

## A Case Report : Cesarean Section of in Vitro Fertilization with Sickle Cell Anemia, Post-op Myomectomy, Gestational Diabetes & Preclampsia. Management



### Case Report

**KEYWORDS :** In vitro fertilization, uterine fibroid, myomectomy, sickle cell anemia, gestational diabetes, preclampsia, caesarean section, epidural anaesthesia.

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### ABSTRACT

*We report a case of in vitro fertilization of a 36 year old female gravida 2, abortion 1, with five months of amenorrhea, who came for a regular ANC registration and checkup. As per the history given by the patient, she was a known case of Sickle cell anemia since 15 years of age on penicillin prophylaxis, she even received swine and influenza flu vaccines as recommended. Patient had a history of myomectomy 3 years back in view of posterior wall uterine fibroid. Besides all these patient also had a negative history of in vitro fertilization with a donor egg last year which ended in a spontaneous abortion at three months of gestation.*

*From our experience of managing one of the most interesting cases in view of precious pregnancy and multiple co-morbidities, we concluded that appropriate monitoring and management of these patients is essential. As so many co-morbidities can rapidly turn the most routine surgery into a deleterious situation. Surgeons and anaesthesiologists should co-ordinate and manage the patient as per protocols and guidelines for the best of outcomes.*

### Case report

We report a case of in vitro fertilization of a 36 year old female gravida 2, abortion 1, with five months of amenorrhea, who came for a regular ANC registration and checkup. As per the history given by the patient, she was a known case of Sickle cell anemia since 15 years of age on penicillin prophylaxis, she even received swine and influenza flu vaccines as recommended. Patient had a history of myomectomy 3 years back in view of posterior wall uterine fibroid. Besides all these patient also had a negative history of in vitro fertilization with a donor egg last year which ended in a spontaneous abortion at three months of gestation.

On examination the general condition of the patient was fair, she was moderately built with pulse rate of 86 beats per minute and blood pressure of 140/90 mm of Mercury. The patient had no pallor but there was pedal edema of grade one present bilaterally. Rest of the general and systemic examination does not show any adverse effect. Patient was advised an anomaly scan, along with complete blood count, blood group, random blood sugar, liver function test, kidney function test, serology tests, coagulation profile, iron studies, urine routine microscopy, 2D-Echo. Other than all these, patient was advised for retinal screening and physician reference in view of the co-morbidities. Patient was advised folic acid, iron, calcium supplements and protein powder. The anomaly scan and routine blood investigations were normal along with the 2D-Echo.

On two occasions her blood pressure was above normal along with the presence of proteinuria of one to two plus. Patient was admitted and was advised tablet labetalol 100mg twice daily, blood and urine investigations. Blood investigations showed Hb-12.6 gm%, TLC-9000, Platelets - 2.5 lakhs, PCV - 32, S. Creatinine 0.7, T. bil.- 0.9, D.bil.- 0.4, SGOT - 40, SGPT - 36, PT- 13 sec., INR - 1.1. Blood group - B-positive, BT- 1'30", CT- 3'45". Patient was discharged with a controlled blood pressure of 130/80mm of Mercury on antihypertensive tablet Labetalol 100mg twice daily.

At 28 wks patient came for a routine check up, during which she was advised repeat obstetric ultrasonography with Doppler study. The USG report showed a single live intrauterine gestation of 27wks and 6 days with polyhydramnios (AFI-22.5) with a

normal Doppler study. Further patient was advised a fasting and post prandial blood sugar, both of which came elevated. Therefore, she was advised a glucose tolerance test (fasting-134 mg% and after 2hrs.-206 mg%) and on the basis of the results she was diagnosed with Gestational Diabetes Mellitus. Patient was admitted and was started on Human Actrapid Insulin on sliding scale, which was converted into inj. Mixtard on discharge.

As patient was a high risk with a precious pregnancy, in view of IVF conception, Sickle cell anemia with GDM with preclampsia and post-op c/o myomectomy, she was planned for an elective caesarean section at 36 completed weeks. For which patient was again admitted at 34 wks of gestation, and was given two doses of inj. Betamethasone 12 mg 24 hrs apart for fetal lung maturation. After a thorough pre-anaesthetic evaluation patient was planned for plain epidural anaesthesia in view of co-morbidities and precious pregnancy. Written informed valid consent checked and confirmed. Electrocardiogram, pulse oximeter, and non-invasive blood pressure monitors were attached. Patient was given left lateral position. Two wide bore cannulas were secured on bilateral upper limbs. Parts painted and draped for epidural catheter placement at L<sub>5</sub>-L<sub>4</sub> level. 16G Tuchy's needle was inserted and epidural space was identified with the help of loss of resistance technique at 4cm of needle depth. Catheter was introduced and fixed at 9cm mark. Test dose was given with 3cc of Inj. Lox 2% + ADR to confirm the placement of catheter. Patient was turned to supine position and epidural analgesia was given with 10cc of 0.25% Inj. Bupivacaine plain block acted.

