

Screening for congenital heart defects: diversified strategies in current China

Xiwang Liu, Weize Xu, Jiangen Yu, Qiang Shu

To cite: Liu X, Xu W, Yu J, *et al.* Screening for congenital heart defects: diversified strategies in current China. *World Jnl Ped Surgery* 2019;2:e000051. doi:10.1136/wjps-2019-000051

Received 21 March 2019
Revised 28 April 2019
Accepted 30 April 2019

ABSTRACT

Background Congenital heart defects (CHD) is the most common type of birth defect and a leading cause of infant mortality in China. Detection of CHD during newborn is still challenging. The contradiction between the increasingly mature technology of diagnosis and treatment and the inability of early detection is the biggest current dilemma. A few pilot studies attempt to establish the universal screening for CHD in newborns; however, the rate of misdiagnosis is still high in most Chinese hospitals, especially in some undeveloped middle-western regions. **Data sources** Based on the recent publications on screening of congenital heart diseases in China. We reviewed the use of diversified screening strategies in current China.

Results Prenatal diagnosis by fetal echocardiography and postnatal detection by pulse oximetry combined with clinical assessment are the useful methods for CHD screening in most areas. The altitude should be taken into account when using pulse oximetry in the middle-western areas of China, where the incidence of CHD maybe higher. Echocardiography is suitable for CHD screening in almost all areas but it could add to financial burden in the developing regions. Genetic analysis could assist clinical doctors to perform more earlier screening and give better counseling regarding the outcome. Due to disparities in economic and medical resources, the screening system should be carried out from multiple perspectives according to the present economic development. Notably, follow-up is an important issue in the screening of CHD, especially for the asymptomatic babies who discharged home. Policies should be formulated to address the epidemiology of CHD in deprived areas to better allocate medical resources and to develop local training programmes to screen and diagnose CHD.

Conclusions Diversified strategies are available in current China. The two-indicator method for CHD screening is recommended to be implemented in routine postnatal care. We can do more in screening for CHD in the future.

INTRODUCTION

The overall prevalence of congenital heart defects (CHD) is 8.98 per 1000 live births in China,¹ of which including two to three neonates with critical CHD (CCHD) which can cause death or requiring invasive surgical intervention during neonatal period.² CHD is the most common type of birth defect and a leading cause of infant mortality in recent years in China.³ In 2016, there were

17.9 million newborns. After adoption of the universal two-child policy since 2015 in China, the incidence of CHD may be increased as a result of high proportion of women with high maternal age. Though with such high incidence of CHD and large population of patients with CHD, the rate of misdiagnosis of CHD before discharge from maternity hospitals is still quite high until 2017.⁴ Without timely detection and treatment, approximately one-third of children with CHD would die in the infant period because of severe anoxia, heart failure, pneumonia or other serious complications. While those survive with missed or delayed diagnosis would have poor life quality. Late CCHD detection was proved to be significantly associated with 52% more admissions, 18% more hospitalized days and 35% higher inpatient costs during infancy.⁵ More seriously, the prenatal detection rate of CCHD was reported to be only 14.04%. As a whole, 52.51% of CCHD cases were undiagnosed at discharge, and 14.09% were still missed after 6-week examination.⁴ Therefore, it is very necessary to screen for CHD in the early neonatal period.

Combined with advances in therapeutic interventions, early detection can enable most children with CHD to have normal productive lives.⁶ Although the great progress in the field of the diagnosis and treatment of CHD has been achieved, as a low-income and middle-income country, there are tremendous variations in socioeconomic status in China, access to antenatal screening and pediatric cardiological care and performance and quality of healthcare across regions and facilities. At present, the contradiction between the increasingly mature technology of diagnosis and treatment and the inability of early detection is the biggest current dilemma in China.⁷ The National Health Council of China had launched the neonatal CHD screening in more than 20 provinces and regions since 30 July 2018. Routine neonatal screening for CHD is still at the pilot stage and has not yet been widely adopted in many Chinese hospitals, especially



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY. Published by BMJ.

Department Heart Center, Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Correspondence to

Qiang Shu; shuqiang@zju.edu.cn

in undeveloped middle-western China. In addition, the prevalence of CHD shows significant spatial clustering pattern in different regions of China.^{8,9} This screening system should be carried out from multiple perspectives according to the present economic development and according to the different regions. In this review, we will summary the present situation and progress of CHD screening in China. Furthermore, we will analyze the advantages and disadvantages of the CHD early detection methods, as well as highlight the cost-effectiveness in neonatal screening for CHD in current China.

