Mini Review

Line Kolding*, Hilal Eken and Niels Uldbjerg

Drug exposure during pregnancy and fetal cardiac function – a systematic review

<https://doi.org/10.1515/jpm-2019-0402>

Received November 7, 2019; accepted January 28, 2020; previously published online February 18, 2020

Abstract

Background: The aim of this systematic review was to describe the effects of drug exposure during pregnancy on fetal cardiac function.

Methods: We searched MEDLINE, Embase, Cochrane and SCOPUS for studies assessing fetal cardiac function in drug-exposed human pregnancies. Risk of bias was assessed by the Risk Of Bias In Non-randomized Studies of Interventions (ROBIN-I) tool.

Results: We included 32 studies on eight different drug groups. They included 51 outcome variables, which were all based on ultrasound techniques primarily assessing systolic function: pulsed wave Doppler, tissue Doppler imaging (TDI), and B- and M-mode. Overall, the risk of bias was moderate. β_2 agonists increased the systolic velocity in the ductus arteriosus and the fetal heart rate. β -blockers caused unchanged or decreased systolic velocity of the pulmonary trunk. Corticosteroids increased the velocity in the ductus arteriosus. Furthermore, in growth-restricted fetuses with an increased myocardial performance index (MPI') on the right side, corticosteroids normalized this variable. Nonsteroidal anti-inflammatory drugs (NSAIDs), but not acetylsalicylic acid, increased the flow velocities in the ductus arteriosus, decreased the shortening fraction and increased the end-diastolic ventricular diameters. Metformin and insulin normalized the diastolic strain and global longitudinal strain in diabetic pregnancies. Highly active

antiretroviral therapy (HAART) exposure increased the E/A ratio on the right side, prolonged the isovolumic relaxation time (IRT) and ejection time, shortened the isovolumic contraction time (ICT), and decreased left myocardial systolic peak velocities. Chemotherapy did not cause detectable changes.

Conclusion: Six of the eight drug groups caused detectable changes in fetal cardiac function. However, the evidence was hampered by only a few studies for some drugs.

Keywords: cardiac function; drug exposure; fetal; pregnancy.

Introduction

More than the half of all pregnant women use prescription medication which exposes the fetus to potential risks [1], including both structural malformations and altered organ function [2, 3]. The risks of malformations are addressed in epidemiological studies, whereas the assessment of fetal organ dysfunction is often challenging. Nevertheless, it may be very important in allowing us to monitor drug exposure in order to adjust the dosage or to discontinue treatment when indicated.

Echocardiography may, to some extent, allow us to assess the fetal cardiac response to drugs [2] even though we lack consensus concerning the relevance of the different outcome variables. We therefore aimed to describe the effects of drugs on fetal cardiac function, including an evaluation of the gestational ages and the duration of exposure needed to obtain the effects.

Materials and methods

The protocol for this systematic review was registered at PROSPERO (CRD42018100454), and the PICOS was defined as follows: Population: human fetuses before the time of labor; Intervention: drug exposure at either maternal or fetal indication; Controls: no intervention, self-controls, alternative interventions or no controls; Outcome: fetal cardiac function (not malformations) divided into global, diastolic or systolic functions;

*Corresponding author: Line Kolding, MD, PhD, Department of Obstetrics and Gynecology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark; and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, Tel.: +45 30714972, E-mail: lkolding@clin.au.dk

Hilal Eken: Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Niels Uldbjerg: Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark; and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Study design: full-text papers. We excluded studies of illegal drug use, drug exposure with suicidal purposes or purposes of termination of the pregnancy as well as fetuses with cardiac dysfunction before the time of exposure. Furthermore, we excluded studies only describing Doppler flow measurement in the ductus venosus or fetal heart rate.

Information sources

The search was conducted on September 6, 2019. The databases used were MEDLINE, Embase, Cochrane and SCOPUS, and they were supplemented with studies found by review of the references in the included studies.

Search strategy

Including Mesh search and free-text search:

MEDLINE: (((“Fetal Heart”[Mesh] AND “Humans”[Mesh])) AND (((“Chemicals and Drugs Category”[Mesh])) OR “Drug Therapy”[Mesh])) AND “Pregnancy”[Mesh].

Embase: “pregnancy”/exp AND “fetus heart”/exp AND “chemicals and drugs”/exp.

