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Impacts of prenatal ultrasound on morbidity and mortality of cardiac pathologies in pediatrics

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Table

Introduction

Background

The literature describes numerous advantages associated with prenatal diagnosis of congenital heart disease (CHD). The main findings indicate that prenatal diagnosis of CHD is associated with lower morbidity and mortality among newborns, as well as other benefits.

For example, it allows the parents to consider termination of pregnancy (TOP), in case of severe disease with poor prognosis, especially when there are associated extracardiac malformations or chromosomal defects(3). Similar cases are handled by a multidisciplinary counseling team when a diagnosis of CHD is found(38).

Furthermore, if the parents decide to continue the pregnancy, it allows them to be better prepared to the postnatal life(51). Thus, the stress induced by a perinatal discovery of a cardiac disease can be reduced. Parents can be reassured by the recommendations of the medical staff and the preparation of the early care after birth.

The malformations that most likely benefit from a prenatal diagnosis are those threatening the children's life soon after birth, and thus necessitating early treatments. Examples of these defects are ductus arteriosus dependent CHD, cyanotic CHD, severe obstructive CHD (valvular stenosis) and arrhythmia(51). In those instances, it is important to manage perinatal care by determining the time and place of delivery, usually in a tertiary care center. Early treatments should be initiated soon after birth, for example prostaglandins use and mechanical ventilation. Surgery or catheterization can be planned during the same period(3).

Moreover, for some defects, it seems that prenatal diagnosis leads to better preoperative conditions, in terms of haemodynamic stability for example(32), and that this could contribute to reduce morbidity and improve neurodevelopmental outcome(62).
In few cases, fetus may benefit from a prenatal intervention. For example, we can proceed to a balloon valvuloplasty in case of aortic or pulmonary valve stenosis, but there are limited indications(62).

Relevance

CHD is an issue often encountered, being "the most common congenital disorder in newborns", with an incidence of 137 per 10'000 births in the canton of Vaud between 2008 and 2012(21). Furthermore, it can have serious consequences, such as cardiogenic shock and pulmonary edema, and can be life-threatening for the newborn(57). Thus, it represents an important source of morbidity and mortality that deserves attention. Therefore, we should focus on prevention of this disease, including secondary prevention, which is useful to detect the disease early. Nowadays, many countries perform obstetrical ultrasound (US) as a part of a screening program of CHD.
In Switzerland, the law governing health insurance (Loi Fédérale sur l'Assurance Maladie, LaMal) covers two obstetrical ultrasounds, between 11th and 14th week of

pregnancy and 20th to 23rd week, as part of a screening program. If it is a "high risk" pregnancy, more examinations could be performed(15). The first ultrasound is used to define the gestational age and nuchal translucency. The second one to investigate for fetal malformations, growth delay and measurement of amniotic fluid quantity(22).

A detailed fetal echocardiography is performed in selected cases. Indeed, there are two main indications to undergo a specialized echocardiographic examination: maternal and fetal. The maternal indications include cases of mother having (i) a CHD, (ii) a previous child with CHD, (iii) a metabolic or systemic disease (e.g. diabetes, Lupus, Sjögren), (iv) a family history of hereditary diseases (e.g. Marfan, Noonan), or (v) previous contact with teratogens (e.g. through drugs or medication use). The fetal indications are (i) the discovery of extra-cardiac malformations or chromosomal abnormalities, (ii) hydrops fetalis or hydramnios, (iii) fetal cardiac arrhythmias, (iv) increased nuchal translucency in first trimester or (v) abnormal cardiac screening by ultrasound(51). Thus, about 30% of the CHD are detected prenatally in the Canton of Vaud, the rest being detected after birth. Moreover, more than 65% of the CHD classified as moderate to severe are prenatally discovered, with the remaining CHD cases identified after birth(49).

Objectives of the study

In light of the previous discussion, the aim of this study is to investigate whether there are benefits of prenatal diagnosis of congenital heart disease (CHD) by obstetrical ultrasound in a population of newborns of the canton of Vaud. These benefits are defined in terms of morbidity and mortality in the concerned newborns.

Expected outcomes

As discussed earlier we expect that prenatal diagnosis of CHD improves the outcome of newborns. Outcome markers are divided in two groups: those concerning morbidity and the ones for mortality. Morbidity markers include the Apgar clinical score, pH of the cord vessels, and referral to tertiary care units. Regarding mortality, we report the pregnancy outcome (born alive, fetal death, TOP) and the survival at one week. We further analyze the impact of the type of CHD (cyanotic or not), the presence of an extracardiac malformation or chromosomal anomaly, maternal age, weight and prematurity on these outcomes.

We expect that prenatal diagnosis would be associated with : (i) a higher rate of deliveries in the University Hospital of Lausanne (CHUV), the only tertiary care center of the Canton of Vaud, (ii) a higher survival at one week because of the early introduction of specialized care, including surgery in the first days or weeks of life.

We planned to analyze the effect of prenatal diagnosis on the outcome of newborn with CHD soon after birth, through early death. Unfortunately, as discussed below, we could not merge the two databases analyzed and associate these variables.

