Changing Epidemiology of Hypoplastic Left Heart Syndrome: Results of a National Swedish Cohort Study

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Background—Norwood surgery provides a palliative surgical option for hypoplastic left heart syndrome and has been available in Sweden since 1993. The practice of prenatal ultrasound screening was gradually implemented in the same era, resulting in an increased prenatal detection rate. Our primary aims were to study changes in the incidence of live births, prenatal detection rate, and the termination of pregnancies over time. The secondary aims were to study the proportion of live-borns undergoing surgery and to identify factors that influenced whether surgery was or was not performed.

Methods and Results—Neonates with hypoplastic left heart syndrome with aortic atresia born 1990-2010 were identified through national databases, surgical files, and medical records. The fetal incidence was estimated from the period when prenatal screening was rudimentary. The study period was divided into the presurgical, early surgical, and late surgical periods. The incidence was calculated as the overall yearly incidence for each time period and sex separately. Factors influencing whether surgery was performed were analyzed using Cox-logistic regression. The incidence at live birth decreased from 15.4 to 8.4 per 100 000. The prenatal detection rate increased from 27% to 63%, and terminations increased from 19% to 56%. The odds of having surgery was higher in the late period and higher in the group with prenatal diagnosis.

Conclusions—We observed a decrease in incidence of live-borns with hypoplastic left heart syndrome aortic atresia. There was in increase in prenatal detection rate and an increase in termination of pregnancy. The proportion of live-borns who underwent surgery increased between time periods. (J Am Heart Assoc. 2019;8:e010893. DOI: 10.1161/JAHA.118.010893.)

Key Words: fetal cardiovascular abnormality • fetal echocardiography • hypoplastic left heart syndrome • outcome

Hypoplastic left heart syndrome (HLHS) is a lethal congenital heart defect constituting 1% to 2% of all cardiac malformations.1 The incidence depends on the definition, but it has been reported to be 8 to 25 per 100 000 live-born neonates in the absence of selection during pregnancy.2-8 Norwood surgery has been available in Sweden since 1993. In many centers worldwide, comfort care is still offered as 1 of the management options.9-11 This was also the approach applied in Sweden during the first few years after the introduction of Norwood surgery, but as a consequence of improving surgical survival, the practice in Sweden changed to recommended surgery for all patients without obvious contraindications. In parallel with this, prenatal ultrasound screening has resulted in an increasing number of terminations of pregnancy due to HLHS.12,13

Aims

The primary aims of this study were to study changes over time in the incidence at live birth, prenatal detection rate, and termination of pregnancy. The secondary aims were to study the proportion of live-born neonates with HLHS who were surgically treated and to identify those factors influencing whether surgery was performed or not.

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010893

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Clinical Perspective

What Is New?

- The implementation of a prenatal screening program for malformations resulted in a decreased incidence of live-born neonates with hypoplastic left heart syndrome in Sweden.
- The proportion of live-born neonates with hypoplastic left heart syndrome that underwent surgery increased.

What Are the Clinical Implications?

- An overall decrease in incidence of live-born neonates with severe cardiac malformations such as hypoplastic left heart syndrome can have implications on planning and organization of pediatric cardiac surgery in a country or a region.
- In this study the decrease in incidence was counterbalanced by an increased proportion of live-born patients who underwent surgery that modified the effect of the observed decrease in incidence.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. The corresponding author had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Setting

