International Journal of Gynecology and Obstetrics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

REVIEW ARTICLE

A systematic review of prenatal screening for congenital heart disease by fetal electrocardiography

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ARTICLE INFO

Article history:
Received 2 February 2016
Received in revised form 21 May 2016
Accepted 27 July 2016

Keywords:
Congenital heart disease
Fetal electrocardiography
Fetal electrocardiogram
Prenatal diagnosis
Prenatal screening

ABSTRACT

Background: Congenital heart disease (CHD) is the most common severe congenital anomaly worldwide. Diagnosis early in pregnancy is important, but the detection rate by two-dimensional ultrasonography is only 65%–81%. *Objectives:* To evaluate existing data on CHD and noninvasive abdominal fetal electrocardiography (ECG). *Search strategy:* A systematic review was performed through a search of the Cochrane Library, PubMed, and Embase for studies published up to April 2016 using the terms "congenital heart disease," "fetal electrocardiogram," and other similar keywords. *Selection criteria:* Primary articles that described changes in fetal ECG among fetuses with CHD published in English were included. *Data collection and analysis:* Outcomes of interest were changes in fetal ECG parameters observed for fetuses with congenital heart disease. Findings were reported descriptively. *Main results:* Only five studies described changes observed in the fetal electrocardiogram for fetuses with CHD, including heart rate, heart rate variability, and PR, QRS, and QT intervals. Fetal ECG reflects the intimate relationship between the cardiac nerve conduction system and the structural morphology of the heart. It seems particularly helpful in detecting the electrophysiological effects of cardiac anatomic defects (e.g. hypotrophy, hypertrophy, and conduction interruption). *Conclusions:* Fetal ECG might be a promising clinical tool to complement ultrasonography in the screening program for CHD.

1. Introduction

Congenital heart disease (CHD) is the most common severe congenital anomaly worldwide [1]. It has been defined as "a gross structural abnormality of the heart or intra-thoracic large vessels that is actually or potentially of functional significance" [2]. Major CHD is usually defined as a form of CHD that is lethal or requires intervention in the first year of life. The incidence of CHD is estimated at 6–12 cases per 1000 live births (4 cases of major CHD per 1000 live births), which makes this disorder six times more common than chromosomal anomalies and four times more common than neural tube defects [3–5]. In Europe, the overall rate of mortality due to CHD (both perinatal deaths and termination of pregnancy) was 0.7 per 1000 births in 2000–2005 [6]. Of the fetuses affected by CHD, 4.5% die in utero and 21.1% die after birth [7].

Diagnosing CHD early in pregnancy enables the identification of associated extracardiac anomalies (present in 29% of cases) and chromosomal anomalies (26% of cases) that have an effect on fetal and postnatal prognosis [8]. Prenatal and genetic counselling by experts can be offered to parents. Thereafter, parents can decide to terminate or continue with the pregnancy. Studies [8,9] have shown that the frequency of pregnancy termination is higher if prenatal diagnosis is made at an earlier gestational age (61% and 44% at 19 and 24 weeks of pregnancy, respectively). If pregnancy is continued, an adequate plan of management can be developed, including intrauterine therapy, timing, mode and location of delivery, and immediate treatment after birth. It has been demonstrated that prenatal diagnosis of CHD increases survival rates and decreases long-term morbidity in both ductus-dependent and foramen ovale-dependent CHD [9–12]. As Yates [13] has pointed out, however, prenatally diagnosed CHD often has a worse prognosis because it is more likely to be severe (i.e. easier to detect by ultrasonography) or associated with extracardiac or chromosomal anomalies.

Fetal cardiac screening during the second trimester was standardized in 2006 [14]. The detection rate of CHD varies widely, from 65% to 81% [15–18]. The challenges encountered include the complex anatomy of the fetal heart, its motion, and small size. Specific echocardiography is performed for fetuses with risk factors for CHD, and this technique has a higher detection rate (sensitivity 90%, specificity 98%) [19].