Methodology

To identify the potential benefits of obstetrical ultrasound screening on newborns with CHD, we use two databases: the Eurocat Registry of Vaud-Switzerland and the Ultrasound and Fetal Medicine database of the CHUV (Diamm). Eurocat contains all cases of fetuses with CHD whose parents are living in the canton of Vaud during pregnancy. The cases include live births, fetal deaths and termination of pregnancy for fetal anomaly following prenatal diagnosis. The Diamm database records all the patients with CHD seen at the Fetal Cardiology Clinic at the CHUV for an echocardiography. The study period is between the 01.01.2003 and the 31.12.2012 for both databases. As mentioned earlier, the two databases could not be merged and are henceforth analyzed separately*.

The first step was to clean the databases. We started with deleting information repeated in more than one column, concerning cardiac and extra-cardiac malformations. Then we normalized the missing values with a unique identifier. We also modified the entries in order to achieve uniform wording. Diamm has one entry for each consultation. We reviewed all these consultation data, and synthetized all the relevant diagnosis information. The consultation date corresponds to the date where most of that information is registered, and is not necessarily that of the last medical visit. We isolated the fetuses with confirmed CHD from all the cases seen in the Fetal Cardiology Consultation at the CHUV.

We created new binary and categorical variables with the nominative ones. In order to focus on cases of CHD with complete scan information, those instances where the morphological scan was incomplete were dropped from the analysis. Note that these incomplete cases may refer to either healthy fetuses or missed CHD, but our information does not allow further characterization. We also excluded clinical signs that do not correspond to an extracardiac malformation (e.g. “subcutaneous edema”).

As a basis of comparison, we reviewed CHD classified as moderate to severe in Eurocat. In the literature, severe CHD corresponds to newborns needing surgical or catheter intervention during the first year of life and represents about 25% of all CHD(7). However, in the database, they are defined as common arterial truncus, transposition of the great vessels, atrioventricular septal defect, tetralogy of Fallot, tricuspid atresia or stenosis, Ebstein’s anomaly†, pulmonary valve atresia, aortic valve atresia or stenosis, single ventricle physiology (including hypoplastic left heart, hypoplastic right heart), coarctation of aorta and total anomalous pulmonary venous return. We exclude ventricular septal defects smaller than 3mm, atrial septal defect, pulmonary valve

* The main obstacle to merging Eurocat and Diamm can be related to important differences in common identifiers that are related to surname and birth date.

† Note that Ebstein’s anomaly exceptionally requires surgery before the age of one year old, whereas valve stenosis may not require any surgery for several years depending on severity.

stenosis and patent ductus arteriosus. Note that a major difference between Eurocat and Diamm is that the latter contains data for all the cases of CHD, and not only the moderate to severe ones. We divide the cases in 2 groups: fetuses with cyanotic cardiac malformation and fetuses with non cyanotic malformation.

We evaluate the impact of prenatal ultrasound diagnosis on various indicators of postnatal morbidity and mortality. This is done by using a quantitative and comparative study between a group with prenatal ultrasound diagnosis and a control group without prenatal ultrasound and/or without prenatal diagnosis, within the group of cyanotic CHD.

Statistical analysis:
Continuous variable are expressed as mean ± SD or median and interquartile range when appropriate. The statistical analyses on these variables are done by two-group mean-comparison test (student t-test). Categorical variables are expressed as N (%). For those ones, we convert them in binary variables and then we use two-group test of proportions (z statistics).

A multivariate statistical analysis takes into consideration the impact of other explicative variables in the measurement of the effect of ultrasound diagnosis.
Binary dependent variables (e.g. one week survival) are regressed using probit and logit estimators, whereas categorical variables (e.g. type of birth) are regressed with multinomial logit estimators. Moreover, a Poisson regressor is used in the case of count variables (e.g. Apgar score). Finally, OLS regressors are relied upon in the case of continuous variables (e.g. pH of the cord vessels).

Results

Eurocat database

Comparison among cyanotic CHD between prenatal vs postnatal diagnosis

Eurocat contains observations from 205 fetuses, from which 204 have a CHD, classified as moderate to severe. Of these 204 fetuses, 74 (36.3%) have non cyanotic and 130 (63.7%) have cyanotic CHD. From the latter group, 3 (2.3%) have missing data about the moment of the diagnosis. The remaining 127 observations with complete information is the main focus of our study and can be split between 95 (74.8%) prenatal and 32 (25.2%) postnatal diagnoses. The relevant data for this group is reported in Table 1.

Average maternal age is 32 ± 6.0 years old for the group with prenatal diagnosis and 30 ± 5.2 years old for the one with postnatal diagnosis. Mean gestational age is respectively 36.9 ± 3.1 weeks and 38.3 ± 2.5 weeks. Mean weight at birth is respectively 2674 ±706 g and 2975 ± 775 g.

Birth type analysis shows that only 41 (43.2%) newborns with prenatal diagnosis are born alive. Indeed, more than half (52 (54.7%)) of the parents decide to undergo TOP in the group with prenatal diagnosis. The multivariate analysis (table 4, appendix) shows that prenatal discovery does not significantly affect TOP. Concerning place of birth, we find that it is CHUV for the majority (39 (95.1%)) of the fetuses with prenatal diagnosis and for about one third (11 (34.4%)) of the ones with postnatal diagnosis (among born alive children). The multivariate analysis (table 5, appendix) indicates that prenatal discovery significantly affects the likelihood of a birth in CHUV. We find no significant difference of prematurity rates between the two groups in both the univariate and in the multivariate analyses (table 6, appendix).