Pfannenstiel incision was taken. Abdomen opened in layers till parietal peritoneum. Doyens retractor introduced. Uterovesical fold identified and separated and Doyens retractor advanced. Horizontal incision taken on the lower uterine segment and extended bilaterally. Artificial rupture of membranes was done and liquor was clear. Baby extracted with vertex presentation. Baby cried immediately after birth. Cord clamped and cut, cord blood samples taken. Uterine angles held with long allis forceps. Lower segment was held by green armytage forceps. The weight of the healthy newborn was 3.1 kg. After the delivery of the baby, inj. Oxytocin 20 IU in 500ml of ringer lactate solution was started. Placenta was removed manually by controlled cord traction method. Uterus was sutured in continuous interlocking manner, hemostasis was achieved. Abdomen closed in layers,

sterile dressing and vaginal toileting done which had no active bleeding and showed no signs of post partum haemorrhage. It was an uneventful caesarean section with no complications to mother and baby. Patient was started on continuous Epidural infusion with 0.125% of Inj. Bupivacaine plain at 5ml per hour for post op analgesia. Infusion was stopped after 48 hours and catheter was removed.

Patient was discharged on day five of surgery after check dressing of wound which was healthy with advice of continuing iron and calcium tablets and avoidance of heavy weight lifting. Patient was counselled regarding exclusive breast feeding for six months and contraception. Patient was asked to follow up for suture removal and then after one month for a routine checkup. Patient was also advised to keep physicians follow up in view of her co-morbidities.

## DISCUSSION

Considering the fact that our patient was a high risk and precious pregnancy, she needed special care, regular follow up and the maximum understanding of her multiple co-morbidities. Like Sickle Cell Disease (SCD) is a group of inherited single-gene autosomal recessive disorders caused by the 'sickle' gene, which affects haemoglobin structure.<sup>1</sup> SCD has its origins in sub-Saharan Africa and the Middle East<sup>2,3</sup>, hence it is most prevalent in individuals of African descent as well as in the Caribbean, Middle East, parts of India and the Mediterranean, and South and Central America. The term SCD includes sickle cell anaemia (HbSS) and the heterozygous conditions of haemoglobin S and other clinically abnormal haemoglobins. These include combination with haemoglobin C (giving HbSC), combination with beta thalassaemia (giving HbSB thalassaemia) and combination with haemoglobin D, E or O-Arab. All of these genotypes will give a similar clinical phenotype of varying severity.<sup>3</sup>

The pathophysiology of SCD is a consequence of polymerisation of the abnormal haemoglobin in low-oxygen conditions, which leads to the formation of rigid and fragile sickle-shaped red cells. These cells are prone to increased breakdown, which causes the haemolytic anaemia, and to vaso-occlusion in the small blood vessels, which causes most of the other clinical features, including acute painful crises. Other complications of SCD include stroke, pulmonary hypertension, renal dysfunction, retinal disease, leg ulcers, cholelithiasis and avascular necrosis (which commonly affects the femoral head and may necessitate hip replacement).<sup>4,5</sup>

SCD is associated with both maternal and fetal complications and is associated with an increased incidence of perinatal mortality,<sup>6-11</sup> premature labour,<sup>6-12</sup> fetal growth restriction<sup>6-13</sup> and acute painful crises during pregnancy.<sup>7-9,14,15</sup> Some studies also describe an increase in spontaneous miscarriage,<sup>12</sup> antenatal hospitalisation,<sup>13</sup> maternal mortality,<sup>16</sup> delivery by caesarean section,<sup>13,16</sup> infection, thromboembolic events<sup>17</sup> and antepartum haemorrhage.<sup>16</sup> An increased risk of pre-eclampsia and pregnancy-induced hypertension has been described in some studies<sup>6,8,9,13,16</sup> but not in others.<sup>7,10,12</sup> SCD is a chronic, lifelong condition and there are recommendations for clinical care which apply to all patients, including women planning to become pregnant.<sup>16</sup> Women should be reviewed at least annually by a specialist sickle service for the monitoring of chronic disease complications and the imparting of information.<sup>18</sup>

