Author's response to reviews

Title: One case of pregnancy with complete endocardial cushion defects

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Version: 2
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Author's response to reviews: see over
Author’s response to reviews

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Version: 2

Date: December 23rd 2013
Reviewer 1’s report

Title: One case of pregnancy with complete endocardial cushion defects

Version: 1

Date: 17 November 2013

Reviewer: Achim Schmaltz

Which of the following best describes what type of case report this is?: Other

If other, please specify:

This is a rare, but typical case of a mother with trisomy 21, endocardial cushion defect and Eisenmenger syndrome (ES), who got pregnant and died after birth. It underlines not only the importance of prenatal screening for CHD and early corrective surgery, but also the dangerousness of ES especially during the weeks after childbirth.

Has the case been reported coherently? Yes

Is the case report authentic? Yes

Is the case report ethical? No

Is there any missing information that you think must be added before publication? Yes

Is this case worth reporting? Yes

Is the case report persuasive? No

Does the case report have explanatory value? Yes

Does the case report have diagnostic value? No

Will the case report make a difference to clinical practice? No

Is the anonymity of the patient protected? Yes
Comments to authors:

Important details of the critical period after birth are missing: how long after birth did the mother die? Were there any trials of therapy? Were the mother intubated and artificially ventilated?

To answer the reviewer’s questions, we have added the following statements in the manuscript on page 6: “The patient died 10 minutes after delivery. When the patient’s heart stopped beating, standard cardiopulmonary resuscitation was performed. The patient was not on ventilator.”

The conclusions are too weak: ES has still a high mortality during pregnancy and postpartum. A pregnancy should be avoided especially in persons, who can intellectually not judge their risk. This ethical problem should be addressed.

To address the reviewer’s concern on the conclusion, we have replaced the old version with the following new sentences in the conclusion: “The mortality of complete ECD during pregnancy and postpartum is high. Thus, women with complete ECD should avoid pregnancy, especially those women who cannot intellectually judge their risks.”

Although the patient is intellectually disabled, we discussed the risks with the patient’s family and strongly advised to terminate the pregnancy when the patient had her first visit in our hospital. We also strongly advised the patient’s family to allow the patient to stay in our hospital so that we can monitor the patient condition closely. Unfortunately, the patient’s family rejected all of our advices. It is illegal in China to operate a medical procedure without patient’s permission or agreement from the family members of patients who are intellectually disabled.

The legend of the figure should be more detailed: what echocardiographic cut is used (I suppose subcostal?), what is illustrated?

Since diagnosis of unrepaired complete ECD with echocardiogram is a standard procedure and one of the reviewers commented that the figure does not add much to the discussion, we have deleted the figure.

Quality of written English: Needs some language corrections before being published.

Declaration of competing interests: The reviewer has no competing interest.
Reviewer 2’s report

Title: One case of pregnancy with complete endocardial cushion defects

Version: 1

Date: 27 November 2013

Reviewer: Matthias Greutmann

Which of the following best describes what type of case report this is: None

Has the case been reported coherently: No

Is the case report authentic: Yes

Is the case report ethical: Yes

Is there any missing information that you think must be added before publication: Yes

Is this case worth reporting: No

Is the case report persuasive: No

Does the case report have explanatory value: No

Does the case report have diagnostic value: No

Will the case report make a difference to clinical practice: No

Is the anonymity of the patient protected: Yes

Comments to authors:

In this case report the authors describe the case of a 20-year old patient with trisomy 21 and unrepaired complete atrioventricular septal defect complicated by severe pulmonary hypertension, who died after delivery.
Although some details of this case (i.e. that a patient with trisomy 21 and Eisenmenger syndrome becomes pregnant) are interesting, I have some major concerns about this manuscript.

It is common knowledge that patients with severe pulmonary hypertension / Eisenmenger syndrome have a high mortality risk during pregnancy. This is well-reported and meanwhile textbook knowledge. What is special about this case? It is certainly not the first case of a patient with Eisenmenger-syndrome due to an atrioventricular septal defect who died after delivery.