In 1993-1994, pediatric cardiac surgery in Sweden was centralized in 2 centers, Lund and Gothenburg. A fetal screening program for congenital malformations was gradually implemented on a national level covering 95% of pregnant women in 2014. In 2009 the national consensus was to recommend the inclusion of the 4-chamber view of the fetal heart in the routine obstetrical scan at 18 to 20 weeks of gestation. Before 2009 the 4-chamber view was used at screening in some regions, and in risk-group screening in others. Outflow tracts and 3-vessel views have still not been fully implemented today (2018). Since 1974, termination of pregnancy has been a free maternal choice before 17 weeks and 6 days, and after approval by the Swedish National Board of Health and Welfare up to 21 weeks and 6 days when a severe congenital malformation exists. The study period included 3 years before Norwood surgery, which was introduced in 1993, and the first 18 years of Norwood surgery in Sweden. The study period was divided into 3 birth periods, each reflecting an evolutionary state of the influencing factors. During the first period, 1990-1992, no surgery was available, and the prenatal detection and termination rates were negligible. In the early birth period, 1993-2000, Norwood surgery was being implemented, and this period covers the initial years including the learning curve. The prenatal detection rate started to increase, although national coverage had not yet been achieved, and it revealed major regional differences. During the late birth period, 2001-2010, Norwood surgery had become an established surgical method available to all patients without obvious contraindications.

Patients

To be included in the study, birth had to have occurred between January 1, 1990 and December 31, 2010. HLHS was defined as aortic atresia (versus aortic stenosis) with mitral atresia or mitral stenosis. The corresponding International Classification of Diseases, 9th Revision (ICD-9) code was 746H but changed in 1997 to the International Classification of Diseases, 10th Revision (ICD-10) code Q23.4. Exclusion criteria were additional cardiac diagnoses apart from coarctation of the aorta and persistent left superior caval vein. Extracardiac malformations and/or chromosomal abnormalities, when noted before 28 days of life in the Swedish Medical Birth Register, were not classified as reasons for exclusion. To be included, patients had to be either deceased within the first 28 days of life without surgery or to have undergone Norwood surgery, a hybrid procedure, or a primary cardiac transplantation at any age. Patients were identified through searches of the Medical Birth Register, the Swedish Causes of Death Register, and the Swedish National Inpatient Register. These registers are managed by the National Board of Health and Welfare, and reporting is compulsory. Patients were identified in the registers from the ICD-10 code corresponding to the anatomical definition. In addition, the national forensic register was searched in order to identify neonates who had died at home without having a known diagnosis of a cardiac malformation. Each case was identified by a key number assigned by the Swedish National Board of Health and Welfare, with the same number in all registries, and the Swedish Registry of Congenital Heart Disease (Swedcon). The cases identified were cross-checked by searching Swedcon and surgical files from the 2 national surgical centers in Lund and Gothenburg and, when applicable, fetal databases. A case had to be registered with a coherent diagnosis in at least 2 of these sources to be included in our cohort. Information on fetal diagnosis for live-born neonates was found in the Medical Birth Register, Swedcon, fetal databases, and medical records. Patients were followed until first surgical intervention or death without surgery.

Ethics

The study was approved by the Regional Ethical Review Board at the University of Gothenburg (Registration number 137-12). No informed consent was required.
Data Analysis

The study period was divided into 3 birth periods, the presurgical period (1990-1992), the early birth period (1993-2000), and the late birth period (2001-2010). The incidence of HLHS at live birth was calculated as the overall yearly incidence and for each time period and sex separately. Possible outcomes for fetuses with HLHS were termination of pregnancy, live birth with no surgery, and live birth with surgery. Cases in which fetal demise had not been diagnosed prenatally were not considered. To evaluate changes in fetal outcome between the early and late birth periods, we assumed the same fetal incidence of HLHS in both periods. The fetal incidence of HLHS was estimated from the highest yearly incidence of HLHS observed during the period 1990-1992, when prenatal screening was still rudimentary. The number of terminations of pregnancy was defined as the difference between the expected and the actual number of live-born neonates with HLHS. The prenatal detection rate was defined as the number of terminations of pregnancy plus live-born neonates with prenatal HLHS diagnosis divided by the total number of fetuses with HLHS. Live-born neonates with HLHS were followed until surgery or death without surgery within 28 days of birth. Factors evaluated as predictors of whether surgery was performed or not were birth period, prenatal diagnosis, birth location, sex, gestational age ≤37 weeks, and birth weight ≤2500 g. Birth location was defined as either a pediatric cardiac surgery center (n=2), a university hospital without such surgery (n=6), or a regional hospital. Birth weight, birth length, and birth head circumference were compared to the norm in the population by using the Swedish standard deviation score.19

