Certain congenital heart defects, which present at birth as complex morphology, are actually the result of a relatively simple primary lesion and the subsequent development of a complex secondary lesion during gestation. Fetal cardiac intervention can prevent simple cardiac lesions from such development. Congenital heart defects can be detected as early as 12 weeks gestation by transvaginal fetal echocardiography. The success of noncardiac fetal surgery has inspired the innovation of fetal cardiac surgery. A number of animal experiments have shown that direct or indirect fetal cardiac approach and fetal cardiac bypass have their own feasibility, reasonability and effectiveness. Effective cardiopulmonary bypass supports the implementation of fetal cardiac surgery. At the end of the last century, Champaur, Sakata and others\[1,2\] foresaw the advent of fetal cardiac surgery and performed a series of investigations on this subject, resulting in outstanding achievements. Since 1998 we have also investigated into this field.\[3\] My colleagues and I thought it was a more complex challenge than adult or pediatric open heart surgery.

To overcome surgical stress on the fetus and placental dysfunction after bypass is of paramount importance. Many researchers have shown that non-physiologic perfusion resulted in endothelial damage to the placental vasculature, further reducing blood flow and producing a series of secondary changes. Therefore, research into the mechanism of endothelial damage and its alleviation must be carried out to protect placental function.

The use of normal temperature and moderate pulsatile perfusion according to fetal circulatory physiology might mitigate the release of inflammatory intermediators, thus decreasing the endothelial damage. However, its clinical practice has a long way to go. Minimally invasive fetal cardiac approach can minimize maternal and fetal damage, so fetoscopic cardiac intervention is another valuable choice.\[4\]

Minityping and no-prime/ultra-low prime are the basic characteristics of a fetal cardiac bypass circuit. Champaur et al\[1\] found that pulsatile flow was conducive to the release of endothelium-dependent vasodilator, mitigating the contraction of placental vasculature. Reddy et al\[5\] established RA-PA bypass in lamb fetuses by axial flow pump driving. At normal temperature and without prime after 30 minutes of bypass, fetuses were returned to the womb and 89% of the fetal lambs reached full term.

There are two types of circuit, one of which includes the placenta, and the other excludes placental circulation by replacement with an oxygenator (artificial placenta\[2\]). Using autoplacenta may simplify the circuit, but our experience showed that the autoplacenta cannot bear the prolonged bypass, for its oxygenation capacity might decrease when bypass time is prolonged. This is the weakness of autoplacenta owing to the placental dysfunction. Therefore, maintaining and restoring placental function after fetal cardiac bypass is a big challenge.

A large amount of primed maternal blood may dilute the hemoglobin of the fetus, decrease its capability of binding oxygen so as to disturb the fetus homeostasis. A large amount of priming fluid in contact with a non-physiologic surface might further activate cytokines, eventually leading to placental dysfunction. A minityping circuit and axial flow mini-pump can decrease the primed volume effectively.

After exposing fetal lamb to non-physiological cardiopulmonary bypass, multiple cytokines are activated and inflammatory reaction is induced, which will increase placental vascular resistance, lower gas exchange and lead to refractory hypoxemia, hypercarponia and acidosis. Placental dysfunction may be the most severe obstacle to fetal cardiac bypass. Based on the literatures\[6,7\] and our experiences, placental dysfunction after fetal bypass is related to the following risk factors.

Hypothermia induces the activation of the sympathetic nervous system, increases blood viscosity, which lowers placental perfusion and decreases oxygen...
diffusion capacity. Hypothermia also induces uterine contraction, especially during the rewarming stage, which further damages placental function, resulting in fetal asphyxia and spontaneous abortion. Hypothermia is therefore not a protective factor in fetal cardiac bypass.\(^4,5\)

Since the fetus is a very vulnerable organism, any disturbance of the external or internal environment toward the end of gestation may cause fetal stress and abortion. The adrenal gland plays a major role in response to the outside stimulus. We found in our experimental study that after 30 minutes of bypass the levels of fetal catecholamine and cortisol increased significantly compared to those before bypass, umbilical blood flow decreased, while the levels of insulin did not change.\(^3\) The levels of blood glucose and free fatty acid increased at the beginning of the bypass, and then gradually declined as the bypass progressed. Fetal hepatic periodic acid schiff staining showed that hepatic glycogen was consumed in large amounts. After 30-minute bypass, the fetal lambs did not survive for more than one hour. They could not tolerate cardiopulmonary bypass well.\(^3\)