The difference of survival at one week between the two groups with prenatal or postnatal diagnosis shows that majority of the newborn are still alive at one week. However, the difference between the two groups is not significant. The multivariate analysis (table 7, appendix) is also unable to identify significant effect of prenatal discovery on survival over one week. A categorization of the most severe pathologies (e.g. left heart hypoplasia) across the various groups does not explain this result either.

Analyzing the timing of surgery shows that, regardless of the moment of diagnosis, about two thirds of newborns (26 (72.2%) vs 20 (74.1%)) undergo surgery before the age of one year. Indeed, the standard of care for newborn with a cyanotic CHD is to perform cardiac surgery before one year of age. To understand this result, we also categorized the most severe malformations threatening newborns' life in the first weeks of life (e.g left heart hypoplasia) across the various groups. Our results indicate that there are more of these severe CHD's in the group without surgery in the first year of life than in the group with surgery within first year (2 (11.8%) versus 1 (2.2%)). This suggests that children with severe malformations might have died without undergoing

any surgery, either due to a medical complication or due to a decision to opt for comfort care.

Table 1: Differences between prenatal and postnatal diagnosis among cyanotic CHD

Variable	**Prenatal diagnosis**		**Postnatal diagnosis**		**P-value**[‡]
	n	**%**	**n**	**%**	
Pregnancy outcome					
- Born alive	41	43.2%	32	100%	<0.01
- Fetal death	2	2.1%	0	0%	
- TOP	52	54.7%	0	0%	
- Missing	0	0%	0	0%	
Total	95	100%	32	100%	
Gestational age at birth					
- Delivery at term	29	70.7%	27	84.4%	0.17
- Prematurity 32-37 weeks	9	22.0%	4	12.5%	0.30
- Prematurity 24-32 weeks	3	7.3%	1	3.1%	0.44
- Missing	0	0%	0	0%	
Total	41	100%	32	100%	
Delivery place					
- CHUV	39	95.1%	11	34.4%	<0.01
- Other	1	2.4%	21	65.6%	<0.01
- Missing	1	2.4%	0	0%	
Total	41	100%	32	100%	
Survival					
- Alive at one week	32	78.0%	30	93.8%	0.09
- Death prior to one week	8	19.5%	2	6.2%	0.09
- Missing	1	2.5%	0	0%	
Total	41	100%	32	100%	
Surgery					
< 1 year	26	63.4% (72.2%)	20	62.5% (74.1%)	0.87
> 1 year or no surgery	10	24.4% (27.8%)	7	21.9% (25.9%)	0.87
Missing	5	12.2%	5	15.6%	
Total	41	100%	32	100%	

‡ P-values refer to test of equality of proportions across pre- and postnatal diagnosis groups, using only non-missing values, where these percentages are reported in parentheses for Surgery.

Comparison cyanotic vs non cyanotic CHD

The relevant Eurocat variables for the comparison between outcome of fetuses with cyanotic CHD and fetuses with non cyanotic CHD are reported in Table 2.

Among the fetuses with cyanotic CHD, we find that 54 (41.5%) have an extracardiac malformation and 29 (22.3%) have a chromosomal anomaly. For the group with non cyanotic CHD, respectively 23 (31.1%) have an extracardiac malformation and 29 (39.2%) a chromosomal anomaly. Maternal age is in mean 32 ± 5.8 years old for the cyanotic group and 32 ± 5.4 years old for the non cyanotic group. Mean gestational age for the newborns is respectively 37.5 ± 2.9 weeks and 37.6 ± 2.8 weeks. Mean birth weight for the newborn is respectively 2808 ± 747 g and 2923 ± 713 g.

We observe that cyanotic CHD have prenatal diagnosis with US in three quarters of the cases (95 (73.1%)) whereas that proportion is less than half for the non cyanotic group (34 (45.9%)). The multivariate analysis (table 9, appendix) confirms an increase of prenatal discovery for the cyanotic group.

We find no significant differences concerning issue of pregnancy (born alive, death in utero or TOP), neither in terms of prematurity. The multivariate analyses (tables 4 and 6, appendix) both confirm that cyanotic CHD does not affect the likelihood of TOP and the prematurity.

We find that more than two third (50 (68.5%)) of the babies who are born alive with cyanotic CHD are delivered in CHUV, compared to almost half (22 (45.8%)) of the ones with non cyanotic malformation. The multivariate analysis (table 5, appendix) does not identify a significant effect of a cyanotic CHD on the probability to deliver in CHUV.

The difference of survival at one week between the two groups shows that it is lower for the group with cyanotic CHD than the other group (63 (86.3%) vs 48 (100%)). However, the multivariate analysis (table 7, appendix) could not identify any effect of a cyanotic CHD on the survival at one week.