Statistics

The incidence rate ratio and 95% CI for the effect of early versus late birth period regarding the incidence of HLHS were estimated from a generalized estimating equation model with Poisson distribution and log-link function. For trend analysis of crude incidence rates over birth periods, the Joinpoint Regression Program, version 4.3.1.0 (National Cancer Institute, Bethesda, MD) was used. Stepwise logistic regression was performed to analyze factors that had a possible correlation to whether surgery was performed or not. The association with outcome was expressed as the odds ratio with 95% CI. The goodness of fit for the multivariable logistic model was tested by the Hosmer-Lemeshow test. For comparisons between 2 groups, Fisher exact test was used for dichotomous categorical variables, the Mantel-Haenszel chi-squared test for ordered categorical variables, and the Mann-Whitney U-test for continuous variables. All tests were 2-tailed and were conducted at a significance level of 0.05. Tests were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC) or SPSS software, version 24 (IBM Corporation, Armonk, NY).

Results

Study Population

There were on average 102 000 live births per year in Sweden during the period 1990-2010, resulting in a total number of 2.143 million live-born neonates during the study period, with a male-to-female ratio of 1.06. The complete national cohort of live-born neonates with HLHS during 1990-2010 included 256 patients. Two patients, undiagnosed before death, died in the community and were identified through the national forensic register.

Postnatal Diagnosis

Most live-born cases were diagnosed after birth (229 of 256), and the majority were diagnosed before discharge from the hospital (225 of 229). Four were registered in the Medical Birth Register as a “healthy neonate discharged from maternity ward.” Two of these 4 cases were readmitted at 2 and 6 days of life, respectively. One had sepsis and died at 8 days of life, and the other, with no additional diagnosis, died at 13 days. Two cases died at home and were diagnosed at postmortem examination. The 2 patients who died at home were excluded from further analysis because their register data were not known.

Background Characteristics of Live-Born Neonates

Of the 254 patients included in the study, 208 were born during the surgical era, of whom 121 underwent Norwood surgery. There were no hybrid procedures or primary cardiac transplantations performed. The mean gestational age at birth was 39.0 (range 29-42) weeks (n=251) and did not differ over time (P=0.71). Twenty-four patients (9.4%) were born prematurely at a mean of 34.0 (range 29-36) weeks. The median birth weight of boys (n=171) was 3340 (range 1645-4650) g, and that of girls (n=83) was 3138 (range 1324-4932) g. No significant differences were found in birth weight or head circumference between the 2 birth periods or between patients who had undergone surgery and those who had not. When adjusted for gestational age, the cohort was numerically lighter, shorter, and had smaller head circumference than the normal population (see Figure 1). Extracardiac malformations and/or chromosomal abnormalities were seen in 16 patients (6.3%). The most common of these were...
urogenital (n=4) and musculoskeletal malformations (n=4). Three patients had isolated severe malformations (esophageal atresia, lung hypoplasia, and malformation of the corpus callosum). Three patients had more than 1 malformation, and 2 of them had multiple malformations including 1 with trisomy 18. Twelve patients (4.7%) were born as 1 of twins, and in each case the other twin was healthy.