Prenatal screening

Prenatal diagnosis of CHD plays a substantial role in improving the outcome of fetal CHD by contributing to optimized perinatal management and providing parents with useful information to make a decision regarding their pregnancy.¹⁰ Fetal echocardiography examination has become the most important technique in the prenatal detection of CHD.¹¹ However, the reported detection rates through fetal cardiac ultrasound examination were still at low level: 25%–65.5% for any CHD^{12,13} and 49%–77% for CCHD¹⁴ worldwide. A considerable proportion of fetuses with major CHD are not diagnosed prenatally, even when combined with those identified through clinical assessment, a significant diagnostic gap remains.¹⁵ The use of fetal echocardiography for detecting CHD is still limited in China. Variation in detection rates depend on both type of lesion and facility. In China, a study indicated that detailed fetal echocardiography performed by skilled physicians had high detection rate for major CHD. However, its value for detecting minor CHD was limited. The overall detection rates by fetal echocardiography examination are 93.8% in high-risk pregnant women and 47.5% in low-risk pregnant populations. The sensitivity and specificity of fetal echocardiography in detecting any CHD are 33.9% and 99.8%, respectively, in the low-risk population and 68.8% and 99.4%, respectively, in the high-risk population.¹⁰ In the study of survey of the patients with CCHD who had duct-dependent CHD and any cyanotic CHD that required early surgery, the prenatal detection rate was 14.4%.⁴ In another study on evaluating the effectiveness of prenatal screening for CHD and its impact on fetal outcome in China,¹⁶ the overall incidence of fetal CHD was 1.5%. Using the basic cardiac ultrasound examination to screen for fetal heart malformations in the general population and the extended cardiac ultrasound examination to screen those with high risk of fetal CHD, 57.6% of fetal CHD cases were identified in China, which is lower than the 82.1%–86.96% detection rate recorded by some developed countries.^{17,18} These data suggest that the fetal echocardiography training programme in China requires strengthening to further improve the accuracy of prenatal screening for CHD. In China, ultrasound screening is performed by physicians trained in obstetric ultrasonography rather than by technician sonographers, which is the common practice in many other countries.

Therefore, it may be possible to train these physicians, who have substantial knowledge of fetal cardiovascular anatomy and physiology, and integrate detailed fetal echocardiography in routine second trimester screening. Furthermore, in China, ultrasound screening examinations for fetal anomalies are typically conducted in regional tertiary obstetric centers and secondary obstetric hospitals. Pregnant women suspected of having fetal cardiac abnormalities on ultrasound screening and those with other indications are recommended to take detailed fetal echocardiography in these obstetric centers and hospitals. The incorporation of fetal echocardiography with multiple cardiac views into routine ultrasound screening may improve the detection rate of fetal major CHD and facilitate appropriate parental counseling. The detection rate of fetal ultrasound is increasing year by year in China though it is still lower than the developed countries now. The improvement can be attributed in part not only to extension of the examination to the outflow-tract view but also to technological developments and better training of the operators.^{10,12}

Postnatal detection

Detection of CHD during newborn assessment is still challenging, though screening in the neonatal period has become a consensus. Before CCHD added to the US Recommended Uniform Screening Panel for newborns, a considerable portion of CCHD was not detected during the birth hospitalization. Clinical examination is unable to detect all forms of CHD.¹⁹ Visible cyanosis is not able to be seen by human eye until oxygen saturation levels are near 80% or lower. Also, heart murmurs, one of the hallmarks of non-critical heart disease typically diagnosed later in life may be absent in many of the critical forms of CHD or misleading because of the underlying anatomy, prolonged decline of pulmonary vascular resistance or reduced ventricular function. In addition, neonates may not become symptomatic until closure of the ductus arteriosus and foramen ovale and transition between fetal and newborn circulation is complete. Variation in rates around detection depend both on types of lesion and facility.^{20,21} It is reported that 52.51% of CCHD cases who had duct-dependent CHD and any cyanotic CHD that required early surgery after born were undiagnosed and 14.09% were still missed after 6 weeks of examination.⁴ The fact suggests that the rate of misdiagnosis of CCHD before discharge from maternity hospitals is still high in China. It is consistent with the results of surveys worldwide.²² This problem may be aggravated by recent trends to earlier discharge and other changes in postnatal care.²³ The most frequently missed lesions included critical coarctation of the aorta, total anomalous pulmonary venous connection, pulmonary atresia with ventricle septal defect, single ventricle and critical. These defects should be regarded as the targets of neonatal screening. However, it has been argued that 'the use of prenatal ultrasound, close clinical observation during the transitional period and thorough physical