The majority of the newborns with CHD undergo surgery before one year, with a higher rate of surgery before one year in the group of cyanotic CHD (46 (73%) vs 20 (51.3%)). The multivariate analysis (table 8, appendix) finds that cyanotic CHD is not a predictor of surgery before one year. Again, this result might be explained by the highest rate of severe CHD's in the group without surgery before one year. Indeed, death is more likely to occur before surgery, either due to a medical complication or due to a decision to opt for comfort care (related to the severity of the CHD or the associated malformation or chromosomal abnormality).

Table 2: Differences between cyanotic and non cyanotic CHD

Variable	Cyanotic		Non cyanotic		P-value[§]
	n	%	n	%	
Timing of diagnosis					
- Prenatal	95	73.1%	34	45.9%	<0.01
- Postnatal	32	24.6%	38	51.4%	<0.01
- Missing	3	2.3%	2	2.7%	
Total	130	100%	74	100%	
Post-mortem examination					
- Yes	42	32.3%	16	21.6%	0.28
- No	51	39.2%	29	39.2%	0.28
- Missing	37	28.5%	29	39.2%	
Total	130	100%	74	100%	
Pregnancy outcome					
- Born alive	73	56.2%	48	64.9%	0.22
- Fetal death	2	1.5%	1	1.3%	0.92
- TOP	55	42.3%	25	33.8%	0.23
- Missing	0	0%	0	0%	
Total	130	100%	74	100%	
Gestational age at birth					
- Delivery at term	56	76.7%	38	79.2%	0.75
- Prematurity 32-37 weeks	13	17.8%	7	14.6%	0.64
- Prematurity 24-32 weeks	4	5.5%	3	6.2%	0.86
- Missing	0	0%	0	0%	
Total	73	100%	48	100%	
Delivery place					
- CHUV	50	68.5%	22	45.8%	0.01
- Other	22	30.1%	25	52.1%	0.01
- Missing	1	1.4%	1	2.1%	
Total	73	100%	48	100%	
Survival					
- Alive at one week	62	84.9%	48	100%	0.01
- Death prior to one week	10	13.7%	0	0%	
	1	1.4%	0	0%	
Total	73	100%	48	100%	

§ P-values refer to test of equality of proportions across cyanotic groups, using only non-missing values, where these percentages are reported in parentheses for Survival and Surgery.

Variable	Cyanotic		Non cyanotic		P-value**
	n	%	n	%	
Surgery					
< 1 year	46	63.0% (73.0%)	20	41.6% (51.3%)	0.03
> 1 year or no surgery	17	23.3% (27.0%)	19	39.6% (48.7%)	0.03
Missing	10	13.7%	9	18.8%	
Total	73	100%	48	100%	

** P-values refer to differences in outcome across diagnosis groups using only non-missing values, where these percentages are reported in parentheses for Surgery.

Diamm

Comparison cyanotic vs non cyanotic CHD

The following analyses concern the fetuses of the Fetal Cardiology Consultation in CHUV with CHD (all the cases of CHD, not only the moderate to severe). The initial database contains 3421 observations (one line for one consultation). From these 3421 observations, we can isolate 1852 cases of pregnant women seen in the Fetal Cardiology Consultation between 2003 and 2013. Of these 1852 cases, there are 449 (24.2%) fetuses with confirmed CHD. From the latter group, 106 (23.6%) have a cyanotic CHD and the rest a non cyanotic CHD. The descriptive statistics for the cyanotic and non cyanotic groups are reported in Table 3.

Among the fetuses with cyanotic CHD, we find that 19 (17.9%) have an extra-cardiac malformation and 5 (4.7%) a chromosomal anomaly. Concerning the fetuses with non cyanotic CHD, 30 (8.8%) have an extracardiac malformation and 18 (5.3%) a chromosomal anomaly. Mean maternal age is respectively 32 ± 5.3 years and 32 ± 5.5 years. Mean gestational age for the alive newborns is 37.5 ± 2.7 weeks for the ones with cyanotic CHD and 37.9 ± 3.1 weeks for the others. Mean birth weight for the born alive is respectively 2719 ± 713 g and 3030 ± 770 g, with significant difference.

The majority of the children with CHD are born alive. Parents opt for TOP in 14 (13.2%) of the cases with cyanotic CHD and 6 (1.7%) with non cyanotic CHD. The multivariate analysis (table 10, appendix) confirms that a cyanotic CHD increases the number of TOP.

Delivery technique is similar in both groups, without significant differences. Thus, about half undergo a cesarean-section (at term of pregnancy) and the other half usually give birth naturally without instrument, regardless of the group. The multivariate analysis (table 11, appendix) confirms that cyanotic CHD has no effect on delivery technique.

A clinical marker of newborns' adaptation in the first minutes of life is its Apgar score. The medians are in the normal range for both groups. The multivariate analyses (tables 12, 13, 14, appendix) confirm that cyanotic CHD has no effect on the Apgar score at 1, 5, and 10 minutes of measurement.

We also analyze pH in the umbilical artery and vein, and find no significant differences between the two groups. The multivariate analyses (tables 15, 16, appendix) also find no effect of cyanotic CHD on either artery or vein pH. The norm for the umbilical artery is between 7.12 and 7.42. A lower pH is a marker of perinatal asphyxia and associated with a worse prognosis(1,41).