Incidence of HLHS in Live-Born Neonates

The change in incidence over time in relation to sex and whether Norwood surgery was performed is illustrated in Figure 2. Data presented as event rates per 100 000 live-born with confidence limits are provided in Table S1. The average incidence was 11.6 per 100 000 live births over the whole study period. The yearly incidence decreased from 15.3 per 100 000 in 1990 to 6.9 per 100 000 in 2010, resulting in an annual decrease of −3.8% (95% CI −5.8 to −1.7, P=0.001). A significant decrease in incidence was seen between the early and late birth periods, from 15.4 per 100 000 (1993-2000) to 8.4 per 100 000 live births (2001-2010) (incidence rate ratio 1.84 (95% CI 1.39-2.42, P<0.0001). A significant change in incidence was observed for male neonates after 2004, who showed an annual decrease of −18.8% (95% CI −28.3% to −7.9%, P=0.003). The numerical decrease for female neonates was found to be linear during the period 1990-2010, with a nonsignificant annual decrease of −2.8% (95% CI −5.6% to 0.1%, P=0.06). The male-to-female ratio, was 1.9:1 during both birth periods.

Prenatal Detection Rate and Fetal Outcome

The fetal incidence of HLHS was 19 per 100 000, estimated as described above. The estimated outcomes of the fetuses...
with HLHS are shown graphically in Figure 3. The prenatal detection rate increased significantly between the birth periods, from 27% to 63% (P=0.001), and termination of pregnancy increased significantly, from 19% to 56% (P=0.001). The termination rate after a prenatal diagnosis also increased significantly (P=0.009). No change was seen in the proportion of live-born neonates with a prenatal diagnosis. The proportion of all fetuses with HLHS born alive decreased from 81% to 44% (P=0.001). The proportion of all fetuses who were born alive and underwent Norwood surgery did not change significantly (40% during the early period and 31% during the late period). In the early period 50% of the live-born neonates underwent surgery, compared with 70% in the late period (P=0.003). In total, 27 (14 male and 13 female) of the 254 live-born neonates in the cohort had a prenatal diagnosis. In 22 of these 27 cases the mother was transferred to 1 of the 2 centers for pediatric cardiac surgery before delivery.

Factors Influencing Whether Surgery Was Performed or Not in Live-Born Neonates

The results of the logistic regression analysis on the influence of selected variables on the outcome are given in Table. Patients with extracardiac malformations and chromosomal abnormalities were excluded from this analysis because none of the 7 patients with multiple or single severe extracardiac malformations or trisomy 18 underwent surgery. The odds of having surgery were higher in the late period than in the early period and higher in the group with prenatal diagnosis than in the group with no prenatal diagnosis. The odds of having surgery were significantly lower in those born ≤37 weeks of gestation compared with those born at >37 weeks of gestation. Sex was not a significant predictor of surgery, and neither was birth weight ≤2500 g. No significant rejection of multivariable model fit could be shown by the Hosmer-Lemeshow test (P=0.77). Low birth weight (≤2500 g) was seen in 20 patients, of whom 9 (43%) underwent surgery; the lowest birth weight when surgery was performed was 1800 g. The percentage who underwent surgery in this group was lower compared with the 58% who underwent surgery in the entire cohort, and in a subanalysis using the Fisher exact test, there was a significant difference for body weight ≤2500 g (P=0.04). In the initial logistic regression analysis, birth place influenced whether surgery was performed or not, with a higher likelihood of surgery when a neonate was born at a university hospital with cardiac surgery compared with a university hospital without cardiac surgery. In a subanalysis including information on whether there had been a prenatal diagnosis, there was no correlation between birth location (university hospital with or without pediatric cardiac surgery) and whether surgery was performed (12 of 20 versus 87 of 161; P=0.61).

