Review paper

TRANSPLACENTAL DIGOXIN TREATMENT IN PRENATAL CARDIAC PROBLEMS IN SINGLETON PREGNANCIES - META ANALYSIS (BASED ON LITERATURE: 1992-2015)

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Prenat Cardio 2016 Jan; 6(1):67-74
DOI: 10.1515/pcard-2016-0009

Abstract

Based on fourteen case reports from various centres from 1992–2015 and three original studies in 2006–2011, 122 fetuses were subjected to analysis. In these reports, transplacental digoxin treatment was administered to different cardiac anomalies such as SVT , Ebstein's anomaly, critical AS , absent pulmonary valve syndrome, complete heart block, in foetuses with aneurysm/diverticulum of LV, in tricuspid atresia or dysplasia, rhabdomyoma, pulmonary atresia, HLHS with fibroelastosis, in TTTS and in extracardiac anomalies such as atriovenous malformation or sacrococcygeal teratoma. There was no statistical difference to suggest (Chi-square test) that digoxin was more efficient to control fetal arrhythmias than fetal congestive heart failure in nonarrhythmic patients.

Conclusions: Foetal cardiac insufficiency may appear due to different reasons (in normal heart anatomy or in heart defects, in normal sinus rhythm or due to foetal arrhythmias: tachycardias or severe bradycardia) and may be a cause of intrauterine demise. So far, we do not have strong evidence that digoxin treatment may prevent foetal death or prematurity. More research is needed to ascertain if the prolonging of pregnancy resulted from digoxin treatment or if improvement in foetal circulatory insufficiency was influenced by spontaneous regression of foetal cardiac symptoms.

Key words: *Digoxin, fetus treatment, cardiac arrhythmia, fetal oedema.*

INTRODUCTION

Digoxin, a purified cardiac glycoside derived from digitoxin extracted from the woolly foxglove (Digitalis kabata) purple foxglove (Digitalis purpurea), has strong inotropic and chronotropic effects on the heart. The positive inotropic activity increases the stroke and minute volume, while the negative chronotropic action slows the cardiac rhythm, which results from direct action of digoxin on the sinus node and stimulation of the centres of the vagus nerve. The primary indication for digoxin was to improve disorders of circulatory hemodynamics.[1] Digitalis glycosides are among the oldest drugs used in cardiology .Today, digoxin is occasionally used in the treatment of atrial fibrillation, atrial flutter and congestive heart failure that cannot be controlled by other medication. Currently, the general use of digoxin has been curtailed because of difficulties in efficient dosing, as well as the availability of newer and more effective drugs in paediatrics and adult cardiology.

How to cite this article:
Strzelecka I, Respondek-Liberska M, Słodki M, Zych-Krekora K, Cuneo B. Transplacental digoxin treatment in prenatal cardiac problems in singleton pregnancies - meta analysis (based on literature: 1992-2015). Prenat Cardio 2016; 6(1):67-74

Digoxin side effects are mainly cardiac arrhythmias, observed in about 20% of patients (A-V blocks type I, II and III AV, ventricular or supraventricular extrasystoles[2]. Other symptoms of side effects are gastrointestinal symptoms (nosea, vomiting) and CNS disturbances (blurred vision). Because there is usually a small difference between the treatment dose and toxic dose, it is very easy to overdose the patient or to give subtherapeutic doses. Thus, close monitoring of plasma levels of digoxin and of the electrocardiogram are necessary.

In obstetrics, the transplacental treatment in healthy pregnant women with digoxin has been used for the management of prenatal cardiology for many years.[3,4,5,6,7,8,9,10,11,12,13,14,15,16]. Probably because of an increased blood volume in the third trimester of pregnancy and possibly other mechanisms, no side

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Submitted: 2016-07-05, accepted: 2016-07-07