Cochrane: MeSH descriptor: [Pregnancy] explode all trees AND MeSH descriptor: [Fetal Heart] explode all trees AND MeSH descriptor: [Pharmaceutical Preparations] explode all trees.

Free-text search in MEDLINE and Embase: “Fetal Heart” AND “drug effects” AND “Maternal Exposure”. “Fetal Heart” AND “drug effects”. “Fetal Heart” AND “medicine”. “Fetal cardiac function”. “Fetal heart function”.

The literature search was conducted by LK and research librarian Anne Vils Møller. LK checked for duplicates and conducted an initial screening and selection of full-text articles based on abstracts. LK and HE independently assessed full-text articles for eligibility based on the predefined PICOS and independently evaluated the risk of bias; any conflicts were resolved by NU.

Risk of bias in individual studies

With the exception of studies with case reports/series design, we evaluated all the studies for the risk of bias using the Cochrane ROBINS-I tool (Risk Of Bias In Non-randomized Studies of Interventions) [4]. The first two domains cover the confounding (C) and selection of participants (S). The third domain addresses the classification of the interventions (I). The other four domains

address protentional bias due to deviations from intended interventions (D), missing data (M), measurement of outcomes (O) and the selection of the reported results (R). The seven domains were ranked by the levels of low (green), moderate (light green), serious (rose) or critical risk of bias (red), or by no information on which to base a judgment about risk of bias (yellow) [4]. The certainty of evidence was graded as high, moderate, low and very low based on the GRADE Working Group grades of evidence [5].

Results

Among the 2673 records identified after removal of duplicates, 32 studies were eligible according to the predefined PICOS (Figure 1): Seven randomized controlled trials (RCTs), 16 cohort studies, one case-control study and eight case-series or case-reports. Outcomes were all based on ultrasound methods: pulsed-wave Doppler, tissue Doppler imaging (TDI), and B- and M-mode, with detectable differences of diastolic, systolic and global function. However, not fewer than 51 different variables were used, with the majority assessing systolic function by M-mode or pulsed-wave Doppler.

Due to the majority of non-randomized studies, the risk of bias tool used was ROBINS-I [4]. Baseline and time-varying confounding (C) were categorized with serious or critical risk of bias in 16/24 studies. Selection of participants (S) into the study and classification of interventions (I) were dominated by low and moderate risk of bias, 17/24 and 20/24, respectively. Information of deviations from intended interventions (D) and missing data (M) were purely reported in 11/24 and 7/24 studies, respectively, but when reported the levels of bias were low or moderate (12/14 and 15/17, respectively). The risks of bias in measurement of outcomes (O) and reported results (R) were mainly categorized as moderate (16/24 and 17/24, respectively), hampered by low sample size and reduced ability for adjustments.

Changes were reported in six of the eight drug groups (Figure 2 green/red colored).

Anthracyclines

Anthracyclines are used in cancer chemotherapy.

Relevant effects. In children and adults, anthracyclines cause both acute and chronic cardiotoxicity [24, 30].

Figure 1: Flow diagram of included studies.

Fetal heart function. Diastolic, systolic and global functions: No effects (Figure 2) [24, 30].

Certainty of evidence. Low, as there is only one study with a comparison basis (Figure 3).

β_2 -Agonists

β_2 Adrenergic receptor agonists inhibit uterine contractions and are widely used for the prevention of preterm birth [6].

Relevant effects. In adults, β_2 adrenergic receptor agonists increase the cardiac output, primarily by decreasing the systemic vascular resistance and increasing the heart rate

[6]. In fetal lambs, ritodrine causes hypoxia and tachycardia without changing the blood pressure [7].

Fetal heart function. Fetal heart rate: Increased or unchanged. Diastolic and global effects: Not assessed. Systolic function: In one study, the ductus arteriosus peak systolic flow velocity (PSV) increased, reflecting the constriction of the ductus arteriosus (Figure 2) [8].

Length of exposure needed to obtain the effect. A study on nylidrin demonstrated an effect within 12 h [8], whereas studies on terbutaline and ritodrine did not demonstrate effects even after 60 days of exposure [6, 7, 9–11].

Critical gestational age. The study of nylidrin exposure concerned gestational weeks 24–34 (Figure 4).

Certainty of evidence: High.