Studying the outcome of the children after birth shows that majority of the newborn with cyanotic CHD are transferred in neonatal unit whereas majority of the ones with non cyanotic CHD return home in the first days of life. Only a few are transferred in the same period into another hospital, usually near parents' place of residence. Few are transferred for surgical care. Newborn death in the first days of life is more frequent in the group with cyanotic CHD than the one with non cyanotic CHD. The multivariate analysis (table 17, appendix) confirms that cyanotic CHD leads to an increase in referral to neonatal and surgical care units and death of the newborn in the first days of life. The

normal practice in CHUV is to transfer the newborn in neonatal intensive care unit if the baby needs early care and monitoring before surgery. If the newborn is stable, he can be transferred in the obstetric unit or discharged home.

Table 3: Differences between cyanotic and non cyanotic CHD

Variable	**Cyanotic**		**Non cyanotic**		**P-value**[††]
	n	**%**	**n**	**%**	
Pregnancy outcome					
- Born alive	68	64.1%	224	65.3%	<0.01
- Fetal death	6	5.7%	6	1.7%	0.07
- TOP	14	13.2%	6	1.7%	<0.01
- Missing	18	17.0%	107	31.2%	
Total	106	100%	343	100%	
Delivery technique					
- Normal vaginal delivery	32	47.1%	113	50.5%	0.70
- Vaginal delivery with instruments[‡‡]	2	2.9%	11	4.9%	0.50
- Cesarean-section	33	48.5%	100	44.6%	0.51
- Missing	1	1.5%	0	0%	
Total	68	100%	224	100%	
	Cyanotic		**Non cyanotic**		
	Median [P25;P75]		**Median [P25;P75]**		**P-value**[§§]
Apgar score					
- At 1 minute	8 [6;9]		9 [7;9]		0.62
- Missing	25		9		
Total	68		224		
- At 5 minutes	9 [8;9]		9 [9;10]		0.36
- Missing	21		9		
Total	68		224		
- At 10 minutes	9 [8;10]		10 [9;10]		0.19
- Missing	20		9		
Total	68		224		

[††] P-values refer to test of equality of proportions across cyanotic groups, using only non-missing values.
[‡‡] Forceps, vacuum, Bracht maneuver
[§§] P-values refer to T-stat on cyanotic variable in Poisson regression, using only non-missing values.

Variable	Cyanotic	Non cyanotic	
	Mean [P25;P75]	Mean [P25;P75]	P-value***
pHa	7.25 [7.23;7.30]	7.26 [7.23;7.30]	0.49
Missing	23	22	
Total	68	224	
pHv	7.32 [7.30;7.38]	7.33 [7.29;7.37]	0.43
Missing	17	12	
Total	68	224	

	Cyanotic		Non cyanotic		
	n	%	n	%	P-value
Outcome of newborn in the first days					
- Discharged home	7	10.3%	149	66.5%	<0.01
- Transfer in another hospital	1	1.5%	9	4.0%	0.32
- Transfer to neonatal unit	50	73.5%	55	24.6%	<0.01
- Transfer to operating room	3	4.4%	1	0.4%	0.01
- Death	5	7.4%	6	2.7%	0.07
- Missing	2	2.9%	4	1.8%	
Total	68	100%	224	100%	

*** P-values refer to T-stat on equality of mean across cyanotic variable, using only non-missing values.

Discussion

The aim of this study has been to verify whether prenatal diagnosis of CHD with morphological US has an impact on newborn's prognosis. The initial hypothesis was that it would have benefits on the morbidity and mortality of these diseases.

Prenatal versus postnatal diagnosis (Eurocat)

We analyzed the difference of outcome between prenatal and postnatal diagnosis only in one group, the cyanotic one. The data confirm that almost all prenatally diagnosed CHD are delivered in CHUV, but only in one-third cases for postnatally diagnosed CHD. This corresponds to the routine practice and allows introduction of optimal early specialized care for the newborn. Indeed, according to the literature(24, 31, 63), transporting an unstable newborn is associated with higher risks of morbidity and mortality.

Regarding pregnancy outcome, we find that after prenatal diagnosis of cyanotic CHD, more than half of the parents took the decision to terminate the pregnancy. This is in accordance with the literature(3, 7, 30, 35, 38, 62, 63). It reflects the severity and poor prognosis of cyanotic CHD and the potential implication for the postnatal life if pregnancy is continued.

Our initial hypothesis was that prenatal diagnosis of CHD would improve the mortality outcome. However, the difference of survival at one week is not significant between the prenatally and the postnatally diagnosed group (prenatal 32/40 vs postnatal 30/32. The rate of severe pathologies in the prenatal group cannot explain this result, since it did not differ significantly between the two groups.

Cyanotic versus non cyanotic CHD (Eurocat, Diamm)

The sensitivity of prenatal US is significantly increased in cyanotic CHD. Severity of the CHD and the prenatal detection for the CHD are probably the two parameters leading to a higher rate of delivery at the CHUV for cyanotic CHD.

Regarding pregnancy and neonatal outcome, we confirm that fetuses with cyanotic CHD are less likely to be born alive, because of the higher number of TOP in that group. The rate of fetal death does not differ, but the mortality rate during the first days of life is higher in the group with cyanotic CHD.