We agree with the reviewer’s comment that physicians might have seen that patients with complete ECD die after delivery. However, based on our literature search, it appears that Chinese patients with complete ECD in pregnancy have not been reported. We report this case to further raise the awareness of this rare condition and to emphasize the dangerousness of this condition.

The case is not well presented: The main characteristic of this patient regarding pregnancy risk is not the atrioventricular septal defect by itself but the fact that the patient had severe pulmonary hypertension! Did the patient have Eisenmenger-syndrome (shunt-reversal with cyanosis, or ‘just’ severe pulmonary hypertension but not yet shunt-reversal). Did you try treatment with pulmonary vasodilators (sildenafil, etc.), how long after delivery and under what circumstances died the patient? The case should be presented in much more detail but the details about surgical repair of infants with AVSD can be omitted as it is not important for this case. The manuscript needs to be reviewed by a cardiologist familiar with congenital heart disease.

We have revised the case presentation. The patient had shunt-reversal. We suspected the patient had severe pulmonary hypertension based on the bidirectional shunt, but we did not have a diagnostic catheterization to confirm it. Thus, we did not treat the patient with pulmonary vasodilators. In addition, the clinical benefits of pulmonary vasodilators are contradictory. The patient died from heart failure 10 minutes after delivery. When the patient’s heart stopped beating, standard cardiopulmonary resuscitation was performed.

It is an interesting fact that a patient with trisomy 21 and severe pulmonary hypertension becomes pregnant. This is extremely rare in developed countries as contraception is usually discussed with patients and parents and an appropriate form of contraception is offered. This may be an interesting issue to focus on.
In China, physicians are also obligated to discuss the option of contraception with family of patients who have trisomy 21 and severe congenital heart diseases. Unfortunately, in remote rural areas, access to medical care is very limited. It is our patient’s first hospital visit in her lifetime when she was already 28 weeks pregnant. The issue of how to improve medical service for under-represented groups in China is beyond the scope of this report.

The following statement is interesting: ‘Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.’ How did you get written informed consent from a mentally retarded patient with trisomy 21 who died immediately after delivery?

We discussed the possibility of publishing this case with the patient and patient’s family when the patient had her first visit in our hospital. The patient is mentally retarded. Her family signed the informed consent. We have revised the statement as the following:

“Written informed consent was obtained from the patient and patient’s family for publication of this case report and any accompanying images.”

The list of references is completely inadequate.

We have added several related references in the manuscript.

Quality of written English: Not suitable for publication unless extensively edited.

We have corrected some language errors.

Declaration of competing interests: No competing interests.
Reviewer 3’s report

Title: One case of pregnancy with complete endocardial cushion defects

Version: 1

Date: 27 November 2013

Reviewer: Valerie Schroeder

Which of the following best describes what type of case report this is: Other

If other, please specify:

This is a rare and severe presentation. Patients with severe heart defects are usually identified early and are repaired. Few go un-repaired. Even fewer become pregnant. In decades part, the prognosis of such patients was poor. However, in the modern era, we can do more to help. I suspect that readers might benefit form learning about a modern approach to an old and rare problem.

Has the case been reported coherently: Yes

Is the case report authentic: Yes

Is the case report ethical: Yes

Is there any missing information that you think must be added before publication: Yes

Is this case worth reporting: Yes

Is the case report persuasive: No

Does the case report have explanatory value: Yes

Does the case report have diagnostic value: No

Will the case report make a difference to clinical practice: Yes
Is the anonymity of the patient protected: No

Comments to authors:

Please remove the date of admission. In some countries, this is a breech of confidentiality to list this information.

We appreciate the reviewer’s concern and have removed the date of admission from the manuscript.

Quality of written English: Needs some language corrections before being published

None to disclose

General Comments:

This is an interesting case and this reviewer agrees it is a rare and serious situation.

As we all care for the poor in under-served area or immigrants from countries where a high level of medical care is not possible, I suspect we will see patients like this from time to time. Unless a doctor has been practicing for many decades, this would be a very novel and helpful case for a younger and less experienced care team.