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http://dx.doi.org/10.1016/j.ijgo.2016.05.010
0020-7292/

However, up to 90% of all cases of CHD occur in the low-risk population [3,4,20–22], indicating the necessity of an effective screening procedure that is available to all pregnant women.

Therefore, there is need for a reliable noninvasive diagnostic method with improved predictive value for the diagnosis of CHD. Noninvasive transabdominal fetal electrocardiography (fetal ECG) is a new field that is being investigated. This technique can be used early in pregnancy (from 18 weeks), is safe to use, and easy to apply [23]. A big advantage is that fetal ECG is a potentially non-expensive long-term diagnostic tool, and raw data can be forwarded for evaluation elsewhere.

Extraction of fetal ECG data was first described in 1906 by Cremer [24], and the approach was first reviewed in 1986 by Pardi et al. [25]. Despite this early documentation, the development of fetal ECG has lagged behind other techniques for fetal monitoring, partly because of technical challenges. The fetal signal has low amplitude (2–50 microvolts, 1/50th of the maternal ECG), and is masked by both the maternal electrocardiogram and background noises (maternal electromyogram), resulting in a low signal-to-noise ratio [25,26]. The fetus is surrounded by amniotic fluid and maternal tissues, which enlarge the distance to the electrodes and cause a non-homogenous tissue conduction that interferes with signal quality. Additionally, the vernix caseosa is electrically isolating and a main cause of the poor signal-to-noise ratio from 30 to 34 gestational weeks [23,27]. Other challenging factors are the complex three-dimensional form of the fetal electrocardiogram and the movements of the fetus, which makes it difficult to evaluate the heart from one direction. Furthermore, at 20 gestational weeks, the fetal heart is approximately one-tenth of the size of an adult heart and the fetal heart rate is two to three times faster than the adult heart rate [28]. With improvements in technology and knowledge of information theory, however, fetal ECG is becoming more and more attractive.

In addition to the challenges in the conduct of fetal ECG, it is also difficult to interpret the data. By contrast with postnatal life, the systemic circulation in the fetus is fed from the left and right ventricles in parallel with equal intraventricular pressure [29]. The right ventricular outflow is slightly larger than the left ventricular outflow. The ductus arteriosus propels 40% of the combined cardiac output during the second trimester. Right-sided obstructive lesions (e.g. tetralogy of Fallot or pulmonary stenosis) with a dominance of the right ventricle are difficult to diagnose in utero; however, they are often accompanied by septal defects or by left-side obstructive lesions (e.g. aortic stenosis or coarctation of the aorta), which can be detected more easily. Owing to the fetal circulation in utero, fetuses affected by CHD do not always show overt signs of cardiac failure, because one side of the heart can compensate for an abnormality on the other side. At present, the changes in the fetal ECG amplitudes, segment intervals, and heart axis that are characteristic of CHD are not known. Although the changes due to CHD seen on neonatal ECG are documented, these data are not likely to correspond with those of fetal ECG because the circulation changes markedly directly after birth. The aim of the present review was to evaluate the existing data on CHD and noninvasive abdominal fetal ECG.

2. Materials and methods

As part of a systematic review, the Cochrane Library (2016, Issue 4), PubMed, and Embase electronic databases were searched to identify all studies published on fetal ECG and CHD up to April 30, 2016. The following keywords were used: “congenital heart disease,” “congenital heart defects,” “fetal electrocardiogram,” “fetal electrocardiography,” and “fetal ECG”. The outcomes of interest were changes seen in fetal ECG parameters, such as ECG intervals, ECG segments, and the electrical heart axis among fetuses with CHD.

Primary articles that described the changes in fetal ECG among fetuses with CHD were selected. The reference lists of the selected articles were also searched. The study language was restricted to English. Review articles and studies describing diagnostic tools other than noninvasive abdominal fetal ECG were excluded. Articles that solely described fetal arrhythmia were excluded because only few arrhythmias are associated with CHD.