examination alone' may be sufficient for timely diagnosis of CCHD.²⁴ This may be true in the specific setting of this single-center study, but the prerequisites mentioned are probably not encountered in most hospitals or maternity units.²⁵ China is the largest low-income and middle-income country in the world, with an annual birth rate of roughly 16 million. Nearly 5.6% of newborn babies have a birth defect, 27% of which is CHD.³ Therefore, a reliable and feasible strategy for detecting CHD in neonates is needed.

Pulse oximetry (POX) in CHD screening

POX has been shown to be simple, quick, non-invasive, inexpensive and acceptable to both staff and parents.^{26 27} The algorithm recommended involves screening measurements on two limbs, the right hand of the infant (preductal measurement) and either foot (postductal measurement). Using POX to assist in the detection of CHD has met the criteria for universal newborn screening. Based on the evidence provided by several clinical studies, POX has been recommended as a strategy for CHD screening in neonates by the American Academy of Pediatrics.²⁸ More and more countries have introduced this screening as a routine practice.²⁷ During the past few years, several pioneering studies have provided compelling evidences for the addition of POX to fetal ultrasound screening and routine clinical assessment as a complementary method for detection of CCHD in China which is the largest low-income and middle-income country in the world.^{2 29} Data from the studies suggested that all cases with CCHD and 94% of cases of major disease cases could have been detected by POX plus clinical assessment (two-indicator) before discharge. In asymptomatic newborn babies, the two-indicator method was 93.2% for CCHD and 90.2% for major disease. The addition of POX to clinical assessment improved sensitivity for detection of CCHD from 77.4% to 93.2%. The false-positive rate for detection of critical disease was 2.7% for clinical assessment alone and 0.3% for POX alone. The sensitivity of combined POX with auscultation screening method was 95.5% for CCHD and 92.1% for major CHD. In addition, POX could significantly enhance the early detection of CCHD in neonatal intensive care units (NICU).³⁰ In two large sample, prospective, multicenter studies, the two-indicator detection method is well documented to significantly improve detection rates with reasonable false-positive rate.^{2 29} This simple and accurate combined method was recommended to be used in maternity hospitals to screen for CHD.⁴ It has been successful in decreasing missed cases to 4% before hospital discharge.¹⁵ In China, two-indicator for CHD screening strategy has been recommended to be implemented in routine postnatal care in 24 provinces and regions since 30 July 2018.

POX screening improves early detection of CHD in newborn babies by identifying those with low oxygen saturations, which is characteristic for many forms of CCHD and may not be recognized by clinical examination. Most simple but serious cases of CHD, such as

severe left heart obstructive lesions and large left-to-right shunt lesions, cannot be recognized early enough by POX to avoid heart failure, collapse or even irreversible pulmonary vascular disease at a later stage.³¹ Therefore, all major CHD can cause death or require invasive intervention during infancy should also be regarded as main targets of neonatal screening.²⁹ Unfortunately, there has been no effective screening strategy on the use of POX to screen CHD in the NICU. Babies are usually admitted to the NICU because they are unwell or premature, which might affect oxygen saturation. In addition, a large proportion of infants in the NICU are on supplemental oxygen. Most published studies on POX have excluded babies admitted to the NICU for these reasons. Additionally, babies in the NICU usually undergo continuous POX monitoring. When national screening programmes are to include all babies, then consideration of whom, how and when to screen is important. The best approach has yet to be determined. In a single-center study, POX screening based on clinical evaluation can significantly enhance the early detection rate of CCHD in NICU.³⁰ However, there was still a high false-positive rate in these screened population, of which 69% requiring echocardiograms assessment. A high false-positive rate will make it a poor screening method for CHD, increasing the overall cost of echocardiograms or consulting services and inducing parental stress and anxiety.

