The New Noble Management of Morbidly Adherent Placenta in a case of Repeat cesarean section with Placenta Previa

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IN A CASE OF

REPEAT CAESAREAN SECTION WITH PLACENTA PREVIA

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Abstract

INTRODUCTION

Over the last century worldwide, the incidence of placenta accreta spectrum (PAS) has been rising dramatically, mainly due to a rising caesarean delivery rate. The reported incidence of placenta accreta has increased from approximately 0.8 per 1000 deliveries in the 1980s to 3 per 1000 deliveries in past decade. Although elective caesarean hysterectomy is the standard practice the choice of conservative management has emerged into practice. Conservation of the uterus reduces major obstetric haemorrhage and numerous short and long-term complications as well as psychological sequelae due to loss of femininity and fertility.

METHODS

The scope of this paper is to describe a model case of placenta accreta managed conservatively in Institute of Post Graduate Medical Education and Research and SSKM Hospital in India in 2021. This case is successfully managed by leaving the placenta in situ followed by postpartum administration of multiple doses of chemotherapeutic agent methotrexate. Sequential changes in serum beta-HCG and ultrasonographic estimation of volume of placental mass with colour doppler were used as combined methods for follow-up of this case.

RESULT

The result is analysed by measuring the response to the treatment. There was a 60 % drop in the placental volume from day 10 to 60 and a total 90% drop in serum beta-HCG in the same span of time. After 4months USG showed absolutely normal uterus with no residual placental mass. However there were certain complications in this case following this treatment viz. Idiosyncratic reaction to methotrexate, febrile neutropenia, sepsis, surgical site infection, hypokalaemia. Each complications were dealt with care.

CONCLUSION

While PAS is sure to increase in the years to come, there is a lack of robust evidence regarding the most appropriate management ; thus management must be individualized keeping in mind the age of the patient, number of living issues and desire to preserve fertility and menstruate further.

Keywords: Placenta accreta; Conservative treatment; Methotrexate

Background

The incidence of placenta accreta spectrum (PAS) disorders has been rising dramatically over the last century worldwide, mainly due to a rising caesarean delivery rate [3,4]. Antenatal diagnosis and making no attempt to remove any part of the placenta is associated with reduced levels of haemorrhage and therefore less blood transfusions [5,6]. Although elective caesarean hysterectomy is the standard practice, the choice of conservative management has emerged into practice [3]. Conservation of the uterus reduces numerous short- and long-term complications including massive blood transfusions, disseminated intravascular coagulopathy (DIC), high morbidity/mortality rates, adjacent pelvic organ damage, and infection, as well as long-term psychological sequelae due to the loss of femininity and fertility [7,8].

The scope of this article is to describe a model for the follow-up of the conservative management of PAS with the placenta in situ approach followed by multiple methotrexate injection postpartum, while summarizing the follow-up findings of this case managed in Institute of Postgraduate Medical Education and Research and SSKM Hospital in India in 2021. Sequential changes in serum beta-HCG, and ultrasonographic volume of placental mass were used as combined methods for the follow-up of this case.

Introduction

Morbidly adherent placenta (MAP) is a histopathological term, which includes three categories according to the depth of placental villous invasion into the uterine wall: first, placenta accreta in which the placental villi are directly attached to the myometrium without interposing decidua; second, placenta increta in which the villi penetrate the myometrium up to the uterine serosa; and, third, placenta percreta in which the villi penetrate through the serosa and invade surrounding tissues and organs such as the bladder [9-11].

In clinical practice, the term placenta accreta is often used for the three types of MAP. Placenta accreta is associated with high maternal mortality of up to 10% and morbidity of about 75%, including uterine rupture before viability, massive obstetric haemorrhage, multi-organ failure and need for hysterectomy[12,13]. .One of the leading causes of maternal deaths in a developing nation like India is Obstetric haemorrhage and majority of these deaths are contributed by abnormal placentation and has surpassed uterine atony. Once a rare occurrence, morbidly adherent placenta is now becoming an increasingly common complication of pregnancy, mainly due to the increasing rate of Caesarean delivery [20] The reported incidence of placenta accreta has increased from approximately 0.8 per 1000 deliveries in the 1980s[3] to 3 per 1000 deliveries in the past decade[21]Placenta accreta is now the most common reason for Caesarean hysterectomy[14,15]

The two main risk factors for MAP are placenta previa and history of Caesarean delivery[16-19], and the risk increases with the number of Caesarean sections from 3% for one, to

11% for two, 40% for three and > 60% for four or more[18]

