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during surgery to prevent a preterm labor. Adrenaline was not used during or after surgery because of its vasoconstrictive effects over placental vessels.

The fetal ultrasonography after the operation showed a live fetus in 16th week of gestation. The patient was hemodynamically stable after the operation, and continued to receive antibiotic and low molecular weight heparin therapy. On discharge at 20th postoperative day, the patient was free of any symptoms, with a live fetus in the 19th week of gestation.

Infective endocarditis during pregnancy carries a high mortality risk, both for the mother and for the fetus. However, over the last three decades, successful medical and surgical management has helped in lowering mortality rates in those groups of patients. There are previous case reports of cesarean sections in the 29th and 36th weeks of pregnancies in mothers with infective endocarditis with live fetuses weighing 1400 and 2530 grams, respectively. The mothers underwent heart surgery a few days after cesarean delivery (3, 4). In a pregnant patient, the ideal time for cardiac surgery is between 13th and 28th gestational weeks. In pregnant patients during cardiac surgery, maternal mortality rate is reported between 1% and 5%, with an average of 2.5% in the literature. This rate does not differ from non-pregnant women undergoing cardiac surgery. Fetal loss or preterm labor might also occur during surgery, and perioperative administration of adrenaline, dopamine or furosemide might cause reduced placental perfusion and increased fetal loss (5).

The decision to keep the fetus or to terminate the pregnancy should be given by a team of obstetricians, cardiac surgeons and the patient. The patient should also be informed about the advantages and disadvantages of mechanical and tissue valves to be able to make a choice between them.

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# Further expanding possibilities of successful stem cell transplantation in coronary artery disease/An alternative approach of stem cell delivery to myocardium: combined usage of antegrade coronary arterial infusion and retrograde venous obstruction

## *Koroner arter hastalığında başarılı kök hücre transplantasyonunun gelecekteki olasılıkları/ Miyokard dokusuna kök hücre nakline alternatif bir yaklaşım: Antegrad koroner arteryel infüzyon ve retrograd venöz obstrüksiyonun birlikte kullanımı*

Dear Editor,

We read with great interest the manuscript entitled "An alternative approach of stem cell delivery to myocardium: combined usage of antegrade coronary arterial infusion and retrograde venous" by Nisancı et al. (1), in which they showed advantages of cardiac venous occlusion during intraarterial injection of stem cells. Stem cell therapy has recently attracted attention of cardiologists investigating methods of replacement of the damaged myocardium and recreation of autonomously functioning cardiomyocytes. Despite obvious advances in purification of stem cells and their delivery to the site of myocardial affection, there are still many unresolved issues related to transportation, implantation and differentiation of stem cells (2, 3). Success of the therapy is primarily subjected to the cellular environment and intercellular cooperation at the site of myocardial affection. Coronary ischemia itself may cause local immune reaction, inflammation and necrosis, which are not favorable for stem cells survival and differentiation into functioning cardiomyocytes. Not less important is the issue of stem cells penetration into the infarction site and cooperation with viable myocardium. De novo myocardial regeneration can be reached by intracoronary, intravenous and intramyocardial delivery of stem cells. Each route of the delivery has advantages and disadvantages. Intracoronary injection is less invasive compared to direct myocardial injection and guarantees transport of the cells through the blood flow directed to injured myocardium. At the same time, one of the major limitations in this case is related to the difficulties with tissue penetration, especially to the ischemic zones. Regardless of the delivery mode, cellular survival in ischemia is an even more serious issue. Not surprisingly, majority of the transplanted cells die soon after stem cells transplantation. The latter makes it more practical to perform revascularization alongside with stem cells transplantation. Quite problematic is the differentiation of transplanted stem cells in a desirable way. Transformation of stem cells into cardiomyocytes is not a guaranteed process and it occurs rarely. More concerning is the fact that transplanted cells can deliberately transform into fibroblasts, chondrocytes, osteocytes and sometimes can accelerate myocardial fibrosis and calcification. Previously documented arrhythmogenic and oncogenic potentials of stem cell therapies should also be cautiously weighed and taken into account while following patients over months and years. Of diverse adverse effects of transplantation, arrhythmias

occur quite frequently necessitating monitoring and administration of anti-arrhythmics. As for oncogenic differentiation of the cells, it is rather medicolegal issue, which needs to be addressed during planning of the therapy. Of note, external contamination during handling and storage may influence malignization behavior.

Lastly, in various studies it has been shown that intraarterial injection of stem cells is related to no-reflow phenomenon and distal embolisation. To ensure safety and efficacy it is recommended to monitor levels of creatine-kinase (CK), CK-MB, troponin and D-dimer after the injection. In conclusion, the presented case of stem cells transplantation (1) deserves appreciation. It further expands our knowledge of possibilities to improve immediate results of stem cells transplantation in patients with coronary artery disease.

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## Author's Reply

Dear Editor,

We thank the authors for the interest and supportive letter on our case report "An alternative approach of stem cell delivery to myocardium: combined usage of antegrade coronary arterial infusion and retrograde venous obstruction" (1).

Cardiac stem cell therapy is a novel, promising method for the treatment of cardiovascular disease. Many previous studies demonstrated the beneficial effects of stem cells on left ventricular function after acute or chronic ischemic injury (2-4). The cardiac stem cells supposed to be efficient by either engraftment or differentiation into cardiac and vascular cells or by secretion of paracrine factors that promote tissue survival and recovery. However, there is a challenge with the selection of cell types, methods of cell delivery, myocardial homing, pathways of cell survival, and the goals of cell differentiation. Identification of the most safe and efficient delivery method is one of the leading problems in cardiac regenerative therapy.

Because the strategy of cell therapy is to repair injured tissue through delivery of an adequate cell dose to an area of interest, determination of the best delivery method may have an important role that may affect the success of the treatment. The conductive microenvironment for cell survival, retention, and homing are also important. Currently available routes for stem cell administration are; intravenous, intracoronary, transmyocardial, catheter-based transendocardial injection using electromechanical mapping and a recently implemented approach of transvenous injection (2-5). Intravenous injection is the less preferable route due to poor homing rates (<5%) in the targeted area (2). Majority of intravenously injected cells are trapped by the lungs, liver, kidneys, and spleen. Therefore, the intracoronary delivery techniques became forefront of the intravenous injection technique. However, the cell retention may still be insufficient due to rapid washout that follows balloon deflation (3).

Intramyocardial delivery may yield better retention than intracoronary delivery. However, side effects such as arrhythmias due to electrical instability and myocardial perforation are reported with this method (5). Transendocardial injection may be more safe and complementary to intramyocardial injection method. However, this method requires specific catheter and mapping systems, which may not be cost effective for clinical usage. Similar to our case, combination of the two delivery techniques may enhance the homing and retention of the stem cells in targeted area (1). We think that combination of the delivery methods may improve the inadequate sides of the methods and ameliorates the efficiency of the delivery routes (6).

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