Year	Author…	Cardiac diagnosis	Transplacental Digoxin / time of treatment	Symptoms before treatment	Prenatal Results	Delivery	Newborn's condition	Neonatal /infant Follow-up
1992	Ishikawa S & co.	Complete heart block (CHB) + AVC and circular insufficiency	10 weeks	Bradycardia Poor contractility of heart muscle Pericardial effusion	Gradual improvement of fetus condition	CS 33 week	Stable (Baby girl)	Implantation of stimulator
1997	Koike I & co.[4]	Ebstein S with generalised oedema of one of monozygotic twins	6 weeks	Fetus oedema	Oedema regression	CS 33 week	Severe	Death of the sick newborn 22 hours after the birth. The healthy twin survived
1998	Hsieh I & co.[5]	Ebstein S with generalised oedema	6 weeks. + Continuation after birth	Fetus oedema Congestive Heart Failure Cardiomegaly TR	Gradual improvement: Oedema regression, continued TR	Vaginal 38 week.	Severe	Postnatal treatment with Digoxin continued and gradually stopped
2000	Brakley KJ & Co.[6]	Complete heart block (CHB) with oedema	7 weeks	Fetus oedema	CHB stayed but the oedema regressed	CS 37 week	Stable	At the age of 8-month-old HR 45min without stimulator and medications
2006	Respondek-Liberska M. & Co.[7]	SVT >200/min	* data presented in table 4					
2008	Dhaval… Huhta J & Co.[8]	Congestive heart failure	* data presented in table 2					
2008	Radzymińska-Chruściel B. & Co.[9]	Critical artery stenosis	+	Cardiomegaly Circulation insufficiency	Improvement of the circulation efficiency	CS	Balloon valvuloplasty after delivery	At the age of 2 months general good condition
2008	Pradhanl & Co.[10]	Isolated congenital diverticulum of LV+ Cardiac arrhythmia	5 weeks	Cardiac arrhythmia, ectopia of ventricles	Sinus rhythm within 48 hours	Vaginal 38 weeks	Stable	
2010	Śliwa J & Co.[11]	Ebstein syndrome	12 weeks	HA/CA 0.62 CVPS 5/10 SF RA 0% SF RV 18% Oxygen test - negative	HA/CA 0.5 CVPS 7/10 SF RA 11% SF RV 28% Oxygen test – positive	CS		Death – 8th day of postnatal life (no cardiac surgery)
2011	Sokol V & Co.[12]	SVT oedema	7 weeks	SVT in 29th week of pregnancy	Oedema reduction, sinus rhythm	CS 36.6 week	Stable	Improvement of the newborn's condition
2011	Jaegii ET & Co.[13]	SVT + atrial flutter (AF)	* data presented in table 3					
2013	Hirose A, I & Co.[14]	LV aneurysm, Generalised oedema	10 weeks	Severe fetus oedema with pericardial effusion and ascites	Oedema regression	CS 33 week	Stable	Aneurysm resection ion 10th hour of life
2014	Dayton JD & Co.[15]	SVT	1-2 weeks	SVT	Sinus rhythm	2 CS 1 TOP	Stable	No side effects of treatment
2015	DeJong S I & Co.[16]	Arrhythmia	10 weeks	Cardiac arrhythmia	Gradual improvement of heart rhythm		Very good	

Table 1. Data from the 11 case reports published in years 1992 to 2015 and three oryginal studies