Development of ‘PAS’ is complex and multifactorial. Normal placentation does not proceed beyond the inner third of the myometrium. However, an invasive placenta proliferates

and invades local structures like a malignant tumour. Underlying mechanisms are poorly understood. Proposed theories include absence of decidua or basal plate, abnormal maternal vascular remodelling and excessive trophoblastic invasion [22]As a consequence of partial or total absence of decidua basalis and imperfect development of the fibrinoid or the Nitabuch layer, placental villi are directly attached to the myometrium in placenta accreta.[23] Benirschke et al suggested this to happen as a consequence of failure of reconstitution of the decidua basalis after repair of caesarean incision, thus resulting in absence of intervening decidual tissue between the invading trophoblast and the myometrium[24] . It has been proposed that the abnormality of the placental uterine interface leads to leakage of foetal alpha-fetoproteins into the maternal circulation resulting in elevated levels of maternal serum alpha-fetoproteins [25][26]

Uterine preservation , referred to here as conservative management, is usually defined as removal of placenta or utero-placental tissue without removal of the uterus. For patients with focal placental adherence, removal of the placenta by either manual extraction or surgical excision followed by repair of the resulting defect has been associated with uterine preservation in some cases [27]

Expectant management is defined as leaving the placenta either partially or totally in situ. In patients with more extensive placenta accreta spectrum, expectant management is considered an investigational approach. [27]The degree of success with expectant management of placenta accreta spectrum appears to correlate with the degree of placental attachment abnormality.

Taking the limited published data together, and the accepted approach of hysterectomy to treat placenta accreta spectrum, conservative management or expectant management should be considered only for carefully selected cases of placenta accreta spectrum after detailed

counselling about the risks, uncertain benefits, and efficacy and should be considered investigational.

Methotrexate, a folate antagonist, can be used as an *adjunct* to expectant management. Its use in expectant management of placenta accreta spectrum is advocated by some authors who contend that it will hasten placental involution and resorption [28]. The biologic plausibility of this premise may be questioned because methotrexate targets rapidly dividing cells and is effective against proliferating trophoblast. Division of third trimester placental cells is limited. Also, as after delivery of the foetus the placenta is no longer dividing, a significant effect of methotrexate on degenerative tissue seems unlikely . It has been hypothesized that methotrexate acts by inducing placental necrosis and expediting a more rapid involution of placenta. This contradicts the belief that it acts only on rapidly dividing cells, given that trophoblastic proliferation does not occur at term. Thus, there is controversy regarding the effectiveness as an adjuvant treatment. Also, there is a lack of consensus regarding optimum dosing, frequency or route of administration [3].

Although conservative management of MAP appears to be successful at preventing hysterectomy in most cases but there is always a potential for morbidity. Methotrexate use can be associated with a variety of adverse effects over a wide range of severity; The side effect profile of Methotrexate varies markedly according to dose. Regimens containing Methotrexate are classified as high (≥500mg/m2), intermediate (between 50-500mg/m2), or low-dose (<50mg/m2). The most commonly observed side effects at intermediate doses are rarely life threatening, this includes gastrointestinal problems such as nausea, stomatitis, soreness of mouth, fever, fatigue and headache. Most commonly reported complication in morbid adherent

placenta cases managed with Methotrexate is haemorrhage (post-operative Methotrexate was associated

the blood loss of 1000–2000 mL) and fever which is mostly secondary to endomyometritis or florid sepsis. Fever may also represent an inflammatory response to tissue necrosis in the absence of any infectious source. There may also be myelo-suppression, hepatotoxicity, renal failure, and pulmonary fibrosis may still occur with its use. The bone marrow suppression associated with methotrexate may increase further the risks of postpartum infection or anaemia. Infectious morbidity can be reduced by use of prophylactic broad-spectrum antibiotic therapy.[31]

Further, methotrexate is contraindicated in breastfeeding because of neonatal morbidity [29][30].Methotrexate does transfer into breast milk, although the levels detected are very low. However, caution should still be used in counselling mothers regarding breastfeeding with this toxic drug. Because Methotrexate is very water soluble, it may be due to rapid renal clearance of water postnatally. Based on the drug's poor lipid solubility, 98% of Methotrexate is polar or lipid insoluble at physiological pH. This could account for its minimal secretion into breast milk. Although this is only a single case report of a rather high dose, more such studies are warranted to determine whether kinetics of transfer is similar for all women [32]

In a large case series of expectant management of placenta accreta spectrum, there was one maternal death, which was ascribed to severe methotrexate toxicity and subsequent septic shock[30].

The prognostic implications of decreasing serum b-hCG levels following administration methotrexate are better described in the setting of ectopic pregnancy. For placenta accreta, it is not clear whether decreasing levels correlate with the rate of involution of placental tissue. [48]

Case

A 35 year old woman, third gravid, with a previous history of two caesarean delivery and one IUFD and 1 living issue ,reported to our obstetric casualty at 22 weeks of gestation with a complaint of bleeding per vagina few hours ago. Patient was otherwise in good health. There was no history trauma .

On examination vitals were stable with a 22week size uterus and soft abdomen . On inspection we didn't find active bleeding from the vagina. However there was spotting. A sonogram was done immediately.