Discussion

The purposes of this study were to analyze changes over time in the incidence of HLHS in live-born neonates in a complete national cohort and to identify those factors influencing whether or not Norwood surgery was performed. The incidence of HLHS before the implementation of general prenatal ultrasound screening has been reported to vary between 8 and 28 per 100 000 live births in different studies.4,7,8,20 In a study in Norway Leirgul et al identified 244 registered cases of HLHS during 1994-2009, including terminations of pregnancy and stillbirths, resulting in an incidence of 26 per 100 000 pregnancies.1 Our slightly lower incidence of HLHS in neonates born before the implementation of prenatal screening could be explained by the fact that we excluded cases with aortic stenosis. We did so to avoid including cases with a potential for biventricular outcome. We used the early postnatal incidence as the best possible estimate of the incidence of fetal HLHS because at the time of the study it was not a reliable registration of terminations due
to malformations. The decreasing incidence of HLHS in live-born neonates was most likely the result of a gradually increasing prenatal detection and termination of pregnancy. A reduction in live-born neonates with HLHS after more widespread use of a 4-chamber view of the heart at screening has been reported by others. We also observed an increase between the periods in the proportion who chose termination of pregnancy after a prenatal diagnosis. This was a rather unexpected finding because it has been suggested that improved surgical results mitigate the trend toward increasing numbers of terminations; a decrease in terminations from 44% to 25% was observed in Birmingham, United Kingdom in 2002-2004, compared with a historical cohort. The authors raised concerns that the decrease could be explained in part by information given by Web-based support groups emphasizing a successful outcome after surgery, although this was not based on a true improvement in surgical results.

Table. Logistic Regression Analysis of Factors Influencing Whether Surgery Was Performed or Not in the Cohort of Patients With HLHS Born During the Surgical Era 1993-2010

<table>
<thead>
<tr>
<th>Total number</th>
<th>Surgery, n (%)</th>
<th>No Surgery, n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth period</td>
<td>Early</td>
<td>60 (50)</td>
<td>61 (50)</td>
<td>Ref</td>
<td>2.4 (1.3-4.3)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>61 (70)</td>
<td>26 (30)</td>
<td></td>
<td>2.5 (1.3-4.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>83 (60)</td>
<td>55 (40)</td>
<td>Ref</td>
<td>0.8 (0.4-1.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>38 (54)</td>
<td>32 (46)</td>
<td></td>
<td>0.5 (0.2-1.0)</td>
<td></td>
</tr>
<tr>
<td>Birth location</td>
<td>CS</td>
<td>32 (76)</td>
<td>10 (24)</td>
<td>Ref</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>UH</td>
<td>16 (38)</td>
<td>26 (62)</td>
<td>0.2 (0.1-0.5)</td>
<td>0.001</td>
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<td></td>
<td>RH</td>
<td>73 (59)</td>
<td>51 (41)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.05</td>
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<td>99 (55)</td>
<td>82 (45)</td>
<td>Ref</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22 (81)</td>
<td>5 (19)</td>
<td>3.6 (1.3-10.0)</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Gestational age ≤37 wk</td>
<td>No</td>
<td>103 (62)</td>
<td>64 (38)</td>
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<td></td>
<td></td>
</tr>
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<td></td>
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<td>18 (44)</td>
<td>23 (56)</td>
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<td>0.04</td>
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<td>111 (60)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>9 (43)</td>
<td>11 (57)</td>
<td>0.5 (0.2-1.3)</td>
<td>0.2</td>
<td></td>
</tr>
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</table>

CS indicates pediatric cardiac surgery center; Ref, referent category for the odds ratio; RH, regional hospital; UH, university hospital without pediatric cardiac surgery.

It has been debated whether a prenatal diagnosis is beneficial in terms of postnatal morbidity and mortality. In this study most of the neonates were diagnosed after birth. Four patients were discharged from the maternity ward without a diagnosis, and all 4 died. Prenatal detection would likely have prevented these deaths, as would postnatal pulse oximetry screening, implemented in Sweden after the study period. The majority of pregnant women with a diagnosis of fetal HLHS were referred for centralized delivery. In a population-based study in Texas in the United States, prenatal diagnosis was found to reduce neonatal mortality resulting from HLHS in cases in which the mother would otherwise have given birth far from a cardiosurgical center.
diagnosis were hemodynamically more stable. In a study on the effect of centralized delivery in Finland, a country with long distances to tertiary care, better postnatal right ventricular function, less metabolic acidosis, and less end-organ failure were found in neonates with HLHS with a prenatal diagnosis.