No	Group	First CVPS	Diagnosis	Time of starting the treatment with digoxin (week)	Time of death or labour (weeks)	Time of treatment with digoxin (weeks)	Digoxin concentration in maternal blood (ng/dl)	Change in result of CVPS	CVPS at the labour or death	Result	Type of taken intervention
1	3	≤5	Fetus oedema, Cystic hygroma Turner S	26	29.5	3.5	2.3	-1	5	Intrauterine death	None
2	2	6-7	Fetus oedema. Sacrococcygeal teratoma	29	30	1	1.8	1	6	Alive birth (AB)	None
3	2	6-7	Fetus oedema. Ebstein's S	31	36.2	5.2	1.5	-1	6	AB	Closure of ductus arteriousus
4	1	8-9	Fetus oedema. Tof F+ no pulmonary valve	23	38	15	2.1	1	9	AB	Cardiac surgery
5	3	≤5	Fetus oedema, critical AS tricuspid valve dysplasia	28	34	3	1.4	1	4	Intrauterine death	No
6	2	6-7	Recipient in TTTS	24.5	29	5	1.5	0	6	AB	No
7	3	≤5	Fetus oedema, cardiomyopathy	26	29	3	Very good	0	2	Intrauterine death	
8	1	8-9	Rhabdomyoma subaortal	31	36.5	5	2.1	1	9	AB	Tumour resection
9	2	6-7	Fetus oedema, critical AS, MR	30	35	4	1.8	-1	6	AB	In utero balloon valvuloplasty + neonatal Norwood's procedure
10	2	6-7	Critical artery stenosis	31	38	6	0.8	0	7	AB	In utero, balloon valvuloplasty + after birth valvuloplasty + , Ross-Kono's surgery
11	1	8-9	Fallot's tetralogy, no lung vlave	29	36	6	Very good	0	7	AB	Surgery
12	1	8-9	Fetus oedema, recipient in TTTS	25	33	7	1.7	0	7	AB	None
13	2	6-7	Fetus oedema, critical AS	25	38	4	1.7	1	9	AB	In utero valvuloplasty + neonatal Norwood's surgery + modified Blalock-Taussig shunt + , Glenn surgery
14	2	6-7	Fetus oedema, critical AS, tricuspid valve dysplasia	33	34	4	0.4	-1	7	AB	Balloon valvuloplasty after the birth, closure of arterial duct
15	2	6-7	Arteriovenous malformation in OUN	34	38	4	1.6	1	8	None	None
16	1	8-9	Recipient in TTTS	29.5	34	7	0.9	0	9	AB	None
17	3	≤5	Fetus oedema, critical artery stenosis	25	37	13	1.4	2	7	AB	In utero balloon valvuloplasty + valvuloplasty after birth
18	2	6-7	Ebstein's anomaly	32	36	4	1.4	1	6	AB	Newborn's death

Table 2 (part 1). Data from Dhaval & Huhta and co8 : retrospective analysis of transplancental digoxin treatment of the congestive heart failure without fetal arrhythmia in 28 fetuses.

No	Group	First CVPS	Diagnosis	Time of starting the treatment with digoxin (week)	Time of death or labour (weeks)	Time of treatment with digoxin (weeks)	Digoxin concentration in maternal blood (ng/dl)	Change in result of CVPS	CVPS at the labour or death	Result	Type of taken intervention
19	2	6-7	Ebstein's anomaly	25	33	7	2.4	1	6	AB	None, newborn's death
20	1	8-9	Recipient in TTTS	27	34	7	1.4	1	9	AB	None
21	3	≤5	No pulmonary valve	20	29	9	2.2	1	3	AB	None, newborn's death
22	2	6-7	Fallot's tetralogy, no pulmonary valve	21	In utero		2.4	1		In utero	In utero
23	2	6-7	Critical AS	20	38.5	18.5	0.5	2	8	AB	Norwood's operation, POD
24	3	≤5	Tricuspid atresia + TGA + PR	37.5	40	2.5	Very good	1	7	AB	
25	3	≤5	Fetus oedema, tricuspid valve dysplasia	27	36	9	1.2	1	7	AB	Balloon pulmonary valvuloplasty after birth
26	3	≤5	Fetus oedema, HLHS, endocardial fibroelastosis	21	38	17	Not applicabe	3	8	AB	Norwood's operation, POD
27	3	≤5	Fetus oedema, PV atresia, no VSD	28	28.5	0.5	3	0	3	IUD	
28	2	6-7	Donor TTTS	21	In utero		1.1	2		In utero	In utero

Table 2 (part 2). Data from Dhaval & Huhta and co8 : retrospective analysis of transplancental digoxin treatment of the congestive heart failure without fetal arrhythmia in 28 fetuses.

effects from digoxin affected majority of pregnant women, whereas an improvement of foetal hemodynamics was usually observed.

The literature about the use of digoxin during pregnancy is somewhat limited and there is no exhaustive analysis that directly answers questions about foetal hemodynamic improvement resulting from transplacental treatment with digoxin or spontaneous regression of earlier observed disorders.