The search and selection of articles were performed independently by two authors (K.M.J.V. and N.B.E.). The guidelines and quality assessment forms of the Dutch Cochrane Center were used to evaluate the quality of the studies. The findings were reported descriptively and no statistical analysis was performed.

3. Results

The search and selection of articles is summarized in Fig. 1. In total, five articles met the inclusion criteria and were reviewed, including case reports by Hamilton et al. [30] and Brambati and Bonsignore [31]. Three articles by Siddiqui et al. [32], Velayo et al. [33], and Yilmaz et al. [34] were prospective cohort studies including normal fetuses and cases of CHD. The five studies were published between 1977 and 2016.

Owing to the low numbers of fetuses, the variation in outcome measures described, and the differences in signal processing techniques used in the five studies, it was not possible to directly compare or pool the results. The basic characteristics and a quality assessment of the two case reports are given in Table 1, whereas the basic characteristics and a quality assessment of the prospective studies are given in Tables 2 and 3. Table 4 presents an overview of the fetal ECG parameters of the fetuses with CHD included in the review.

Hamilton et al. [30] described a case of complex CHD, in which a complete heart block was seen in 1977. They used a cardiotocograph with the capacity to process fetal phonocardiographic and abdominal fetal ECG signals. The bizarre QRS complexes found on fetal ECG (not otherwise specified) suggest that the pacemaker was distal to the bundle of His, with a fetal heart rate of 50 beats per minute. After delivery, cardiac catheterization and angiocardiography were performed to confirm the existence of complex CHD (Table 4).

Seven years later, Brambati et al. [31] described a case of an atrioventricular septal defect in which cardiac arrhythmia was seen. The signal processing method is not extensively described, but data extraction was mainly performed manually and a median fetal ECG constituting 50 heartbeats was generated. Extrasystoles without a preceding P wave were found, suggestive of ventricular origin. Additionally, a prolonged QRS time was found, which was stated to be suspicious of cardiac enlargement and/or a cardiac anomaly. After delivery, ventricular extrasystoles, left axis deviation, and right ventricular

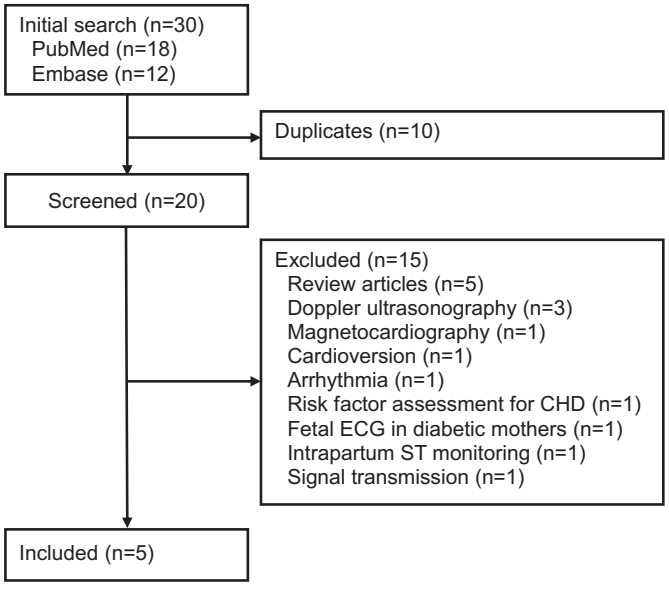

Fig. 1. Flowchart showing the search and selection of articles. Abbreviations: ECG, electrocardiography; CHD, congenital heart disease.

Please cite this article as: Verdurmen KMJ, et al, A systematic review of prenatal screening for congenital heart disease by fetal electrocardiography, Int J Gynecol Obstet (2016), http://dx.doi.org/10.1016/j.ijgo.2016.05.010