Emergency Sonography showed a single live foetus with good cardiac activity, cephalic presentation, with one macerated foetus in a separate sac. It showed low placenta covering internal os suggestive of **placenta previa.**

Since the patient is a hemodynamically stable case of placenta previa at 22 weeks of gestation , the patient was planned for expectant management[Mcafee Johnson Regimen]. Pregnancy was continued with blood in hand and with regular antenatal monitoring of both mother and foetus. All the routine investigations were done. Her pregnancy was complicated with gestational diabetes mellitus and obstetric cholestasis which was taken care of with oral hypoglycemics and ursodeoxy-cholic acid respectively. The antepartum haemorrhage resolved spontaneously.

Among all the investigations which raised suspicion is the value of **alpha fetoprotein(301ng/ml)**. As the value of alpha fetoprotein was raised, at first neural tube defect was ruled out. A repeat alpha fetoprotein was sent. It was again **365.2ng/ml**(normal 0.5 - 5mg/ml).Another detailed sonogram was done. It showed typical findings like

- Multiple lacunae in placenta
- Thinning of myometrium beneath the placenta near the bladder
- Increased vascularity at uterine serosa junction

The raised alpha fetoprotein and above mentioned usg findings directed towards the diagnosis of **morbidly adherent placenta**.

We wanted to know the extent of invasion. An MRI with multiplanar images like T1, T2 and IR sequences was done. **"**The placenta was noted in the lower uterine segment predominantly along the posterior myometrial wall , and a small part of the placenta noted along the lower anterior myometrial wall . Placenta partially covering the internal os, not crossing it. Grossly thinned out myometrium with intact serosa noted along posterior myometrial wall. Multiple flow voids noted in cervix. Congested bilateral parametrial veins" . A diagnosis of Morbidly Adherent Placenta was made.

Hence, alpha fetoprotein may be used as a biomarker of morbidly adherent placenta.

Pregnancy was continued with expectant management and complete bed rest.

At 26 weeks of gestation the sonogram showed grossly reduced liquor along with nonreassuring features in cardiotocography. So we had no other option but to plan for Elective caesarean section with prior notice to neonatologist. Meanwhile steroids were administered for the lung maturity of the foetus.

Patient along with party were counselled about the condition of mother and baby. They were told about all the available options. Patients choice was taken into account.

The abdomen was opened by a vertical midline incision .Intra-operatively dense adhesion was found throughout the abdomen especially between the anterior wall of the uterus with the bladder wall with limited space in the anterior cul-de-sac and also in the posterior pod. Posterior lower segment of the uterus was totally thinned out and bulging.

Incision was given spanning from one round ligament to the other to identify and grasp bilateral uterine arteries and subsequently ligate them.

Access to the uterine cavity was made by giving a fundal vertical midline incision . The baby was delivered without disturbing the placenta and immediately handed over to the neonatologist. The cord was clamped and ligated as close as possible to the placental insertion. Injection methotrexate was administered directly into the umbilical vein.

Magically with the administration of methotrexate the bleeding stopped drastically . The placental tissue was not handled at all. The uterus was closed with the placenta left in situ. After uterine closure bilateral internal iliac artery was dissected and ligated. Haemostasis was ensured and the abdomen closed.

Methotrexate was administered on day 0, day 2 , day 4 and day6. Day 0 it was injected in the operative table directly into the umbilical vein. Rest other days it was injected intramuscularly at a dose of 1mg/kg body weight. Every alternate day free of methotrexate, folinic acid was injected at the dose of 0.1mr/kg body weight intramuscularly.

Follow up

- The patient was monitored regularly on the basis of her vital parameters and laboratory investigations, haemoglobin and complete blood counts including total leucocyte count, platelet counts and PT,APTT, INR.

  Follow up was done by serial estimation of serum beta hCG and serial sonogram to measure the placental volume.

  Figure 1 shows relationship between regression in the placental volume and days after delivery.
- On postoperative day 10, approximately **538cc** of placental tissue volume was found ultrasonographically. On day 60 it dropped down to **226cc**
- Fall of beta hcg can also be appreciated from the figure 2.
- On day 1 post operation beta hCG was 21,861mIU/ml. On day 10 it came down to 5,370 mIU/ml . It was less than 0.6 mIU/ml at day 60

Complications after Conservative Management

- Most dreaded complication of this type of management is development of **DIC(Disseminated Intravascular Coagulopathy)**. Serial estimation of platelets ,PT, APTT,INR was done .Figure 3 shows changes in platelet count in the post operative period. Figure 4 shows changes in prothrombin time, activated prothrombin time and international normalized ratio in the same period.

  It can be appreciated in the figure 3,there was a slight decrease in platelet count on day 14.But it was normalised soon with transfusion of blood products. There is a single value rise of PT,INR(figure 4) but all the subsequent values were normal.

- The patient had high grade intermittent fever associated with chills and rigor. The other most dreaded complication was **sepsis**. Serial estimation of total leucocyte count, C-reactive protein, procalcitonin was done besides fever profile and blood culture sensitivity.