MATERIALS AND METHODS

Fourteen case reports from various centres in the USA, Japan, Poland and Croatia during 1992–2015 (Table 1) and three original studies in 2006–2011 (Tables 2, 3 and 4) were subjected to our analysis.[7,8,13] In these reports, transplacental digoxin treatment was administered to different cardiac anomalies accompanied by generalised foetal oedemas, cardiac arrhythmia, cardiac insufficiency (Table 1). For statistical analysis Chi-square test was used to analyse was digoxin more efficient to control fetal arrhythmias or fetal congestive heart failure?

DISCUSSION

Although Digitalis parviflora was used by medical doctors in 16th and 17th centuries, the publication, entitled "An Account of the Foxglove and some of its Medical

Year	Author…	Cardiac diagnosis	Transplacental Digoxin / time of treatment	Symptoms before treatment	Prenatal Results	Delivery	Newborn condition	Neonatal /infant Follow-up
2011	Jaegii ET & Co. [13]	SVT + atrial flutter (AF)	24 fetuses means 50 days (min 12–max 143) SVT in case of and 23 days (2–98) in case of AF	Broken or continuous arrhythmia, fetus oedema	Postive result STV or heart block NHA 13 and 10 (AF)	No data	No side effects of the treatment	Improvement of the condition of the 23 fetuses and 1 neonatal death

Table 3. Data from Jaeggi ET and co13. : Comparison of Transplacental Treatment of Fetal Supraventricular Tachyarrhythmias with Digoxin: Results of a Nonrandomized Multicenter Study: 24 fetuses .

Year	Author…	Cardiac diagnosis	Transplacental Digoxin / time of treatment	Symptoms before treatment	Prenatal Results	Delivery	Newborn condition	Neonatal /infant Follow-up
2006	Respondek-Liberska M. & Co.[7]	SVT >200/min	4 weeks	SVT	Sinus rhythm	CS 63%-	No side effects of the treatment	Positive effect during fetal life - 44 Persistent SVT 7 fetuses/ neonates Deaths 8 fetuses

Table 4. Data from Respondek-Liberska M. and co.: Outcome 59 fetuses with Tachyarrhythmias >200/min - Bicenter Łódź Study (with transplacental Digoxin)

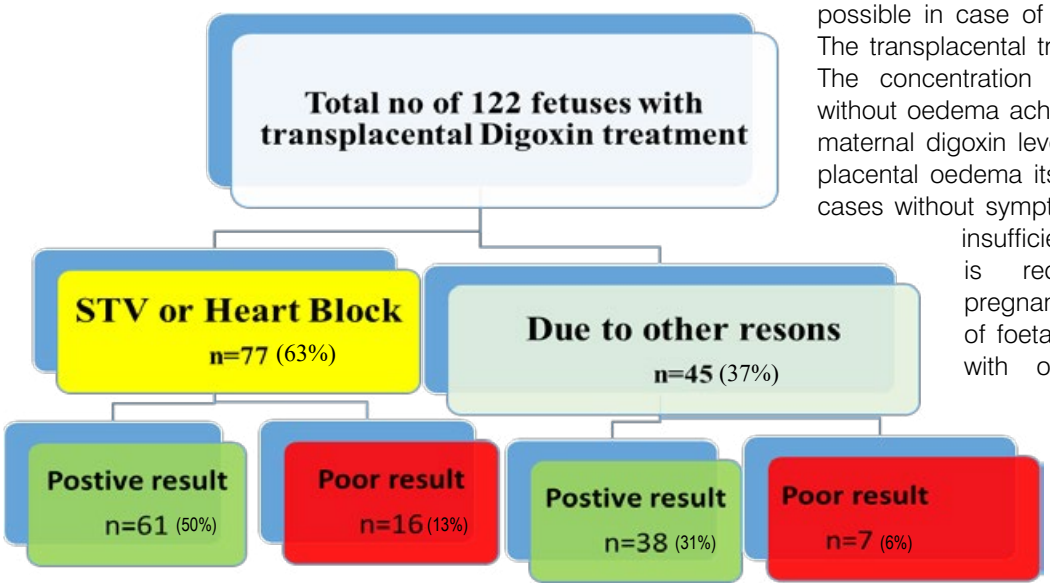

Figure 1. Total no of 122 fetuses with transplacental digoxin treatment(cases selected from the literature), the statistical analysis by Chi-squre for 1 degree of freedom = 23,672 it gives df1\p<0,001. (For STV Heart Block Chi-squre=13,149 it givses df1\p<0,001; Due to other reasons Chi2 =10,677 it gives df1\ p=0,001).