We find, as expected, that the probability to return home in the first days of life is lower for newborn with cyanotic CHD. Moreover, they are more likely to require neonatal intensive or surgical cares, and to have surgery before the age of one year. These findings are in accordance with the literature, which describes that the most severe pathologies should be directed towards tertiary care centers, avoiding postnatal

transport of an instable newborn and allowing immediate and appropriate cares (3, 7, 24, 29, 38, 63). The standard of care for ductal-dependant CHD and cyanotic CHD is to perform surgery before the first month of life and the first year of life respectively. However, the available data could not provide any explanation for the high number of patients who did not undergo surgery before one year of age.

Limitations

The study had some limitations. First, merging the two databases was impossible because there was no common identifier between them. Hence, there were some errors concerning mothers' and newborns' birthdates and names. For future investigations, we could find a common identifier, for example the Id that encodes mother's presence in hospital for consultations and care. This information was present in Diamm but not in Eurocat. It would have been interesting to analyze the difference in clinical scores (Apgar) between prenatal and postnatal diagnosis. Secondly, the collecting of data in Eurocat was not by multiple choices categories but free text. This led to many denominations of same pathologies and was a source of potential errors due to interpretation. Thirdly, both databases unfortunately presented large shares of missing variables, which had a detrimental impact on the multivariate analyses in particular, since information on many regressors was incomplete. This could explain why many findings of the univariate analyses could not be confirmed through the multivariate ones. Hopefully, future design of the data collection should attempt to minimize missing variables occurrence. Finally, we decided to analyze the difference between prenatal and postnatal diagnosis, which didn't separate diagnosis with morphological US from other techniques of investigations (serum combined test, chorionic villi sampling, amniocentesis, echocardiography).

Conclusion

The objective of the study was to verify whether prenatal diagnosis of CHD had an effect on the fetuses' morbidity and mortality. We did not find any result supporting this hypothesis. On the contrary, we find a tendency for a higher rate of mortality associated with the prenatal diagnosis. The available data could not provide any explanation regarding this unexpected result. A difference in CHD severity and decision to opt for comfort care in severe cases are the more likely hypotheses.

The outcome of pregnancies after prenatal detection of moderate to severe CHD, cyanotic and non cyanotic, is termination of pregnancy in more than 50% of the cases. For the ongoing pregnancies, delivery is almost always planned in a tertiary care center. Fetuses with cyanotic CHD will more often require surgery and admission in neonatal care unit.

Further investigations should allow a better understanding of the lack of improved morbidity and survival with the prenatal detection of moderate to severe CHD. The completion and correction of missing and erroneous data should be encouraged. Other parameters of morbidity (mechanical ventilation, prostaglandins use, vasoactive drug use, infection rate, hospitalization length of stay) could be looked for in order to describe more precisely postnatal outcome. The improvement of the two databases, by adding those parameters and more importantly by entering a common identifier, would result in a much more complete and robust database.

Finally, it is important to emphasize that beyond fetal and neonatal outcome, prenatal diagnosis allows parents and medical teams to plan and prepare the perinatal and postnatal cares. It is reassuring for both to know that everything has been set up for optimal care and for parents to get prepared for a different postnatal course than expected.

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Appendix

Multivariate analysis

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Table 4: Birth type

Multinomial logistic regression — Number of obs = 191
LR chi2(12) = 137.42
Prob>chi2 = 0.00
Log likelihood=-70.3087 — PseudoR2 = 0.4943

Birth type	Coef.	Std. Err	z	P>z
1 = Born alive	(base outcome)			
2 = Fetal death				
born in chuv	-4.86	1.63	-2.98	0.00
extracardiac malformation	-0.41	1.36	-0.30	0.76
chromosomal anomaly	-16.62	3368.34	-0.00	0.99
cyanotic CHD	-1.35	1.42	-0.95	0.34
prenatal discovery	21.36	2992.72	0.01	0.99
mother's age	-0.02	0.11	-0.14	0.89
_cons	-18.65	2992.72	-0.01	0.99
3 = TOP				
born in chuv	-3.39	1.05	-3.22	0.00
extracardiac malformation	0.48	0.46	1.05	0.29
chromosomal anomaly	1.35	0.53	2.53	0.01
cyanotic CHD	-0.12	0.54	-0.22	0.83
prenatal discovery	20.85	1007.50	0.02	0.98
mother's age	0.01	0.04	0.20	0.84
_cons	-18.42	1007.50	-0.02	0.99

Table 5: Birth in CHUV

Logistic regression — Number of obs = 191
LR chi2(6) = 58.45
Prob > chi2 = 0.00
Log likelihood = -100.2986 — Pseudo R2 = 0.2256

Birth in CHUV	Coef.	Std. Err.	z	P>|z|
extracardiac malformation	-0.33	0.37	-0.89	0.37
chromosomal anomaly	0.01	0.41	0.03	0.97
cyanotic CHD	0.22	0.37	0.60	0.55
prenatal discovery	3.72	0.70	5.32	0.00
prematurity	-0.95	0.25	-3.82	0.00
mother's age	-0.04	0.03	-1.29	0.20
_cons	0.67	0.98	0.68	0.49

Table 6: Delivery at term

Logistic regression — Number of obs = 119
LR chi2(6) = 9.76
Prob>chi2 = 0.1352
Log likelihood = -58.844 — Pseudo R2 = 0.0766

