lastly, our series includes cases diagnosed between 2008 and 2013, so the accuracy of diagnosis should be quite uniform.

### Conclusion

Gestational age at diagnosis is an independent predictor of postnatal prognosis for children presenting isolated CDH. This result provides new information that sheds light on the embryological mechanisms leading to CDH. It may also help to advise parents with an antenatal diagnosis of isolated CDH. However, caution should be exercised when counseling parents because our results concerned only isolated cases of CDH and not all the associated anomalies that may be seen on the first-trimester ultrasound scan. ∎

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