The assessment for chronic disease complications should include: screening for pulmonary hypertension with echocardiography. The incidence of pulmonary hypertension is increased in patients with SCD and is associated with increased mortality.<sup>19</sup> A tricuspid regurgitant jet velocity of more than 2.5 m/second is associated with a high risk of pulmonary hypertension.<sup>20</sup> Screening should be performed if this has not been carried out in the last year.<sup>18</sup> Blood pressure and urinalysis should be performed to identify women with hypertension and/or proteinuria. Renal and liver function tests should be performed annually to identify sickle nephropathy and/or deranged hepatic function.<sup>18</sup> Retinal screening is also very important, as proliferative retinopathy is common in patients with SCD, especially patients

with HbSC, and can lead to loss of vision.<sup>21</sup> General practitioners have a key role to play in partner screening and genetic counselling. Women should be encouraged to have the haemoglobinopathy status of their partner tested. If a partner is a carrier of, or affected by, a major haemoglobinopathy, the couple should receive appropriate counselling regarding the risk of having affected offspring.<sup>22</sup> The methods and risks of prenatal diagnosis and termination of pregnancy should be discussed with the couple.<sup>23</sup>

Patients with SCD are hyposplenic and are at risk of infection, in particular from encapsulated bacteria such as *Neisseria meningitidis*, *Streptococcus pneumonia* and *Haemophilus influenzae*. There is clear evidence that penicillin prophylaxis is of benefit in with SCD.<sup>24</sup> Folic acid is recommended in all pregnant women to prevent neural tube defects.<sup>25</sup> Hydroxycarbamide has been demonstrated to decrease the incidence of acute painful crises and ACS in individuals with severe clinical manifestations of SCD.<sup>26</sup> Hydroxycarbamide is teratogenic in animals and, consequently, current UK advice is that women with SCD on hydroxycarbamide should use effective contraception and stop taking hydroxycarbamide 3 months before they conceive.<sup>27,28</sup> Renal dysfunction, proteinuria and microalbuminuria are common in SCD. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are used routinely in patients with SCD with significant proteinuria (protein-creatinine ratio of more than 50 mg/mmol), since there is evidence that these agents reduce proteinuria and microalbuminuria.<sup>29,30</sup> These drugs are not safe in pregnancy and should be stopped in women who are trying to conceive.

While older studies demonstrated iron deficiency to be common in SCD, a more recent study examining a small number of pregnant women with SCD showed no evidence of iron deficiency, and some of these women were iron overloaded.<sup>31,32</sup> Iron status should be assessed and iron supplementation should be recommended only if there is evidence of iron deficiency. Women who are at increased risk of pre-eclampsia are advised to take low-dose aspirin 75 mg from 12 weeks of gestation, unless they have aspirin sensitivity. While there is no specific evidence that aspirin decreases the risk of pre-eclampsia in women with SCD, such women are probably at increased risk of developing preeclampsia.<sup>33,34</sup> There is some evidence that the incidence of venous thromboembolism is increased among pregnant women with SCD. Thromboprophylaxis advice should be based on the RCOG Green-top Guideline for women with additional risk factors.<sup>35</sup> The use of graduated compression stockings of appropriate strength is recommended in pregnancy for women considered to be at risk of venous thromboembolism, as discussed in the RCOG Green-top Guideline on thromboprophylaxis.<sup>35</sup>

Women with SCD probably have an increased risk of pregnancy-induced hypertension;<sup>6,8,9,13,16</sup> therefore, blood pressure and the presence of proteinuria should be assessed at each visit. Women with pre-existing proteinuria or known renal impairment will require more frequent monitoring. Women with SCD often have a low blood pressure, so an upward trend in blood pressure, even if modest, should be monitored carefully. Studies have also demonstrated an increase in the incidence of urinary tract infection and asymptomatic bacteriuria,<sup>16</sup> so urinalysis should be performed at each antenatal visit and midstream urine should be sent for culture and sensitivity monthly.