Figure 2: Ultrasound variable used and detected changes after drug exposure. The arrows show unchanged, increased or decreased measurements. The colors indicate unchanged (yellow), improved (green) or impaired cardiac function (red). HAART, highly active antiretroviral therapy; NSAID, nonsteroidal anti-inflammatory drug.

The arrows show unchanged, increased or decreased measurements. The colors indicate unchanged (yellow), improved (green) or impaired cardiac function (red). HAART, highly active antiretroviral therapy; NSAID, nonsteroidal anti-inflammatory drug.

constriction of ductus arteriosus, and have pronounced growth-suppressing properties [3, 13–15, 31].

Fetal heart function. Diastolic function: No effects [13, 16]. Systolic function: Mild increase in PSV in the ductus arteriosus [13, 15]. The effect was not confirmed in other studies [12, 14]; however, one case reported severe ductal constriction and tricuspid regurgitation [32]. Synergism: Not with thyrotropin-releasing hormone (TRH) but may aggravate fetal ductus constriction due to indomethacin

Relevant effects. In rats and sheep, corticosteroids induce fetal myocardial hypertrophy, increased contractility and

Figure 4: β_2 Agonist.

[14]. Global function: In growth-restricted-fetuses, corticosteroids normalized the abnormal right side [myocardial performance index (MPI') and isovolumic contraction time (ICT'')] (Figure 2) [16].

Length of exposure needed to obtain the effect. The effect on PSV in the ductus arteriosus was detected within 30 min to 12 h [13–15] and normalized 1–3 days after discontinuation [13, 15, 16, 32].

Critical gestational age. The studies concerned exposure between gestational weeks 24 and 37 (Figure 5).

Certainty of evidence: High.

β -Blocker

β -Adrenergic blockers are antihypertensive drugs [21].

Relevant effects. In adults with hypertension, atenolol decreases the heart rate, cardiac contractility and cardiac output [21], whereas pindolol and labetalol decrease peripheral vascular resistance with minor effects on cardiac output [21, 22].

Fetal heart function. Diastolic and global function: Not assessed. Systolic function: Atenolol decreased the PSV

in the pulmonary trunk probably by an increased afterload as fetal heart rate, valve and vessel sizes as well as the fractional shortening of the ventricles remained stable (Figure 2) [21, 22].

Length of exposure needed to obtain effects. The effect of atenolol did not appear until 30 min after exposure [21, 22]. Exposures of labetalol and pindolol for 15–20 min were without effects.

Critical gestational age. The studies concern exposure from gestational week 28 to 40 (Figure 6).

Certainty of evidence: High.

Antidiabetic

These drugs normalize the glucose level in diabetic patients.

Relevant effects. We have no hypotheses about their direct effects on cardiac function. However, indirect effects by improved glycemic control are most likely [23, 33].

Fetal heart function. Systolic function: Not assessed. Global function: In a subgroup analysis of diabetic pregnancies with fetuses characterized by abnormal global

Figure 5: Corticosteroids.

Figure 6: β -Blocker.

Figure 7: Antidiabetic.

Figure 8: Highly active antiretroviral therapy.

function, treatment normalized the left ventricular longitudinal strain as well as the early and late diastolic strain rate (Figure 2) [23].

Length of exposure needed to obtain the effect. No information.

Critical gestational age. The examinations were performed between 30 and 33 weeks of gestation (Figure 7).

Certainty of evidence: Low, as it was based on a sub-analysis in only one study.

Highly active antiretroviral therapy (HAART)

Highly active antiretroviral therapy (HAART) is used for HIV. The drugs include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) [25].

Relevant effects. In adults, an indirect effect on the immune reconstitution inflammatory syndrome is well established [25, 34].

Fetal heart function. Diastolic dysfunction: Increased E/A ratio on the right side. Systolic dysfunction: Decreased mitral S' (systolic annular peak velocity) and increased left ICT and IRT [25, 26]. Global function: No effects (Figure 2); however, zidovudine (NRTI) caused hypertrophy of the myocardial walls [26].

Length of exposure needed to obtain effects. Both studies examined only the long-term effects.

Critical gestational age. The studies concerned gestational weeks 26–32 (Figure 8).

Certainty of evidence: Moderate, due to a substantial risk of confounding by indication.

Nonsteroidal anti-inflammatory drug (NSAID)

NSAIDs inhibit cyclo-oxygenase but with different selectivity for COX-1 and COX-2. Indications are pain, fever, tocolysis and polyhydramnios.