Some heterogeneity indeed exists in the POX screening algorithms used in the published studies, including differences in the timing of initial screening, the use of single or dual sites for measuring oxygen saturation (postductal only or preductal and postductal) and the cut-off values of oxygen saturation for a positive test.³² POX screening implementation challenges exist but solutions will in many cases. Challenges include the question of whether to screen infants in special care or NICU, and if so, under what eligibility criteria and algorithm.³³ Also challenging is how to adjust the screening algorithm to account for moderate-altitude and high-altitude locations. A study conducted at moderate altitude had significantly higher fail rates (more false positives) than at sea level which suggests adjusting cut-off points for those infants screened at high and moderate altitudes.³⁴ The big data epidemiological investigations had confirmed that high altitude is a significant environmental risk factor for CHD in China.^{8 9}

Cost-effectiveness and economic consideration analysis

Several elements that affect CHD screening costs have been assessed in varying numbers of studies, including screening staff time, instrumentation and consumables, as well as costs of diagnosis and treatment; however, most of the data of the previous studies were from the developed world. In these countries, POX screening has been widely endorsed for inclusion in routine practice to increase the detection of asymptomatic infants with CHD before discharge from birth hospitals.³⁵ Although a large scale, multicenter, prospective screening study conducted

in China confirmed the feasibility and accuracy of POX screening for the detection of CCHD in neonates before discharge and recommended its widespread use in maternity hospitals, most of these hospitals are located in the municipalities, provincial cities and in economically developed coastal cities. This screening method is considered feasible for the majority of Chinese neonates in these areas because the pulse oximeter is readily available in most secondary and tertiary hospitals, screening can also be provided by outreach services and the proportion of neonates delivered at hospitals exceeds 90%. However, there are tremendous variations in socioeconomic status, access to antenatal screening and pediatric cardiological care and performance and quality of healthcare across regions and facilities. Neonatal screening for CCHD is still at the pilot stage and has not yet been widely adopted in most hospitals, especially in western or even middle China,³¹ in where, there are large undetected and underserved population of children with CHD. In China, the cost-effectiveness of postnatal oximetry screening compared with no intervention varied across regions.³⁶ Under base-case assumptions, clinical assessment is a very cost-effective preliminary choice for neonatal screening of CHD at the national level.³⁷ The intervention is highly cost-effective in the development regions than that in the unprivileged regions. POX plus clinical assessment yield the best health outcomes on averting Disability-Adjusted Life Years, and is cost-effective only in more economically developed regions of China with better accessibility to pediatric cardiac medical care,³⁶ which reflects similar findings of the cost-effectiveness of screening in developed countries.³⁸ The two-indicator detection method is considered crucial for realizing the benefits of CHD screening. The economic balance between the costs and benefits of screening has been recognized as a desirable attribute of population screening programmes. The success of POX screening in the low-income and middle-income countries depends on the availability and affordability of pediatric cardiac medical care. In China, in terms of cost-effectiveness and feasibility, the application of postnatal oximetry screening is recommended first to be implemented in developed metropolitan regions to maximize the benefits of neonatal CHD screening.

Important barriers to screening for CHD have been identified. These include out of hospital births, cost and knowledge deficits among healthcare professionals. There are certainly costs and harms associated with both screening and subsequent testing that ensues. In China, the echocardiograms triggered by positive screening test are additional charges which are not covered by medical insurance and are the family's own expense. Although pediatric cardiac medical care is available in China, it is highly concentrated in urban tertiary hospitals. In addition to the anxiety triggered by a failed screening and the costs of additional screening, some babies may need to be transferred from their birth setting to another facility for echocardiography. The issue of transfer is particularly true in rural states where the nearest available

echocardiography may be a great distance away, and the associated medical costs are catastrophic for most families of infants with CHD.³⁹ Improvement in the coverage and reimbursement rate of the current medical insurance scheme is an urgent task, particularly for those living in unprivileged regions.

Useful complementary methods for CHD screening

It is reported that the POX screening system with the cut-off SpO₂ <95% is inapplicable to high altitude for a number of reasons.⁴⁰ The study from moderate altitude showed significantly higher failure rates of POX screening than those at sea level, even with a cut-off value of 90%.³⁴ Unfortunately, the altitude increased significantly in the middle-western areas of China. So the echocardiography as an intensive methodology is suitable for the newborn in such areas,⁴⁰ still more accurate even in the plain area in the east region of China.¹¹ However, the prevalence of CHD of live infants determined by echocardiography screening was found to be relatively high,^{11 40 41} either in the plain area or in the plateau area. When all infants with or without symptoms and physical signs of CHD participated in the echocardiography CHD screening, many asymptomatic CHD cases were diagnosed. Since most atrial septal defect with defects smaller than 6 mm and most ventricular septal defect with muscular defects would have a higher possibility of spontaneous closure before 1 year, which may explain the reason for higher prevalence of CHD determined by echocardiography in newborn. To some extent, it will increase the overall cost of echocardiograms and consulting services in the developing region, as well as will induce parental stress and anxiety in all. This may make it a poor screening method for CHD.