- Figure 5 shows procalcitonin and c-reactive protein values done during the postoperative period. From day 9 onwards there was a dramatic increase in crop and procalcitonin values which spiked on day 16. After 16^{th} day with the change of antibiotics the inflammatory markers began to fall.

- Figure 6 shows total leukocyte trend immediately following the caesarean section On day 8 onwards there was a dramatic fall in leucocytes. the leucocyte dropped to as low as 500. the trend continued even after Filgastrim injections. This has a differential diagnosis of

1.Idiosyncratic reaction to methotrexate

2. febrile neutropenia

3. sepsis

To combat falling leucocytes injection leucovorin was given 10mg/m2 intramuscular 6 hourly until it rose to satisfactory level.

To arrest sepsis broad spectrum antibiotics were started viz. injection meropenem 1gram TDS and injection Teicoplanin 12mg/kg every 12 hours for 5 doses followed by 12mg/kg once daily

- Our patient had also developed surgical site infection. Daily dressing were done with povidone iodine ointment and solution. Unfortunately she was later found to be allergic to povidone iodine. Soon we stopped its use. With regular dressing with other antiseptic and antibiotic solution it healed completely

- Post operatively ultrasonography was done to know about the residual placental volume. however it showed ascites with mesenteric inflammation. The blood albumin was also low Patient was transfused albumin solution daily until it reached normal value.

- Electrolyte disbalance

  She developed hypokalaemia (figure 7) following which Iv fluid normal saline with one ampoule of KCL in alternate bottle was started 8horly. later patient was switched to syrup potchlor 15ml TDS with normalisation of serum potassium values.

- The patient did not had any bleeding per vagina or any pelvic pain. The patient had a continuous brownish discharge per vagina. This ensured there was no placental separation but placental dissolution.

Discussion

With the rising incidence of PAS there is a need to have an established treatment protocol. We have to compare and analyse the different methods of management and follow the outcomes so that we can provide the best treatment possible to the patients.

Treatment however should always be individualised.

Here in this paper we study and analyse the outcome and results of conservative management of morbidly adherent placenta especially with the help of chemotherapeutic agent methotrexate. In this study we enlighten not only the how the patient is successfully treated ,with conservative management by keeping the placenta in situ and administering injection methotrexate first in the umbilical vein and intramuscularly subsequently, but also the adverse reactions the patient had to this type of treatment.

The standard management for confirmed cases of morbidly adherent placenta has been caesarean hysterectomy as described by Fox in 1972.[40] An alternate approach of conservative rather than extirpative treatment was first described by Arulkumaran et al. in 1986 in which systemic Methotrexate was administered postnatally, and the placental mass was expelled 11 days postnatally.[42]The dose and method of methotrexate administration varied among different studies. Among the patients who received methotrexate, administration routes included intramuscular injection 48%; umbilical vein injection with subsequent intramuscular injection 19%, oral administration 4%; and iliac catheter administration with subsequent intramuscular injection 4%. Treatment by these routes of administration was successful in 6 of 11 patients (55%), 3 of 4 patients (75%), 0 of 1 patient (0%), and 0 of 1 patient (0%), respectively [39]

In a study conducted by Kayem et al. a comparison was made between the outcomes of conservative and extirpative management of placenta accreta. They concluded that leaving the placenta in situ is a safe alternative to hysterectomy.[43] Conservative management may be attempted in carefully selected cases, with hemodynamic stability, normal coagulation status, desire for fertility preservation. Thorough prior counselling regarding risks involved in conservative management is mandatory.[41] There are multiple options available including methotrexate administration, uterine artery ligation, internal iliac artery ligation, uterine artery embolization and radiofrequency ablation to name a few.[44]

As our patient delivered an extremely premature and low birth weight baby with low chances of survival. Hence, fertility preservation was a primary concern in her management.

A multidisciplinary approach involving the obstetrician, neonatologist, surgeon, interventional radiologist, pathologist, transfusion medicine specialist is important in managing these patients to reduce morbidity and mortality associated with MAP.[45]

Methotrexate (MTX) has been used as an adjuvant to expectant management with the aim of expediting placental resorption[46]. MTX, an anti-folinic agent acting on rapidly dividing cells, is hypothesized to induce placental necrosis

Tong et al pioneered the conservative management of morbidly adherent placenta by systemic administration of methotrexate.[47]The outcome varies widely ranging from expulsion at 7 days to progressive resorption in roughly 6 months[48]. Some studies have questioned the benefit of methotrexate and noted little benefit in enhancing placental resorption.[49]

As of now there are no accepted protocol regarding dose and duration of methotrexate as only limited experience is available in literature[50]. Although, conservative management with methotrexate appears to be safe there are potential risks of infection and bleeding[48].Also, in cases of placenta in situ, monitoring for early signs of postpartum haemorrhage, infection or disseminated intravascular coagulation (DIC) is of paramount importance. The most common postoperative complication is haemorrhage, as retained products are a risk factor for uterine atony.