Relevant effects. NSAIDs decrease prostaglandin synthesis.

Fetal heart function. Diastolic and global function: Not assessed. Systolic dysfunction: All NSAIDs increased the PSV in the ductus arteriosus, indicating constriction which might also cause tricuspid regurgitation [17, 28, 35]. Furthermore, one of the two studies found decreased right ventricular fractional shortening probably associated with an increased ventricular inner end-diastolic diameter (Figure 2) [14, 28]. Synergism: Betamethasone may aggravate the effect of indomethacin on the ductus arteriosus [14]. It might be of importance that the transfer of sulindac through the placenta is less than that of indomethacin [36].

Length of exposure needed to obtain effects. The constriction of the ductus arteriosus occurred within 4–30 h and resolved (partly or totally) within 72 h of discontinuation.

Critical gestational age. The sensitivity to indomethacin increased with gestational age: 5–10% of fetuses at weeks 26–27; 50% at week 32 [37]. The included studies concerned gestational weeks 21–40 (Figure 9).

Certainty of evidence: High.

Low-dose acetylsalicylic acid

Aspirin is an NSAID and a platelet aggregation inhibitor used for prevention of preeclampsia [18].

Figure 9: Nonsteroidal anti-inflammatory drug.

Relevant effects. The effect of the NSAID indomethacin on ductus arteriosus is well described. Therefore, other prostaglandin synthesis inhibitors such as aspirin and prednisolone might have similar effects, and animal studies on high-dose aspirin have shown constriction the fetal ductus arteriosus [17, 19].

Fetal heart function. Systolic and diastolic function: No effects. Global function: Not assessed [18–20]. Synergism: Not for low-dose aspirin in combination with corticosteroids (Figure 2) [17].

Critical gestational age: The studies concerned gestational weeks 14–40 (Figure 10).

Certainty of evidence: Moderate.

Discussion

This systematic review is the first on drug effects on fetal cardiac function. It describes significant effects in six of eight drug groups assessed in 32 studies including 51 different types of ultrasound outcome variables. However, the evidence was hampered by only a few studies for some drugs.

The strength of this review is that the literature search was conducted systematically and that the risk of bias was assessed by a well-established tool [4]. However, the limitation is that due to the heterogeneity of the studies we could not conduct metaanalyses. Furthermore, we did not describe the possible effects of important drugs such as magnesium and sildenafil as the relevant publications did

Figure 10: Acetylsalicylic acid.

not fulfill our inclusion criteria. It is also a challenge that the simultaneous use of multiple medications sometimes rendered proper interpretation impossible as illustrated by the synergistic effect of corticosteroid and indomethacin. Finally, it was not possible, due to the underlying studies, to observe the drug effect individually in the drug groups of HAART and antidiabetics.

We must interpret the results with appropriate humility as illustrated by these examples. Risk of statistical type 2 error: No effect of anthracyclines despite a well-established cardiotoxicity in adults [24, 30]. Lack of dose-response studies: No effect of aspirin on the ductus arteriosus, a finding that may be associated with the inclusion of studies covering only low-dose exposure (60–100 mg/day) [18, 20]. The duration of exposure might be too short: No effects of labetalol and pindolol. Gestational age: Most studies evaluated outcomes from gestational week 15 to 40; only studies investigating long-term effects included exposure during the first trimester (HAART and antidiabetics).

Despite these limitations, we can conclude that safety evaluations concerning the use of drugs during pregnancy must include not only an assessment of the risk of fetal malformations but also an evaluation of the risk of fetal cardiac dysfunction, as the certainty of evidence is relatively high for several drugs. One must keep in mind that even when there are no detectable effects in fetal life, harm could evolve later in life. Therefore, we need postnatal follow-ups of organ functions.

However, the lack of gold standards concerning the choice of outcome variables and their interpretation is remarkable. We therefore suggest this topic should be addressed on an international consensus decision.