CHD is a complex disease which may be caused by both environmental and genetic factors.⁴² Approximately, 5%–8% of CHD is due to chromosomal abnormalities, and 3% due to classical genetic defects with a high recurrence risk in first-degree family members.⁴³ In the past decades, a series of CHD-causing genes have been identified based on Chinese population, such as *TBX20* and *CITED2*, as well as some gen copy number variations of chromosomal region.^{43–45} The gene mutations can cause cardiac malformations through affecting the transcription activity of critical genes involved in heart development pathways. In addition, gene analysis combined with MRI or prenatal ultrasound were accurate prenatal genetic techniques for identifying fetal chromosomal abnormalities associated with cardiac defects and more effective for diagnosing fetal CHD.^{46 47} This can assist clinical doctors to perform early postnatal screening for CHD and appropriate genetic counselling with regard to outcome. It is undoubtedly more effective in improving the prognosis of the patients if it is possible to discover and diagnose CHD, especially the critical lesions, before birth, together with the fetal interventions and perinatal managements. We can do more in the field of CHD genetics in the future.

Follow-up system

Follow-up is an important issue in the screening of CHD. Although many cases of CHD are detected prenatally or through clinical examination, infants who appear normal might be discharged home and subsequently undergo life-threatening crises.^{4 48} Effective follow-up for screens with positive results must be implemented in order for screening programmes to be successful. Sometimes, the follow-up system should be extended to the asymptomatic babies who discharged home. Impact of screening in regions with less access to intervention will be important to track. A low follow-up rate was found, especially for rural populations in China.

At present, many coastal cities and provinces have established CHD screening, treatment and surveillance networks. However, due to disparities in economic and medical resources, many children with CHD in deprived areas in western China are still not diagnosed and treated in a timely manner.^{31 40} Policies should be formulated to address the epidemiology of CHD in deprived areas of middle-western China to better allocate medical resources and to develop local training programmes to screen and diagnose CHD in these areas. A national CHD screening network and a so-called 'green channel' network are also needed to improve the diagnosis rate of CHD in these areas and to establish follow-up and treatment plans.¹ Public investment and insurance coverage for children with CCHD are crucial for exploiting the health benefits of the screening.³⁹ Although the hierarchical treatment and referral system has not been established throughout the country,⁴⁹ the importance and feasibility of CHD screening have been demonstrated in China.⁷ The national CHD screening network system consisting of screening, referral and information transmission will make it possible for early detection, timely diagnosis and appropriate management of CHD in the country.

CONCLUSIONS

The overall prevalence of CHD is still high in current China. Due to the tremendous variations in socioeconomic status and disparities in medical resources, universal screening system for CHD is difficult to adapt to the current situation in China. The developed regions have established relatively well CHD screening, treatment and surveillance networks, while the vast developing areas have not. Currently, the screening of CHD in China should be tailored to local conditions and effective safeguard mechanism and follow-up system should be established to improve the prognosis of CHD. It is undoubtedly more effective in improving the prognosis of the patients if it is possible to discover and diagnose CHD in timely, especially the critical lesions, before birth, together with the fetal interventions and perinatal managements.

Contributors WL and WX drafted the initial manuscript and contributed equally to this paper. All authors reviewed, revised and approved the final manuscript.

Funding This work was financially supported by the Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents to Professor Shu Q (2016-6) and Natural Science Foundation of Zhejiang Provincial to Dr Xiwang Liu (LY19H150005).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