Hence patient needs close observation, repeated investigations and thorough follow up. Our case study had some unexpected findings like idiosyncratic reaction to methotrexate, ,febrile neutropenia, hypokalaemia, allergic reaction to Poviodine iodine. Each reaction has been dealt with care.

In our cases, systemic administration of methotrexate resulted in reduction of placental size, decreased uteroplacental vascularity eventually resulting in decrease and disappearance of the placental tissue.

A flowchart is helpful in describing the treatment received by the patient. It is demonstrated in figure 8.

Conclusion

While the incidence of morbidly adherent placenta, including placenta percreta, is sure to increase in the years to come, there is a lack of robust evidence regarding the most appropriate management; thus management must be individualised. Conservative management of placenta percreta appears to be a possible, high-risk alternative to surgical management and should be reserved for women who refuse caesarean hysterectomy and wants to preserve fertility or with a strong desire to undergo conservative management.

While treating a case of morbidly adherent placenta we need to have a sensitive approach. It is a tremendous challenge to an obstetrician because we have to keep in mind the age , number of living issues , and desire to menstruate further.

In this paper we present a case of a successfully managed placenta percreta with methotrexate and serial ultrasonography and beta hCG, which resulted in placental regression and uterine preservation.

We thereby conclude that

Morbidly adherent placenta can thus be managed conservatively , preserving the uterine function and fertility. The efficacy of methotrexate however needs more case studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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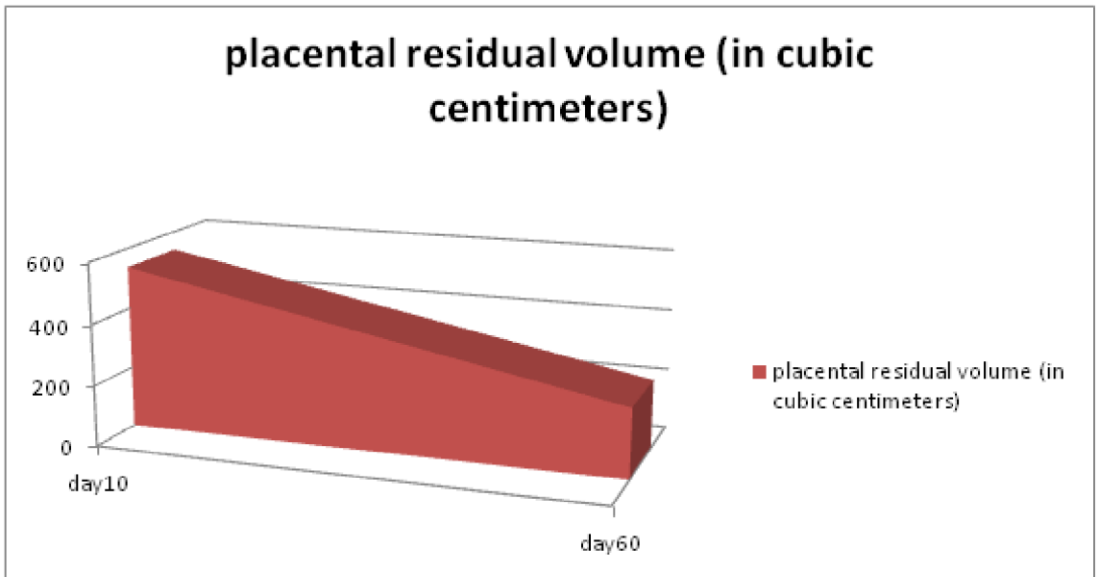
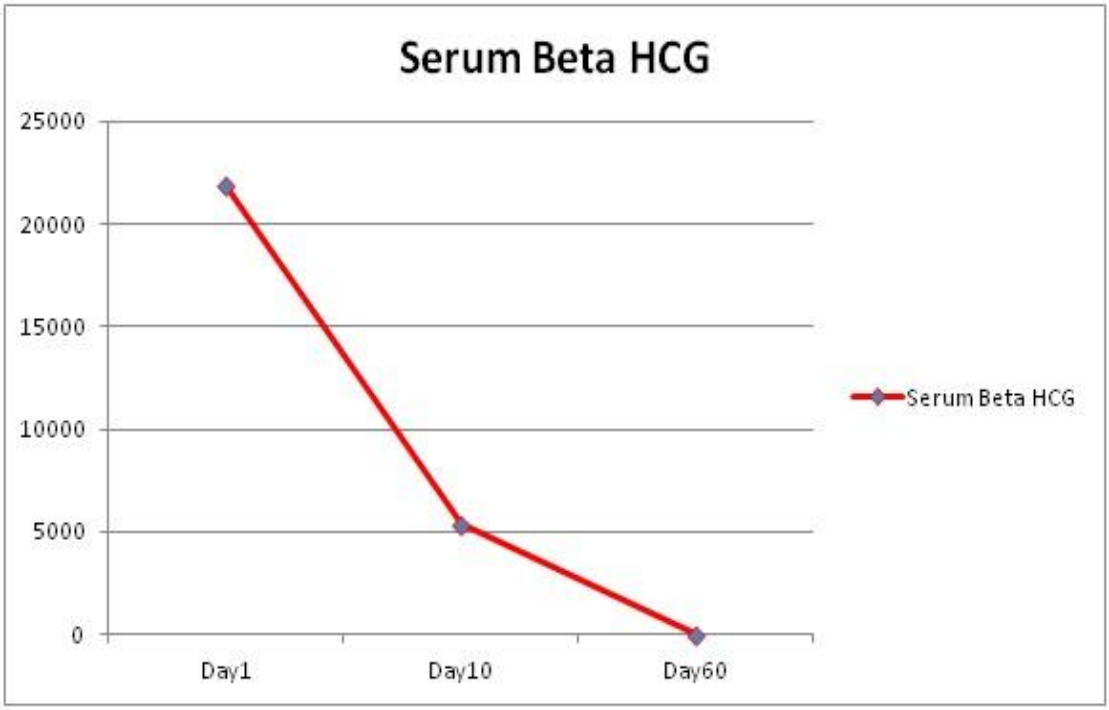
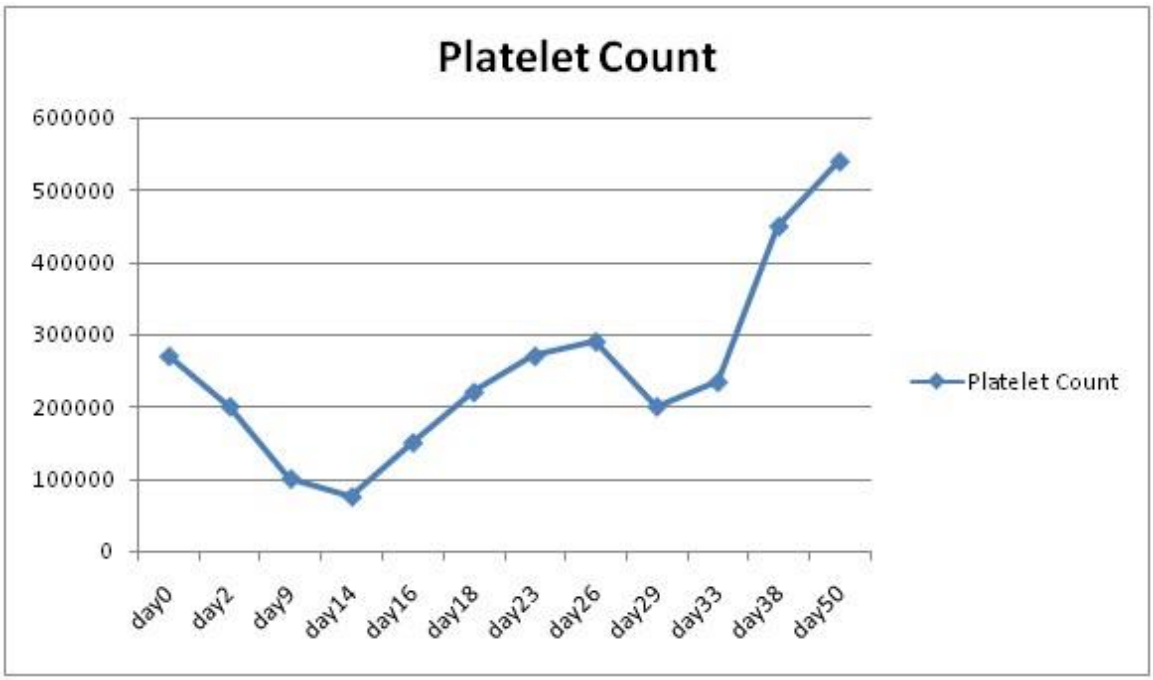
Figures