Delivery at term	Coef.	Std. Err.	z	P>z
born in chuv	-0.92	0.65	-1.41	0.16
extracardiac malformation	-0.76	0.48	-1.58	0.11
chromosomal anomaly	-0.56	0.56	-1.00	0.32
cyanotic CHD	0.25	0.52	0.49	0.63
prenatal discovery	-0.28	0.60	-0.47	0.64
mother's age	0.04	0.05	0.82	0.41
_cons	1.06	1.47	0.72	0.47

Table 7: Survival at one week

Logistic regression — Number of obs = 72
LR chi2(7) = 11.88
Prob > chi2 = 0.1044
Log likelihood = -23.0699 — Pseudo R2 = 0.2048

Survival > 1 week	Coef.	Std. Err.	z	P>|z|
born in chuv	0.03	1.36	0.02	0.98
extracardiac malformation	1.63	1.05	1.56	0.12
chromosomal anomaly	-0.84	1.05	-0.79	0.43
cyanotic CHD	0 (omitted)			
prenatal discovery	-1.23	1.16	-1.06	0.29
prematurity	-2.24	1.08	-2.07	0.04
weight	-0.00	0.00	-1.03	0.31
mother's age	0.03	0.08	0.33	0.74
_cons	4.90	3.92	1.25	0.21

Table 8: Surgery before one year

Logistic regression — Number of obs = 101
LR chi2(8) = 8.98
Prob > chi2 = 0.3439
Log likelihood = -60.6825 — Pseudo R2 = 0.0689

Surgery < 1 year	Coef.	Std. Err	z	P>|z|
born in chuv	-0.67	0.63	-1.06	0.29
extracardiac malformation	0.18	0.52	0.35	0.73
chromosomal anomaly	0.14	0.62	0.22	0.82
cyanotic CHD	0.78	0.47	1.65	0.10
prenatal discovery	0.81	0.62	1.32	0.19
prematurity	-0.89	0.60	-1.49	0.14
weight	-0.00	0.00	-0.54	0.59
mother's age	-0.03	0.04	-0.60	0.55
_cons	2.01	2.22	0.90	0.37

Table 9: Prenatal diagnosis

Logistic regression — Number of obs = 199; LR chi2(3) = 28.20; Prob > chi2 = 0; Log likelihood = -114.95727; Pseudo R2 = 0.1093

Prenatal diagnosis	Coef.	Std. Err.	z	P>z
extracardiac malformation	0.41	0.35	1.18	0.24
chomosomal anomaly	1.21	0.40	2.99	0.00
cyanotic CHD	1.45	0.35	4.20	0.00
_cons	-0.72	0.31	-2.35	0.02

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Table 10: Birth type

Multinomial logistic regression — Number of obs = 324; LR chi2(8) = 47.76; Prob > chi2 = 0.0000; Log likelihood = -101.73718; Pseudo R2 = 0.1901

Birth type	Coef.	Std. Err.	z	P>|z|
1 = born alive	(base outcome)			
2 = fetal death				
extracardiac malformation	0.55	0.87	0.63	0.53
chromosomal anomaly	2.36	0.94	2.50	0.01
cyanotic CHD	1.34	0.62	2.17	0.03
mother's age	-0.03	0.06	-0.60	0.55
_cons	-2.85	1.82	-1.57	0.12
3 = TOP				
extracardiac malformation	2.15	0.57	3.79	0.00
chromosomal anomaly	2.18	0.87	2.52	0.01
cyanotic CHD	2.37	0.59	4.04	0.00
mother's age	-0.03	0.05	-0.59	0.55
_cons	-3.52	1.66	-2.12	0.03

Table 11: Delivery technique

Multinomial logistic regression

Number of obs = 291
LR chi2(12) = 50.90
Prob > chi2 = 0.0000
Pseudo R2 = 0.1036

Log likelihood = -220.10105

Delivery technique	Coef.	Std. Err.	z	P>|z|
0 = vaginal birth	(base outcome)			
1 = vaginal birth with instrument				
weight	0.00	0.00	1.55	0.12
issue GA	0.64	0.28	2.28	0.02
extracardiac malformation	-13.62	1084.07	-0.01	0.99
chromosomal anomaly	1.96	4204.38	0.00	1.00
cyanotic CHD	0.55	0.89	0.62	0.54
mother's age	0.04	0.05	0.74	0.46
_cons	-32.09	11.26	-2.85	0.00
2 = cesarean-section				
weight	0.00	0.00	-0.18	0.86
issue GA	-0.20	0.07	-2.82	0.05
extracardiac malformation	-0.02	0.49	-0.05	0.96
chromosomal anomaly	16.41	1432.07	0.01	0.99
cyanotic CHD	0.11	0.30	0.76	0.72
mother's age	0.01	0.02	0.64	0.53
_cons	6.91	2.39	2.89	0.00