Pulsatile perfusion with high blood flow is beneficial to preservation of the placental function and improves microcirculation. Moderate high flow perfusion mimics the physiology of placental circulation and lowers resistance. They both improve endothelial function.\(^6,7\)

Vedrinne et al.\(^8,9\) concluded that during fetal pulsatile-flow bypass, improved placental and peripheral perfusion may be mediated by preservation of fetal/maternal endothelial nitric oxide biosynthesis and/or decreased activation of the fetal rennin-angiotensin pathway. Their experimental results showed better aortic and umbilical flow and lower placental umbilical vascular resistance in pulsatile-flow compared with steady-flow.

The endothelium is not only the interface between blood and vessel tissue but also the sensor receiving signals which regulate dilation of constricted vessels. They release NO to regulate the tension of umbilical vessels, and mitigate the constrictive effect of embroxane and endothelin.\(^9\)

Oishi et al.\(^10\) found that increased umbilical artery resistance is due to deterioration of the endothelium dependent vasodilator effect. The endothelium independent vasodilator (nitroprusside) function is not altered. Fetal cardiac bypass damages endothelium dependent relaxation function selectively, so protection of the endothelium and avoidance of the inflammatory response during fetal cardiac bypass would be a key to preserving placental function. Carotti et al.\(^11\) suggested the use of continuous hemodiafiltration combined with steroid administration to suppress the inflammatory response which causes post-bypass placental dysfunction.

Spontaneous abortion may occur after the womb is incised in most pregnant animals, and there is no exception in humans. Therefore, to find tocolysis agents is of extreme importance in the field of fetal cardiac surgery. Constriction of the womb can be controlled by indomethacin, halogen inhalant, combined with magnesium sulfate and β-synpathomimetic agents, which may be effective in monkeys. Inhalation of halogenoid during the course of procedure can relax the uterus but suppress the myocardium of the fetus and mother. Indomethacin may result in closing of the ductus arteriosus. Magnesium sulfate combined with β-synpathomimetic agent may induce pulmonary edema in the mother. Because NO showed outstanding tocolysis in rhesus experiments, further case control studies are desirable. For achieving tocolysis in baboons, Fenton and his colleagues used spinal anesthesia, and Ikai et al.\(^12\) used isofluane inhalation, and the fetuses were still alive after cardiopulmonary bypass.

Using microinvasive fetal cardiac intervention to decrease the damage to fetus/mother is a new approach to correcting congenital cardiac disease before birth. Through abdominal wall puncture and insertion of a cannula into the uterine cavity by fluoroscopy, a balloon catheter or pacemaker wire can be inserted into the umbilical artery to alleviate fetal cardiovascular lesions. Since 1977, Kohl and his colleagues have demonstrated the feasibility of this innovation in fetal lamb experiments, they analyzed the results of dilation for fetal aortic stenosis in humans. The result was not satisfactory. We hope further researches might improve this condition.

Fetal cardiac surgery aims to deal with serious heart lesions in the womb which have poor prognosis post partum, reduce the high incidence of critical congenital heart diseases, and lower operative mortality and morbidity in cardiac surgery after birth. The prerequisite is the optimal placental preservation technique during fetal cardiac surgery. The management of negative effects on the mother/fetus from a cardiac procedure is another major concern before it becomes a clinical practice. By fetoscopy technique, fetal cardiac lesions may be corrected without complex cardiopulmonary bypass. Not only can it correct fetal cardiac defect but may also lessen the harmful effects to the mother and fetus. We deem that it would be a promising and potential therapy for fetal cardiac defects.

**Funding:** This study was supported by grants from the National Natural Science Foundation of China (No. 39770734 and No. 30471712).
Ethical approval: This study was approved by the Data Inspectorate of China and by the Regional Committee for Medical Research Ethics.

Competing interest: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Contributors: Su ZK proposed the study and wrote the first draft. Chen E is the guarantor.

References

Received March 23, 2007
Accepted after revision October 17, 2007