Uses", by the physician William Withering in 1785 is generally credited as marking the breakthrough of its use[2,17]. Since the original report, cleaner preparations were developed and the purified compound was achieved in 1930. The foxglove has been saving lives of cardiac patients for more than 200 years. Today, despite significant side effects, digoxin still occupies a significant position in pharmacotherapy of heart diseases, however its application in cardiology has been reduced significantly[18]. At present, it is used mainly in monitoring the fast rhythm in persistent atrial fibrillation and in some cases of circulatory insufficiency.

The pioneers of the transplacental treatment of foetuses with digoxin were Kerenyi and Kleinman. In 1980 Kerenyi described treatment with digoxin in foetuses with SVT[19], and in 1982 Kleinman published a case of a foetus with oedema caused by SVT and successful treatment with digoxin[20]. At present, it is assumed that the type of supraventricular contraction plays the most important role in the choice of anti-arrhythmia medication. Jaeggi and co-workers in 1998 and Fouron in 2000 commenced the new era in prenatal SVT treatment based on the selection of the medicine depending on the type of arrhythmias[21,22]. In this review we analyzed the reports focusing on singleton pregnancies, but DeLia and Arabin published about digoxin in twin transfusion syndrome as an addition to laser resulting in foetal improvement[23, 24].

Various ways of Digoxin application are possible in case of foetuses heart problem. The transplacental transfer is a main issue[25]. The concentration of digoxin in foetuses without oedema achieves about 40 – 90% of maternal digoxin level[26]. However, in case of placental oedema its level is only 10%[2,26]. In cases without symptoms of foetal circulatory insufficiency, oral administration is recommended for the pregnant woman[27,28]. In cases of foetal circulatory insufficiency with oedema, the treatment with digoxin is started intravenously with subsequent oral administration[28]. In the most difficult cases, it is possible to apply digoxin directly to the foetus: via the umbilical vein, intramuscularly, intraperitoneally, to the amniotic fluid or to the heart [29,30,31,32,37]. It is assumed that the digoxin level in maternal serum should be about 2–2.5 ng/dL which is usually difficult to achieve and in 2-3 weeks of maternal digoxin treatment even lower level seems to be effective. Also maternal clinical condition and maternal ECG (prolongation of PR, QT , repolarisation, arrhythmias). are important.

The laboratory methods of serum digoxin assessment might be another problem as well as digoxin level in umbilical neonatal cord. In majority of the publications this was never mentioned.

Thus far, the international standards for prenatal treatment of foetal tachyarrhythmia have not been strictly unified. In Poland, the treatment of this group of arrhythmias is indicated in the Recommendations of Polish Gynaecology Association since 2006 [33], which are in agreement with the experiences of Polish Foetal Cardiologists[34,35].

Apart from foetal arrhythmias, digoxin may be used for foetuses with congestive heart failure, which might be due to different pathogenetic mechanisms:

- Ventricular diastolic overload (in the course of valvular incompetence, ventricular shunt)

- Ventricular systolic overload (in the course of arterial pulmonary and systemic hypertension, aortic or pulmonary stenosis)
- Myocardial dysfunction due to myocarditis or cardiomyopathy

In the publications about prenatal digoxin treatment, majority of information concern SVT [7, 12, 13,,14,15,16,19, 20, 21, 22, 26, 28, 29, 30, 31, 32, 34, 35, 38,39,40,41]. Digoxin treatment in cases other than SVT was applied in such abnormalities as: in foetuses with Ebstein's anomaly, critical AS , absent pulmonary valve syndrome, complete heart block, in foetuses with aneurysm/diverticulum of left ventricle, in tricuspid atresia or dysplasia, rhabdomyoma, pulmonary atresia, HLHS with fibroelastosis, in twin twin transfusion syndrome and in extracardiac anomalies such as atriovenous malformation or sacrococcygeal teratoma [4,5,6,8,9,10,11,23,24, 37,42].