REFERENCES

- Zhao Q-M, Liu F, Wu L, *et al.* Prevalence of congenital heart disease at live birth in China. *J Pediatr* 2019;204:53–8.
- Zhao Q-ming, Ma X-jing, Ge X-ling, *et al.* Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. *Lancet* 2014;384:747–54.
- National Health Commission of the People's Republic of China. Report on the prevention and control of birth defects in China, 2012. Available: <http://www.gov.cn/gzdt/att/att/site1/20120912/1c6f6506c7f811b acf93 01.pdf> [Accessed 27 Jun 2018].
- Zhao QM, Liu F, Wu L, *et al.* Assessment of undiagnosed critical congenital heart disease before discharge from the maternity hospital. *Zhonghua Er Ke Za Zhi* 2017;55:260–6.
- Peterson C, Dawson A, Grosse SD, *et al.* Hospitalizations, costs, and mortality among infants with critical congenital heart disease: how important is timely detection? *Birth Defects Res A Clin Mol Teratol* 2013;97:664–72.
- Mahle WT, Martin GR. Section on cardiology and cardiac surgery Executive Committee. Endorsement of health and Human services recommendation for pulse oximetry screening for critical congenital heart disease. *Pediatrics* 2012;129:190–2.
- XJ M, Huang GY. Current status of screening, diagnosis, and treatment of neonatal congenital heart disease in China. *World J Pediatr* 2018;14:313–4.
- Chun H, Yue Y, Wang Y, *et al.* High prevalence of congenital heart disease at high altitudes in Tibet. *Eur J Prev Cardiol* 2018;12.
- LG M, Chen QH, Wang YY, *et al.* Spatial pattern and variations in the prevalence of congenital heart disease in children aged 4–18 years in the Qinghai-Tibetan Plateau. *Sci Total Environ* 2018;627:158–65.
- Chu C, Yan Y, Ren Y, *et al.* Prenatal diagnosis of congenital heart diseases by fetal echocardiography in second trimester: a Chinese multicenter study. *Acta Obstet Gynecol Scand* 2017;96:454–63.
- Zhao Q-ming, Ma X-jing, Jia B, *et al.* Prevalence of congenital heart disease at live birth: an accurate assessment by echocardiographic screening. *Acta Paediatr* 2013;102:397–402.
- Oggè G, Gaglioti P, Maccanti S, *et al.* Prenatal screening for congenital heart disease with four-chamber and outflow-tract views: a multicenter study. *Ultrasound Obstet Gynecol* 2006;28:779–84.
- Hom LA, Martin GR. U.S. international efforts on critical congenital heart disease screening: can we have a uniform recommendation for Europe? *Early Hum Dev* 2014;90(Suppl 2):S11–S14.
- Marek J, Tomek V, Skovráněk J, *et al.* Prenatal ultrasound screening of congenital heart disease in an unselected national population: A 21-year experience. *Heart* 2011;97:124–30.
- Riede FT, Wörner C, Dähnert I, *et al.* Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine—results from a prospective multicenter study. *Eur J Pediatr* 2010;169:975–81.
- Yu Z, Xi Y, Ding W, *et al.* Congenital heart disease in a Chinese hospital: pre- and postnatal detection, incidence, clinical characteristics and outcomes. *Pediatr Int* 2011;53:1059–65.
- van Velzen CL, Clur SA, Rijlaarsdam MEB, *et al.* Prenatal diagnosis of congenital heart defects: accuracy and discrepancies in a multicenter cohort. *Ultrasound Obstet Gynecol* 2016;47:616–22.
- Smrcek JM, Berg C, Geipel A, *et al.* Detection rate of early fetal echocardiography and in utero development of congenital heart defects. *J Ultrasound Med* 2006;25:187–96.
- Dawson AL, Cassell CH, Riehle-Colarusso T, *et al.* Factors associated with late detection of critical congenital heart disease in newborns. *Pediatrics* 2013;132:e604–11.
- Gardiner HM, Kovacevic A, van der Heijden LB, *et al.* Prenatal screening for major congenital heart disease: assessing performance