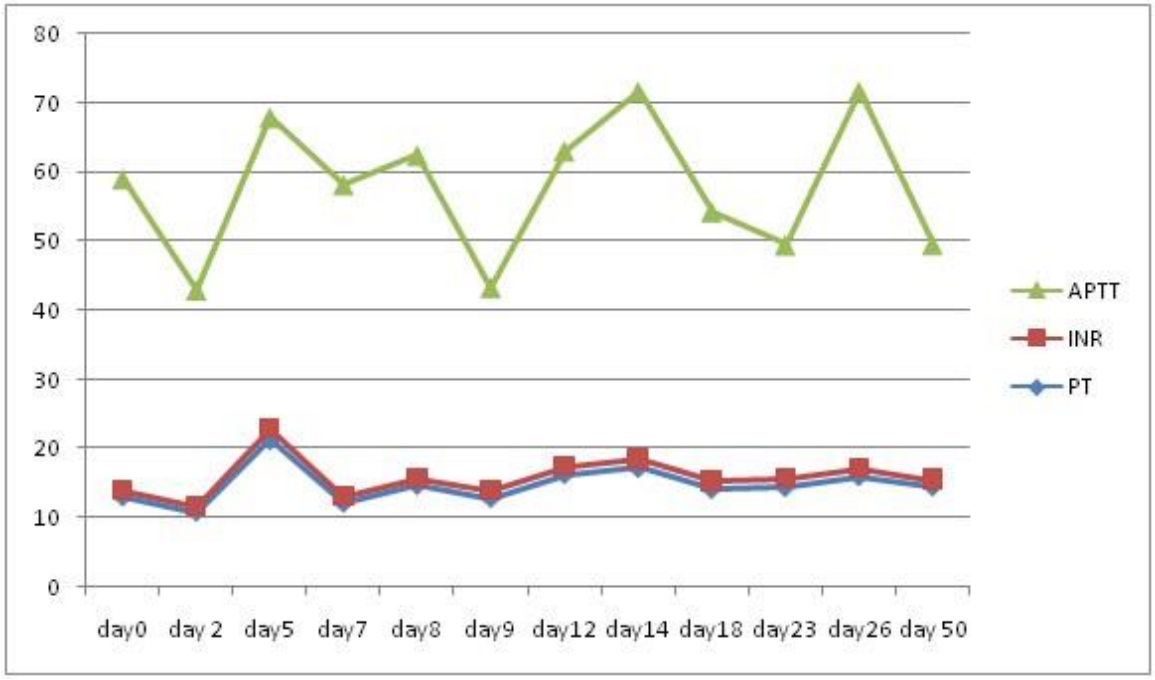
- Figure 2



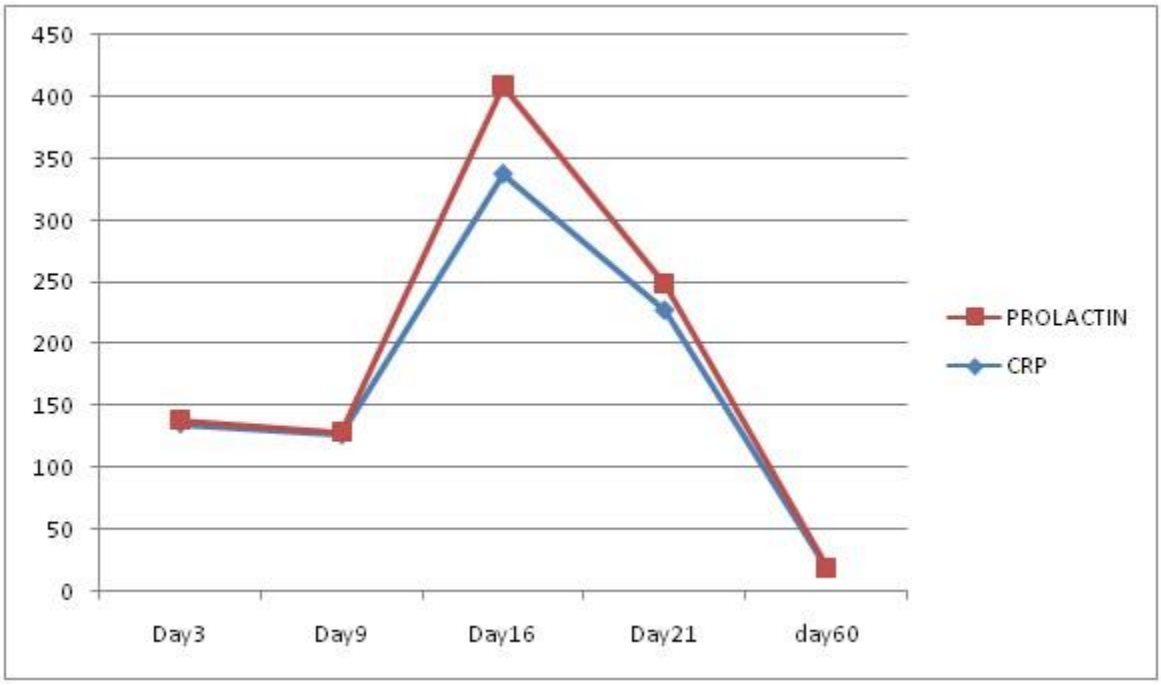
- Figure 3



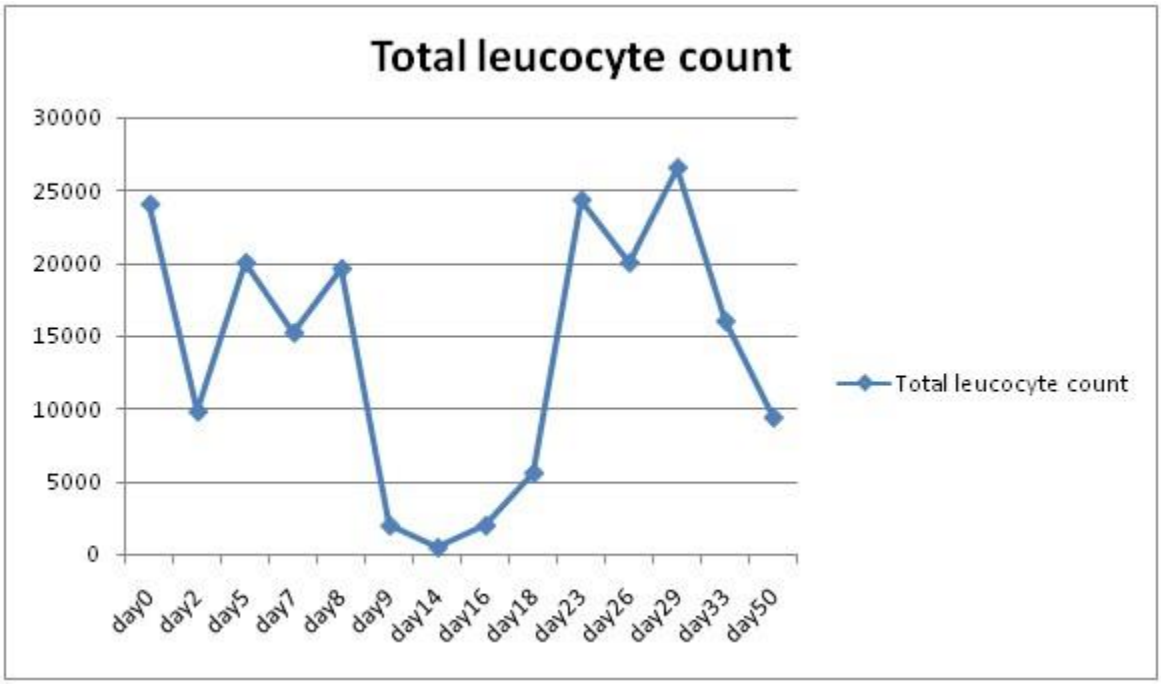