Acknowledgments: Lars H. Pedersen and Anne V. Møller.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Bjorn AM, Norgaard M, Hundborg HH, Nohr EA, Ehrenstein V. Use of prescribed drugs among primiparous women: an 11-year population-based study in Denmark. *Clin Epidemiol* 2011;3:149–56.
2. Miranda JO, Ramalho C, Henriques-Coelho T, Areias JC. Fetal programming as a predictor of adult health or disease: the need to reevaluate fetal heart function. *Heart Fail Rev* 2017;22:861–77.
3. Mone SM, Gillman MW, Miller TL, Herman EH, Lipshultz SE. Effects of environmental exposures on the cardiovascular system: prenatal period through adolescence. *Pediatrics* 2004;113(4 Suppl):1058–69.
4. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Br Med J* 2016;355:i4919.
5. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
6. Rasanen J. The effects of ritodrine infusion on fetal myocardial function and fetal hemodynamics. *Acta Obstet Gynecol Scand* 1990;69:487–92.

7. Friedman DM, Blackstone J, Young BK, Hoskins IA. Fetal cardiac effects of oral ritodrine tocolysis. *Am J Perinatol* 1994;11:109–12.
8. Eronen M, Pesonen E, Kurki T, Ylikorkala O, Hallman M. The effects of indomethacin and a beta-sympathomimetic agent on the fetal ductus arteriosus during treatment of premature labor: a randomized double-blind study. *Am J Obstet Gynecol* 1991;164(1 Pt 1):141–6.
9. Kramer WB, Saade GR, Belfort M, Dorman K, Mayes M, Moise Jr KJ. A randomized double-blind study comparing the fetal effects of sulindac to terbutaline during the management of preterm labor. *Am J Obstet Gynecol* 1999;180(2 Pt 1):396–401.
10. Sharif DS, Huhta JC, Moise Jr KJ, Morrow RW, Yoon GY. Changes in fetal hemodynamics with terbutaline treatment and premature labor. *J Clin Ultrasound* 1990;18:85–9.
11. Sorensen KE, Borlum KG. Fetal cardiac function in response to long-term maternal terbutalin treatment. *Acta Obstet Gynecol Scand* 1988;67:105–7.
12. Bajoria R, Stagiannis KD, Fisk NM. Effect of antenatal administration of thyrotrophin releasing hormone on fetal flow velocity waveforms. *Arch Dis Child Fetal Neonatal Ed* 1997;77:F127–30.
13. Kahler C, Schleussner E, Moller A, Seewald HJ. Doppler measurements in fetoplacental vessels after maternal betamethasone administration. *Fetal Diagn Ther* 2004;19:52–7.
14. Levy R, Matitiau A, Ben Arie A, Milman D, Or Y, Hagay Z. Indomethacin and corticosteroids: an additive constrictive effect on the fetal ductus arteriosus. *Am J Perinatol* 1999;16:379–83.
15. Wasserstrum N, Huhta JC, Mari G, Sharif DS, Willis R, Neal NK. Betamethasone and the human fetal ductus arteriosus. *Obstet Gynecol* 1989;74:897–900.
16. Pedersen LH, Mogra R, Hyett J. The effects of corticosteroids on cardiac function in growth restricted fetuses. *Ultrasound Obstet Gynecol* 2016;48:204–9.
17. Forouzan I, Cohen AW, Lindenbaum C, Samuels P. Umbilical artery and ductal blood flow velocities in patients treated with aspirin and prednisone for presence of anticardiolipin antibody. *J Ultrasound Med* 1993;12:135–8.
18. Miyazaki M, Kuwabara Y, Takeshita T. Influence of perinatal low-dose acetylsalicylic acid therapy on fetal hemodynamics evaluated by determining the acceleration-time/ejection-time ratio in the ductus arteriosus. *J Obstet Gynaecol Res* 2018;44:87–92.
19. Di Sessa TG, Moretti ML, Khoury A, Pulliam DA, Arheart KL, Sibai BM. Cardiac function in fetuses and newborns exposed to low-dose aspirin during pregnancy. *Am J Obstet Gynecol* 1994;171:892–900.
20. Grab D, Paulus WE, Erdmann M, Terinde R, Oberhoffer R, Lang D, et al. Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: results of a randomized, placebo-controlled, double-blind trial. *Ultrasound Obstet Gynecol* 2000;15:19–27.
21. Rasanen J, Jouppila P. Uterine and fetal hemodynamics and fetal cardiac function after atenolol and pindolol infusion. A randomized study. *Eur J Obstet Gynecol Reprod Biol* 1995;62:195–201.