A number of studies suggest that women with SCD are at risk of fetal growth restriction<sup>11,16</sup> as well as pre-eclampsia. Serial growth scans allow early detection of fetal growth restriction and hence aid appropriate timing of delivery to reduce perinatal mortality and morbidity.<sup>36</sup>

Early studies recommended prophylactic transfusion during pregnancy as there was a decrease in maternal morbidity and perinatal mortality among transfused women compared with historical controls.<sup>37-39</sup> There are appreciable risks associated with transfusion in this heavily transfused patient cohort, including alloimmunisation,<sup>15,40</sup> delayed transfusion reactions,<sup>40</sup> transmission of infection and iron overload. A systematic re-

view<sup>41</sup> indicated that there is insufficient evidence to draw conclusions about the role of transfusion in pregnancy.

Regarding post-op case of myomectomy, study was done to analyze effect of abdominal myomectomy on subsequent fertility. Fertility reduced by greater number and deeper localization of myomas. Coexistence of pelvic infection and adhesiolysis reduced pregnancy rate. Growth of myomas is also regulated by progesterone and a number of local growth factors, and the genetic basis of myoma growth may be primarily related to these factors and their receptors.<sup>42</sup> Fibroids interfere with sperm transport, implantation on the tubal lamina, distort the course of the fallopian tube and compress the cervical canal thus interfering with sperm capture, disruption or distortion of endometrial cavity and implantation due to venous ectasia over a submucosal myoma, endometrial inflammation abnormalities of blood supply to the endometrium, atrophy and ulceration may occur thereby preventing implantation.<sup>43,44,45</sup> Some later studies report on myomectomy as the treatment of infertility with pregnancy rates ranging between 50% and 65%.<sup>43,45,46</sup> There are many factors that contribute to the state of infertility and myomas are rarely implicated as the sole cause.<sup>46,48,49,50</sup>

Other than multiple co-morbidities our patient has undergone IVF second time which made us to really treat it as a case of her own kind.

Assisted reproductive technology is commonly defined as any procedure that involves handling eggs, sperm, or both outside the human body (in vitro). ART includes in vitro fertilization, with or without intracytoplasmic sperm injection, with fresh or frozen embryos (by cryopreservation or by vitrification and thawed embryo transfer) and IVF with donor oocytes, gamete intrafallopian transfer, zygote intrafallopian transfer, and assisted zona hatching. ART has expanded to include not only in vitro procedures, but also intrauterine insemination and OS with gonadotropin or ovarian stimulating medications.<sup>51</sup> ART accounts for 1.7% to 4% of pregnancies<sup>52</sup> and has traditionally been used to address primary or secondary infertility.<sup>53</sup> The ethical and philosophical issues involved in AHR are complex and are handled differently in different countries, resulting in varying levels of regulation of these services.<sup>54-58</sup> Infertility, generally considered to be the inability to conceive after one year of attempting pregnancy,<sup>59</sup> has been identified as a significant independent predictor of adverse obstetrical and perinatal outcomes.<sup>60,61,62</sup> Unadjusted analyses suggest a 2-fold increased risk of preeclampsia, placental abruption, Caesarean section, and vacuum extraction, and a 5-fold increased risk of placenta previa in spontaneous singleton pregnancies in women with a history of infertility compared with women in the general population.<sup>63</sup> Maternal factors related to an increased risk of infertility also have an independently associated risk of adverse obstetrical outcomes. Advancing maternal age is associated with both declining fertility and multiple adverse outcomes of ongoing pregnancy, as noted recently in an SOGC committee opinion on delayed childbearing.<sup>64</sup> Research shows obesity impairs fertility,<sup>65,66</sup> although whether this effect is primarily ovarian or endometrial is controversial.<sup>67-69</sup> Along with multiple pregnancy, preterm birth and LBW are the most commonly examined measures of adverse perinatal outcome in singleton pregnancies conceived after AHR.<sup>70,71</sup> There has been some question of whether AHR leads to placental abnormalities as a mediating factor for some adverse outcomes, such as LBW, preeclampsia, abnormal implantation, placenta accreta, antepartum hemorrhage, and postpartum hemorrhage. Possible early placental abnormalities are consistent with the finding of altered levels of maternal serum marker levels for Down syndrome and open neural tube defects in the first and second trimester. Several studies report an increased risk of preeclampsia with AHR.<sup>73</sup> Small studies have linked donor oocytes with an increased risk of preeclampsia over autologous oocytes.<sup>72,74</sup> Other placental complications reported to occur with increased frequency with ART include placenta previa, placental abruption, and antepartum and postpartum hemorrhage.<sup>75</sup>