Digoxin was applied several weeks, rather than days: from 6 up to 10 weeks. Regression of oedema and / or normalisation of foetal heart rhythm were observed. The published literature[9,21,22,27,35,36,37] suggests that despite the reduction of digoxin use in adult cardiology, its use in prenatal cardiology is still important, despite problems of monitoring maternal and fetal heart response.

Digoxin serum level includs both free and serum protein–bound drug. Approximately 20% of digoxin is typically bound to serum proteins, mainly albumin. Free digoxin concentrations reflect approximately 80% of the active compound. Using the radioimmunoassay technique for measuring serum digoxin, it was found that patients who were given 0.25 mg. digoxin orally per day had a mean serum level of 0.83 +/- 0.06 ng. per ml. In patients given 0.5 mg. daily the mean level was 1.30 +/- 0.14 ng. The therapeutic plasma levels are 0.7 to 2.0 ng/ml for digoxin. Individuals who exhibited electrocardiographic evidence of digoxin toxicity had a mean serum level of 2.81 +/- 0.21 ng. The majority of patients with high serum levels had evidence of impaired renal function, but also digitalis intolerance maybe an issue or interaction of glycosides with other drugs. Repeated measurements on the same patient on maintenance therapy showed little variation. To obtain dependable serum levels blood in adults should be drawn at least five hours after oral, and three hours after intravenous administration[43,44].

The situation during the pregnancy is even more complicated due to low molecular compounds - endogenous digitalis-like substances EDLS which cause increase naturesis. These EDLS are like cardiac glycosides and bind to cardiac glycoside-specific antibodies[45].

The serum of women in the third trimester of pregnancy demonstrates increased levels of this digoxin-like immunoreactive substance(s)[46].

Digoxin-like immunoreactive substance (s), are also present in the placenta and are released into the fetal circulation and may play a role in placental control of fetal vascular tone [47].

Digoxin-like immunoreactive substance(s) was isolated from sera and autopsy-derived tissue obtained from premature and full-term neonates. The highest tissue level of DLIS was in the small bowel followed by the adrenal, gallbladder and liver. Of the fluids examined, meconium had the highest level of DLIS. Preparative high performance liquid chromatography fractionation of cord blood generated at least six different fractions of these substances [48].

One of the concern to use digoxin for therapeutic purpose is the possibility of its toxicity. However since 70 ties there is known antidotum such as digoxin-specific antibody fragments (Fab) for treatment of digitalis intoxication [49,50,51] . However even despite the lack of Fab the proper cardiac care of intoxicated patient may by crucial and life saving [52]

With our present knowledge about digoxin and the development of prenatal echocardiography, and with reference to its pioneer, the use of digoxin is still accepted in different cases of prenatal cardiac insufficiency in tertiary centers for fetal cardiology.

Prenatal cardiology is a rather new and growing field. The experiences of administering digoxin in pregnancy might cause a comeback of the digoxin golden era. We were not able to prove its advantages in fetal arrhythmias comparing with other problemes and heart insufficiency (Table 4). Our observations may not be as important as those of William Withering, but may nevertheless contribute to an interest in digoxin by foetal cardiologists who care for pregnant women. Alternatively, newer pharmaceutical preparations, now under development, might replace digoxin as the preferred medication for foetuses with cardiac disease.

CONCLUSIONS

Foetal cardiac insufficiency may appear due to different reasons (in normal heart anatomy or in heart defects, in normal sinus rhythm or due to foetal arrhythmias: tachycardias or severe bradycardia) and may be a cause of intrauterine demise. So far, we do not have strong evidence that digoxin treatment may prevent foetal death or prematurity. More research is needed to ascertain if the prolonging of pregnancy resulted from digoxin treatment or if improvement in foetal circulatory insufficiency was influenced by spontaneous regression of foetal cardiac symptoms.

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Acknowledegement:

The authors would like to thank prof. R. Yanagihara from University of Honolulu for helpful criticism.

Work division:

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