22. Jouppila P, Rasanen J. Effect of labetalol infusion on uterine and fetal hemodynamics and fetal cardiac function. *Eur J Obstet Gynecol Reprod Biol* 1993;51:111–7.
23. Miranda JO, Cerqueira RJ, Ramalho C, Areias JC, Henriques-Coeelho T. Fetal cardiac function in maternal diabetes: a conventional and speckle-tracking echocardiographic study. *J Am Soc Echocardiogr* 2018;31:333–41.
24. Gziri MM, Debieve F, DE Catte L, Mertens L, Barrea C, VAN Calsteren K, et al. Chemotherapy during pregnancy: effect of anthracyclines on fetal and maternal cardiac function. *Acta Obstet Gynecol Scand* 2012;91:1465–8.
25. De la Calle M, Rodriguez R, Deiros L, Bartha JL. Fetal cardiac biometry and function in HIV-infected pregnant women exposed to HAART therapy. *Prenat Diagn* 2015;35:453–5.
26. Garcia-Otero L, Lopez M, Gomez O, Gonce A, Bennasar M, Martinez JM, et al. Zidovudine treatment in HIV-infected pregnant women is associated with fetal cardiac remodelling. *AIDS* 2016;30:1393–401.
27. Sawdy RJ, Lye S, Fisk NM, Bennett PR. A double-blind randomized study of fetal side effects during and after the short-term maternal administration of indomethacin, sulindac, and nimesulide for the treatment of preterm labor. *Am J Obstet Gynecol* 2003;188:1046–51.
28. Rasanen J, Jouppila P. Fetal cardiac function and ductus arteriosus during indomethacin and sulindac therapy for threatened preterm labor: a randomized study. *Am J Obstet Gynecol* 1995;173:20–5.
29. Groom KM, Shennan AH, Jones BA, Seed P, Bennett PR. TOCOX – a randomised, double-blind, placebo-controlled trial of rofecoxib (a COX-2-specific prostaglandin inhibitor) for the prevention of preterm delivery in women at high risk. *BJOG: Ultrasound Obstet Gynecol* 2005;112:725–30.
30. Meyer-Wittkopf M, Barth H, Emons G, Schmidt S. Fetal cardiac effects of doxorubicin therapy for carcinoma of the breast during pregnancy: case report and review of the literature. *Ultrasound Obstet Gynecol* 2001;18:62–6.
31. Wintour EM, Moritz KM, Johnson K, Ricardo S, Samuel CS, Dodic M. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. *J Physiol* 2003;549(Pt 3):929–35.
32. Azancot-Benisty A, Benifla JL, Matias A, De Crepy A, Madelenat P. Constriction of the fetal ductus arteriosus during prenatal betamethasone therapy. *Obstet Gynecol* 1995;85(5 Pt 2):874–6.
33. Hornberger LK. Maternal diabetes and the fetal heart. *Heart* 2006;92:1019–21.
34. Dhasmana DJ, Dheda K, Ravn P, Wilkinson RJ, Meintjes G. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy: pathogenesis, clinical manifestations and management. *Drugs* 2008;68:191–208.
35. Pratt L, Digiosia J, Swenson JN, Trampe B, Martin Jr CB. Reversible fetal hydrops associated with indomethacin use. *Obstet Gynecol* 1997;90(4 Pt 2):676–8.
36. Higby K, Elliott B, King TS, Frasier D, Langer O. Human placental transfer of the prostaglandin inhibitor sulindac using an in vitro model. *J Soc Gynecol Investig* 1995;2:526–30.
37. Respondek M, Weil SR, Huhta JC. Fetal echocardiography during indomethacin treatment. *Ultrasound Obstet Gynecol* 1995;5:86–9.
38. Auer M, Brezinka C, Eller P, Luze K, Schweigmann U, Schwarzler P. Prenatal diagnosis of intrauterine premature closure of the ductus arteriosus following maternal diclofenac application. *Ultrasound Obstet Gynecol* 2004;23:513–6.
39. Paladini D, Marasini M, Volpe P. Severe ductal constriction in the third-trimester fetus Following maternal self-medication with nimesulide. *Ultrasound Obstet Gynecol* 2005;25:357–61.
40. Prefumo F, Marasini M, De Biasio P, Venturini PL. Acute premature constriction of the ductus arteriosus after maternal self-medication with nimesulide. *Fetal Diagn Ther* 2008;24:35–8.
41. Rein AJ, Nadjari M, Elchalal U, Nir A. Contraction of the fetal ductus arteriosus induced by diclofenac. Case report. *Fetal Diagn Ther* 1999;14:24–5.