Table 12: Apgar at 1 minute

Number of obs = 258
LR chi2(6) = 41.59
Prob > chi2 = 0.0000
Pseudo-R2 = 0.0351

Log Likelihood = - 571.82

Apgar 1 minute	Coef.	Std. Err	z	P>|z|
weight	0.00	0.00	1.36	0.18
issue GA	0.03	0.01	2.68	0.01
extracardiac malformation	-0.15	0.10	-1.43	0.15
chromosomal anomaly	0.28	0.16	1.69	0.09
cyanotic CHD	0.01	0.06	0.16	0.87
mother's age	-0.00	0.00	-0.04	0.97
_cons	0.57	0.43	1.34	0.18

Table 13: Apgar at 5 minutes

Number of obs = 262
LR chi2(6) = 20.20
Prob > chi2 = 0.0026
Pseudo-R2 = 0.0179

Log Likelihood = - 553.99

Apgar 5 minutes	Coef.	Std. Err	z	P>|z|
weight	0.00	0.00	0.72	0.47
issue GA	0.02	0.01	2.14	0.03
extracardiac malformation	-0.02	0.09	-0.25	0.81
chromosomal anomaly	0.13	0.16	0.81	0.42
cyanotic CHD	-0.02	0.06	-0.43	0.67
mother's age	-0.00	0.00	-0.28	0.78
_cons	1.21	0.38	3.17	0.00

Table 14: Apgar at 10 minutes

Number of obs = 263
LR chi2(6) = 13.81
Prob > chi2 = 0.0318
Pseudo-R2 = 0.0123

Log Likelihood = - 554.27

Apgar 10 minutes	Coef.	Std. Err	z	P>|z|
weight	0.00	0.00	0.50	0.63
issue GA	0.02	0.01	1.74	0.08
extracardiac malformation	0.02	0.09	0.20	0.84
chromosomal anomaly	0.08	0.16	0.50	0.62
cyanotic CHD	-0.05	0.06	-0.86	0.39
mother's age	-0.00	0.00	-0.36	0.72
_cons	1.48	0.37	4.01	0.00

Table 15: pH umbilical artery

Number of obs = 247
F (6, 240) = 1.11
Prob > F = 0.3599
R-squared = 0.0269
Adj R-squared = 0.0026
Root MSE = 0.7463

pHa	Coef.	Std. Err	t	P>|t|
weight	0.00	0.00	0.25	0.80
issue GA	-0.00	0.00	-1.39	0.17
extracardiac malformation	0.01	0.02	0.43	0.67
chromosomal anomaly	0.05	0.04	1.33	0.19
cyanotic CHD	-0.01	0.01	-0.59	0.56
mother's age	-0.00	0.00	-0.81	0.42
_cons	7.41	0.08	87.24	0.00

Table 16: pH umbilical vein

Number of obs = 263
F (6, 256) = 1.03
Prob > F = 0.4077
R-squared = 0.235
Adj R-squared = 0.0006
Root MSE = 0.07577

pHv	Coef.	Std. Err	t	P>|t|
weight	0.00	0.00	1.57	0.12
issue GA	-0.00	0.00	-1.73	0.09
extracardiac malformation	0.02	0.02	1.27	0.21
chromosomal anomaly	0.01	0.04	0.19	0.85
cyanotic CHD	-0.01	0.01	-0.41	0.68
mother's age	-0.00	0.00	-0.89	0.37
_cons	7.47	0.08	90.48	0.00

Table 17: Newborn outcome in the first days of life

Multinomial logistic regression — Number of obs = 286
LR chi2(24) = 198.31
Prob > chi2 = 0.0000
Log likelihood = -187.06541 — Pseudo R2 = 0.3464

Newborn outcome	Coef.	Std. Err.	z	P>|z|
0 = return home	(base outcome)			
1 = transfer in another hospital				
weight	0.00	0.00	0.02	0.98
issue GA	-0.66	0.20	-3.31	0.00
extracardiac malformation	2.81	1.02	2.75	0.01
chromosomal anomaly	1.29	1.40	0.92	0.36
cyanotic CHD	1.50	1.19	1.27	0.21
mother's age	0.03	0.07	0.47	0.64
_cons	20.05	6.47	3.10	0.00
2 = transfer in intensive care unit				
weight	0.00	0.00	0.21	0.83
issue GA	-0.54	0.11	-4.79	0.00
extracardiac malformation	1.84	0.76	2.43	0.02
chromosomal anomaly	-1.19	1.34	-0.88	0.38
cyanotic CHD	3.21	0.47	6.86	0.00
mother's age	0.02	0.03	0.80	0.43
_cons	18.16	3.87	4.69	0.00
3 = transfer in surgical unit				
weight	0.00	0.00	2.20	0.03
issue GA	-0.48	0.52	-0.91	0.36
extracardiac malformation	-10.31	676.95	-0.02	0.99
chromosomal anomaly	-11.09	1143.12	-0.01	0.99
cyanotic CHD	5.27	1.50	3.51	0.00
mother's age	-0.01	0.11	-0.13	0.90
_cons	3.69	18.75	0.20	0.84
4 = death of the newborn				
weight	0.00	0.00	1.38	0.17
issue GA	-1.03	0.23	-4.53	0.00
extracardiac malformation	3.94	1.07	3.68	0.00
chromosomal anomaly	1.11	1.71	0.65	0.52
cyanotic CHD	4.41	0.94	4.72	0.00
mother's age	0.06	0.08	0.68	0.49
_cons	28.59	6.97	4.10	0.00