However, I would suggest substantial revisions prior to consideration of accepting this report. I would not expect this case report to review aspects of what is otherwise considered a routine diagnosis. Rather I would prefer to discuss crisis management of this patient. Indeed there may not be much published data on this type of case but there is collective knowledge on pregnancy and congenital heart disease in general. The case should more carefully review these data.

Furthermore, many patients urged not to become pregnant will against medical advice. Never the less, we are tasked with helping to keep the Mom and fetus as safe as possible. This report describes a crisis situation. I would ask the authors to expand their discussion on responding to hemodynamic changes of delivery in a patient with heart disease and what fetal risks likely exist.

I would also expect a stronger conclusion. Indeed we want all Moms to have prenatal care and accept medical advice. However, it was too late for that in this case. What other helpful advice can be provided given the situation in this case?
We have replaced the conclusion with the following statements:

“The mortality of ECD during pregnancy and postpartum is high. Thus, women with complete ECD should avoid pregnancy, especially those women who cannot intellectually judge their risks.”

Revisions Necessary for publication:

Abstract:

Introduction: Cardiologists may disagree with some of this content. Oya et al report that survival with Eisenmenger’s is 98% at 1y, 77% at 5y, 58% at 10y. The average age of death with Eisenmenger’s is variable but is probably 29y. Of course this is general data and is not specific to ECD. Outcomes may also vary from country to country depending upon medical resources available. Please provide accurate data or explain why previously published data does not reflect your experience. It might be better to simply delete this statement and explain the consequence of unrepaired ECD and pregnancy.

We have accepted the reviewer’s suggestion and replaced the following statement “Without early surgical intervention, approximately only 4% of patients with complete ECD survive 5 years of age” with the sentence “The mortality of unrepaired ECD in pregnancy and postpartum is high.”

Please scan the abstract for grammatical errors. Conclusion, please see the above/below comments.

We have replaced the conclusion with following new statement: “We believe that the mortality of ECD during pregnancy and postpartum is high and women with complete ECD should avoid pregnancy, especially those women who cannot intellectually judge their risks.”

Introduction:

It is likely that a mixed audience will read this case report. While it is tempting to review cardiac disease, this reviewer does not believe the focus of the introduction should involve a description of the types of AV canal. Instead, the introduction could be improved by simple stating what a complete ECD involves. For example:

A complete ECD involves a large primum atrial septal defect (ASD) and an inlet ventricular septal defect (VSD) of variable size. Additionally, there is only one large
heart valve (common valve) instead of two distinct atrioventricular valves (mitral and tricuspid). An endocardial cushion defect occurs early in fetal development presumably due to a failure of the endocardial cushions to facilitate normal development of each septum and the atrioventricular valves. Surgery is usually performed between 3-6 months of age depending upon severity.

We appreciate the reviewer’s comments and have included the statements provided by the reviewer in the introduction.

After this description you might consider explaining the pathophysiology of the disease, such as chronic congestive heart failure, pulmonary hypertension, Eisenmenger’s syndrome and death. There are studies evaluating the natural history of adults with Eisenmenger’s and this should be mentioned.

For pregnant women with Eisenmenger’s, Freedom et al summarize that in the 1960’s pregnant women with Eisenmenger’s has a 27% mortality. Newer data may show lower numbers (16%). Still birth/spontaneous abortion can be as high as 25%. Low birth weight can be as high as 26%. Other maternal morbidities can be as high as 54%. Thus, the authors should review these data and summarize in the report.

To address the reviewer’s suggestion, we have included the following statements in the manuscript:

“Intracardiac shunting often occurs in patients with ECD. Originally, blood usually flows from left to right, because the pressure on the left side of heart is higher than that of the right side. As the left-to-right shunting is prolonged, continuous exposure of the pulmonary vasculature to systemic arterial pressure leads to progressive changes in the pulmonary microvasculature causing increased pulmonary vascular resistance and pulmonary hypertension. When pressure in the pulmonary circulation exceeds systemic pressures, blood flows from right to left as well, resulting in bidirectional intracardiac shunting. This condition is also called Eisenmenger’s syndrome (ES). The right-to-left shunting can significantly dilute well-oxygenated blood, resulting in cyanosis. Patients suffering ES usually present syndromes such as breathlessness, fatigue, chest pain, and syncope [4]. The pulmonary hypertension occurring in ES imposes serious risks during pregnancy and postpartum. The decreased systemic vascular resistance associated with pregnancy worsens the right-to-left shunting, leading to the deterioration of cyanosis. Gleicher et al. reported that the mortality rate for pregnancy in ES is 52% [5]. The majority of maternal deaths occurred during or within the first week after delivery. Cesarean sections and other operations are associated with extremely high maternal mortality during pregnancy. The maternal mortality rate of
pregnancy with ES is reported to be as high as 50 – 65% with cesarean section [6]. At least 54.9 % deliveries occur prematurely [5]. Low birth weight can be as high as 26% [5].”

Echocardiography and the diagnosis of ECD are standardized and are well understood. Thus, this technique does not need to be described in the introduction. It is adequate (but not necessary) to say the diagnosis of ECD is routinely made by echo, however cath and cardiac MRI can also be used.

We have removed the description about echocardiography.

Case presentation:

There are some typo’s that may have occurred during the upload: “showsa” should say shows a. Please review for more words that might not have proper spacing.

We apologize for the improper spacing, but the spacing problem is associated with the manuscript submission system. We are unable to predict it.

Please review carefully for errors in English translation. For example, menstrual cycle should say cycles. a typical facial feature of- should say typical features of trisomy 21. fatigue from mild physical – consider saying “with” mild physical exertion. lie down- should say lying down.

We have corrected those grammar errors.

“During the examination”- consider starting a new paragraph her electrocardiography- should say her electrocardiogram sinus tachycardia- what was the heart rate? The paragraph describing the echo results could be shortened. Again, this is a well described disease. Most cardiologists will recognize the pattern. Most general readers will not necessarily be interested in these details. Consequently, it might be best to say, a complete echocardiogram was performed and was diagnostic for an unrepaired ECD. You might comment on the sizes of the ASD and VSD (small, medium, large). As this patient has a common valve, one cannot refer to them as a mitral and tricuspid valve. Rather, it would be fine to say there was severe left and right common valve insufficiency.

Given that this patient likely had a large VSD; one cannot determine the right ventricular pressure in the same fashion as someone without a VSD. If a large VSD is
present, the right and left heart pressures are usually equal or nearly and they are essentially connected via the VSD. It would be fine to say left and right heart pressures were nearly equal. You can say based upon the natural history of unrepaired ECD, you suspected severe pulmonary hypertension was present. You did not have a diagnostic catheterization to prove your conclusion.

We have accepted the reviewer’s suggestion and revised the statements.

Aortic valve disease is not part of the ECD disease spectrum. However, some may have sub-valvular aortic obstruction. I would not comment of the aortic valve other than mentioning mild insufficiency.

One confusing point was the comment that the pulmonary artery was at the upper limits of normal. Cardiology readers would think the pulmonary artery would be larger given a life-long left to right shunt and the presence of pulmonary hypertension. Sometime Cardiologists would provide a Z-score of the diameter based upon the patient’s BSA. This might help readers understand the pathology better.

We have removed the confusing statements.

I am not sure that Fig 1 adds much to the discussion as this is a standard diagnosis. The image is off-axis from a traditional 4-chamber view. I suspect windows were limited due to her age and the pregnancy. It is not labeled and most readers would not understand the significance of the images. I suggest deleting the figure.

We have deleted the figure according to the reviewer’s suggestion.

“Due to the extreme high risk of mortality for the mother,” Start a new paragraph with this statement. “suggested the patient to terminate the pregnancy” consider saying offered to terminate “The patient was also strongly recommended” should say the patient was advised.

We have revised the wording according to the reviewer’s suggestion.

The patient came back to our hospital on December 28th 2011- consider saying: The patient returned at 33 and 6/7 weeks – delete the date.

Please provide an oxygen saturation of the patient if this was assessed. The baby was in breech presentation- consider starting a new paragraph.
The baby weighted 1110 g; one minute Apgar score was 5; 5 minute Apgar score was 10. Please correct for English grammar.