- by combining national cardiac audit with maternity data. *Heart* 2014;100:375–82.
21. Peterson C, Ailes E, Riehle-Colarusso T, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using Pulse oximetry. *JAMA Pediatr* 2014;168:361–70.
 22. Chang R-KR, Rodriguez S, Klitzner TS. Screening newborns for congenital heart disease with pulse oximetry: survey of pediatric cardiologists. *Pediatr Cardiol* 2009;30:20–5.
 23. Mellander M, Sunnegårdh J. Failure to diagnose critical heart malformations in newborns before discharge—an increasing problem? *Acta Paediatr* 2006;95:407–13.
 24. Sendelbach DM, Jackson GL, Lai SS, et al. Pulse oximetry screening at 4 hours of age to detect critical congenital heart defects. *Pediatrics* 2008;122:e815–20.
 25. Riede FT, Dähnert I, Schneider P, et al. Pulse oximetry screening at 4 hours of age to detect critical congenital heart defects. *Pediatrics* 2009;123:e542. author reply e542–3.
 26. Manzoni P, Martin GR, Sanchez Luna M, et al. European pulse oximetry screening Workgroup. Pulse oximetry screening for critical congenital heart defects: a European consensus statement. *Lancet Child Adolesc Health* 2017;1:88–90.
 27. Thangaratinam S, Brown K, Zamora J, et al. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. *The Lancet* 2012;379:2459–64.
 28. Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. *Pediatrics* 2011;128:e1259–67.
 29. XJ H, XJ M, Zhao QM, et al. Pulse oximetry and auscultation for congenital heart disease detection. *Pediatrics* 2017;140.
 30. Hu X-J, Zhao Q-M, Ma X-J, et al. Pulse oximetry could significantly enhance the early detection of critical congenital heart disease in neonatal intensive care units. *Acta Paediatr* 2016;105:e499–505.
 31. TC H, Ouyang H, Lu Y, et al. Postprocedural outcomes of rural children undergoing correction of congenital heart lesions in Yunnan Province, China. *Pediatr Cardiol* 2011;32:811–4.
 32. Rosti L. Neonatal pulse oxymetry as a screening for congenital heart disease: single or double recordings? *Eur J Pediatr* 2010;169. author reply 1571–1572.
 33. Fernandes N, Lakshminrusimha S. The limitations of pulse oximetry for critical congenital heart disease screening in the neonatal intensive care units. *Acta Paediatr* 2017;106.
 34. Wright J, Kohn M, Niermeyer S, et al. Feasibility of critical congenital heart disease newborn screening at moderate altitude. *PEDIATRICS* 2014;133:e561–9.
 35. Mahle WT, Newburger JW, Matherne GP, et al. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the American Heart Association and American Academy of pediatrics. *Circulation* 2009;120:447–58.
 36. Tobe RG, Martin GR, Li F, et al. Should postnatal oximetry screening be implemented nationwide in China? A cost-effectiveness analysis in three regions with different socioeconomic status. *Int J Cardiol* 2016;204:45–7.
 37. Tobe RG, Martin GR, Li F, et al. Cost-effectiveness analysis of neonatal screening of critical congenital heart defects in China. *Medicine* 2017;96:e8683.
 38. Peterson C, Grosse SD, Oster ME, et al. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. *Pediatrics* 2013;132:e595–603.
 39. Zhang W, Wang X, Li J, et al. Uncompensated care for children without insurance or from low-income families in a Chinese children's hospital. *Med Sci Monit* 2014;20:1162–7.
 40. Li J-J, Liu Y, Xie S-Y, et al. Newborn screening for congenital heart disease using echocardiography and follow-up at high altitude in China. *Int J Cardiol* 2019;274:106–12.
 41. Liu X, Liu G, Wang P, et al. Prevalence of congenital heart disease and its related risk indicators among 90,796 Chinese infants aged less than 6 months in Tianjin. *Int J Epidemiol* 2015;44:884–93.
 42. van der Bom T, Zomer AC, Zwinderman AH, et al. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol* 2011;8:50–60.
 43. Chen J, Sun F, Fu J, et al. Association of TBX20 gene polymorphism with congenital heart disease in Han Chinese neonates. *Pediatr Cardiol* 2015;36:737–42.
 44. Liu Y, Wang F, Wu Y, et al. Variations of CITED2 are associated with congenital heart disease (CHD) in Chinese population. *PLoS ONE* 2014;9:e98157.
 45. Zhang X, Xu Y, Liu D, et al. A modified multiplex ligation-dependent probe amplification method for the detection of 22q11.2 copy number variations in patients with congenital heart disease. *BMC Genomics* 2015;16.
 46. Luo S, Meng D, Li Q, et al. Genetic testing and pregnancy outcome analysis of 362 fetuses with congenital heart Disease identified by prenatal ultrasound. *Arq Bras Cardiol* 2018;111:571–7.
 47. Wang L, Nie H, Wang Q, et al. Use of magnetic resonance imaging combined with gene analysis for the diagnosis of fetal congenital heart disease. *BMC Med Imaging* 2019;19.
 48. Reich JD, Haight D, Reich ZS. A comparison of the incidence of undiagnosed congenital heart disease in hospital Born and home born children. *NPM* 2017;10:71–7.
 49. Liu Y, Yang L-L, Xu S-Y, et al. Pediatrics in China: challenges and prospects. *World J Pediatr* 2018;14:1–3.