Regarding the Gestational diabetes, which is defined as "carbohydrate intolerance of variable severity with onset or first rec-

ognition during pregnancy"<sup>76</sup> and its screening for gestational diabetes with a glucose challenge test has been proposed<sup>77</sup>; over the past 20 years its use has become relatively routine<sup>7</sup>. A number of risk factors have been associated with a greater likelihood of developing gestational diabetes. By and large these are the same factors that predict overt diabetes, and they include advanced maternal age, a family history of diabetes in a first-degree relative, obesity, and glycosuria. The taking of a history can be considered to be a "screening test"<sup>78,79</sup> Because the prevalence of gestational diabetes, like that of NIDDM, increases with advancing maternal age, using specific maternal age thresholds at which to pursue universal glucose challenge screening has been advocated by some<sup>80</sup>. The 50-g, 1-hour oral glucose challenge proposed by O'Sullivan has been recommended by both the ADA<sup>76</sup> and the ACOG<sup>80</sup>, although the latter group recommends this test only for gravidas age<sup>81</sup> 30 years and younger women if risk factors are present.

Now, considering precious pregnancy and so many co-morbidities, anesthetic considerations require a thorough understanding of the implications involved in this already compromised patient. Preoperatively, inhaled oxygen therapy of at least 30% is of good therapeutic measure but not required unless the patient's condition so dictates. Preoxygenation prior to induction is essential. Preoperative medications should not depress respiratory function in order to avoid respiratory acidosis. Intravenous fluids should be warmed and given in amounts that assure adequate hydration, prevent erythrocyte sludging, and promote good urinary flow. The anesthetist should ensure that the patient is hydrated while at the same time should avoid fluid overload, as most of these patients will have some aspect of cardiac involvement. These patients must be kept warm in order to prevent a crisis. Use of warm blankets preoperatively and intraoperatively, warming the surgical suite, warming of intravenous fluids and preventing unnecessary exposure of the patient intraoperatively are essential. Aseptic technique is required at all times because these patients have an increased risk of infection. They are especially vulnerable to pulmonary infections. Routine monitoring equipment should include an oxygen analyzer, temperature probe, and an electrocardiogram<sup>82</sup>. Intraoperatively, conditions which promote sickling of erythrocytes must be avoided. For this reason, a local anesthetic with intravenous sedation is the technique of choice. Regional anesthesia is the second choice but it has been shown that regional blocks, including axillary, epidural, or subarachnoid, produce compensatory vasoconstriction and a decreased PaO<sub>2</sub> in the nonblocked areas, creating a milieu for infarction in these areas.<sup>83</sup> Spontaneous respirations are maintained with these techniques, and the stresses of general anesthesia are not induced. If a general anesthetic is mandated, an inhalation agent with high oxygen flows is utilized. A very low flow of nitrous oxide may be used. Muscle relaxants must be used with caution and prolonged immobilization should be avoided. The use of succinylcholine is modified by the occasional occurrence of decreased serum cholinesterase activity in these patients.<sup>84</sup> Treatment of a crisis with magnesium sulfate will potentiate muscle relaxants, and the use of a peripheral nerve stimulator is prudent in all patients. Adequate alveolar ventilation and normal cardiac output must be maintained to avoid ventilation-perfusion ratio alterations. Positional changes and the use of tourniquets are undesirable/contraindicated because of the likelihood of intravascular stasis. Movement of the patient's extremities, if possible, in long procedures is also recommended to relieve stasis. Deliberate hypotension is one technique that should be avoided at all costs because this promotes sludging and pooling of erythrocytes in the extremities. There is some evidence that general anesthesia may actually *decrease* the number of circulating sickle cells during and immediately following the anesthetic.<sup>85,86</sup> Postoperatively the patient should be kept warm. Inhaled oxygen therapy is recommended for transport of the patient to the recovery room. In the postoperative area, oxygen should be administered through an aerosol mask at an FIO<sub>2</sub> of 35%. Early mobilization is essential for the patient. Once recovery from anesthesia is complete, oxygen should be administered only intermittently, or as needed, rather than continuously. Two of three patients given oxygen at 5 L/minute over 5 days were reported to have devel-

oped painful episodes following discontinuation of oxygen.<sup>87</sup>

## Conclusion:

From our experience of managing one of the most interesting cases in view of precious pregnancy and multiple co-morbidities, we concluded that appropriate monitoring and management of these patients is essential. As so many co-morbidities can rapidly turn the most routine surgery into a deleterious situation. Surgeons and anaesthesiologists should co-ordinate and manage the patient as per protocols and guidelines for the best of outcomes.

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