In the present study the proportion of live-born neonates with HLHS undergoing surgery increased between the early and late birth periods, probably as the result of changing attitudes among medical professionals and parents, favoring surgery instead of comfort care. The paradigm shift of not offering comfort care has been described and advocated, the main argument being acceptable survival and a reasonable quality of life for survivors. The apparent covariation, in our study, between place of birth and proportion of neonates with HLHS undergoing surgery could not be explained by different attitudes towards surgery but was rather the result of referral of the mother to a pediatric cardiac surgery center before delivery. The probability of undergoing surgery was higher in live-born neonates with a prenatal diagnosis, indicating that there had been a conscious decision to continue the pregnancy and to treat after birth. Prematurity influenced whether surgery was performed, as expected. Previous reports describe prematurity as a factor predicting adverse outcome. Likewise, extracardiac malformations and chromosomal abnormalities precluded patients from surgery.

Strengths and Limitations
The major strength of this study is the complete national cohort of all individuals born in Sweden with HLHS during a 21-year period. Also, the strict definition of HLHS, including only cases with aortic atresia and excluding borderline cases with aortic stenosis in whom a biventricular repair might have been possible, ensured that all cases were truly univentricular. On the other hand, because this was a study based on registry data, it is possible that some cases of HLHS/aortic stenosis might have been included and that some cases with all practical aspects of HLHS but not aortic atresia might have been excluded. Data were collected from registries providing limited depth of information. The interpretation of results in the subgroups was limited by the small numbers, and the statistical power was thus limited. The fetal incidence of HLHS was an estimate based on the incidence at live birth before the implementation of fetal screening and did not take into account possible yearly variations or possible, although unlikely, trends in fetal incidence of HLHS over time.

Future Perspectives
The results of this study, as well as others, raise the question of whether neonates with HLHS will be born in the future. We noted that the decrease in the number of live-born neonates with HLHS was somewhat counterbalanced by a higher proportion of live-borns undergoing surgery. It is reasonable to assume that, although fewer in number, neonates will continue to be born with HLHS in the future, and they will need highly specialized care.

Conclusions
During the 21-year period covered by this study there were increases in the prenatal detection of HLHS and in the number of terminations due to HLHS and a decrease in the number of newborns with HLHS. The proportion of neonates who underwent surgery increased between the 2 birth periods studied and was higher when there was a prenatal diagnosis.

Acknowledgments
All contributors to this study fulfilled authorship criteria and are listed as authors.

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Disclosures
None.

References


Supplemental table 1. The yearly incidence of HLHS (event rate per 100 000 liveborn) in boys and girls and the yearly event rate per 100 000 of liveborn with HLHS that were operated with Norwood surgery. Ninety-five per cent confidence intervals are shown.

<table>
<thead>
<tr>
<th>Year</th>
<th>Boys</th>
<th></th>
<th></th>
<th></th>
<th>Girls</th>
<th></th>
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<td>Liveborn</td>
<td>HLHS liveborn</td>
<td>Event rate per 100 000 (95% CI)</td>
<td>HLHS operated</td>
<td>N</td>
<td>Event rate per 100000 (95% CI)</td>
<td>HLHS operated</td>
<td>N</td>
</tr>
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<td></td>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1990</td>
<td>63571</td>
<td>14</td>
<td>22.02 (12.04 - 36.95)</td>
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<td>.</td>
<td>60363</td>
<td>5</td>
<td>8.28 (2.69 - 19.33)</td>
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<td>10</td>
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<td>.</td>
<td>59654</td>
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<td>5.03 (1.04 - 14.70)</td>
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<td>24.86 (13.92 - 41.01)</td>
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<td>16.39 (7.49 - 31.10)</td>
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<td>48660</td>
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<td>4</td>
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