We have corrected those statements according to the reviewer’s suggestion.

Comments:

“Data on the clinical course of complete ECD are sparse” - this statement as it stands is not exactly accurate. We do know the clinical course of unrepaired congenital heart disease. In decades past, children with trisomy 21 were not often operated on (unlike today). Consequently, we learned what happened to them over time. As you suggest, those at risk for a late diagnosis are patients who are poor or live in medically underserved areas. I suggest revising or deleting this comment or explain why you believe this to be true.

We have removed this statement according to the reviewer’s suggestion.

“Infants with complete ECD exhibit pulmonary hypertension the moment they are born.” I suggest deleting this statement.

We have deleted this statement.

All babies are born with high pulmonary vascular resistance and consequently pulmonary hypertension. In normal babies, resistance returns to normal in 3 mo. In babies with large VSD’s the pulmonary pressures are elevated as the left heart and right heart pressures will be nearly equalized. Over time, high pressure and left to right flow is thought to create pulmonary pathological hypertension. If a child is not operated on early in life, pathological pulmonary hypertension will develop over time. However, if they undergo catheterization as a young infant, we find their pulmonary resistance to be either normal or responsive to oxygen. Once operated on, they usually do well. I think it is fine to say this condition can be corrected in infancy and most children can lead happy and or productive lives.

We have added the following statement: “Surgical repair at early infancy is usually effective. Most children can lead happy and or productive lives after surgical repair.”

I think it is reasonable to say that you concluded the patient was in severe chronic heart failure due to a combination of her heart disease and severe pulmonary hypertension. Pulmonary hypertension is a combination of high pulmonary pressure and fixed resistance. You did not have catheter hemodynamics. However, based upon
the natural history of unrepaired ECD, it is reasonable to infer she had severe pulmonary hypertension and heart failure. You do not present the oxygen saturation but a bidirectional VSD shunt would suggest pulmonary hypertension. Consequently, the delivery would probably be high risk for both the infant and the mother.

This reviewer suspects that readers would want to know how to manage the situation. I agree with reviewing the changes in hemodynamics during and after the delivery. The readers need to understand why the mom was dying. After stating this, was there anything done to stabilize the mom? Aside from oxygen, were any medications provided to sustain blood pressure? Was there anything different about the delivery that other OBGYN’s can learn from? Was there anything you would have done differently? Is there any other data regarding delivery of infants in Moms with other forms of unrepaired congenital heart disease that may help readers be informed? You could also mention that there are scoring systems to rank the risk of pregnancy in women who have heart disease.

Although medical technology has advanced significantly for the past 50 years, the maternal mortality for ES remains unchanged. Thus, we believe that women with ES should avoid pregnancy and early termination of pregnancy should be strongly recommended if a patient with ES becomes pregnant. The following statements have been added:

“The patient condition exasperated very fast after delivery, and she die 10 minutes after childbirth. Cardiopulmonary resuscitation failed. Yentis et al. compared the maternal mortality of ES patient from 1990-1995 with the initial reports from the 1950s and found that maternal mortality associated with ES remains unchanged for the past 50 years [10]. Thus, women with ES should avoid pregnancy and early termination of pregnancy should be strongly recommended if a patient with ES does become pregnant. For the patients who choose to continue pregnancy, a multidisciplinary team including obstetrician, cardiologist, anesthesiologist, neonatologist, and intensive care physician should coordinate the management of the patients.”

Conclusion:

I agree that pre-natal screening is important. However, this is not a novel conclusion that helps readers. Readers might expect better advice. For example, explaining the natural history of disease before and after pregnancy may help a generalist talk to patients and families before a woman becomes pregnant. If the woman is pregnant, suggest helpful steps. The larger question is how to help patients in the setting of
poverty or an underserved area? How might your community deal with this problem? I suspect every country and culture will have unique approaches to dealing with these problems. We might be interested in sharing these ideas.

Our hospital has been routinely sending doctors to the rural areas where the access to medical care is limited. Hopefully, with the improvement of the availability of pre-natal screening, congenital heart defects can be detected and repaired promptly.