- Figure 4



- Figure 5



- Figure 6



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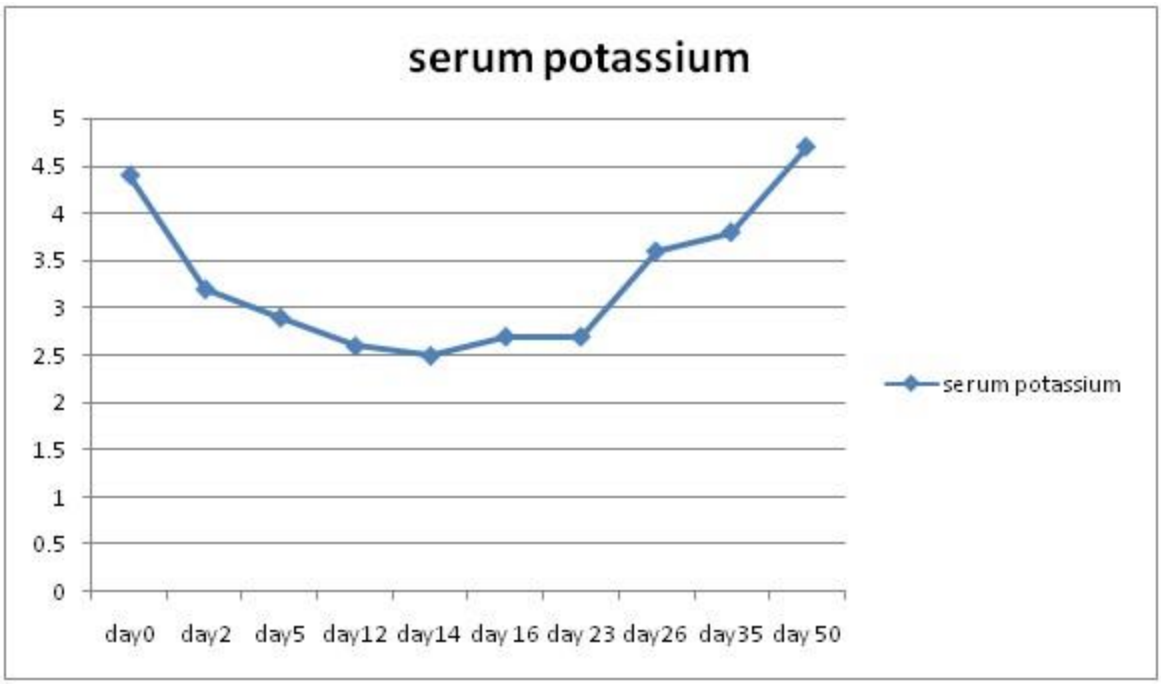
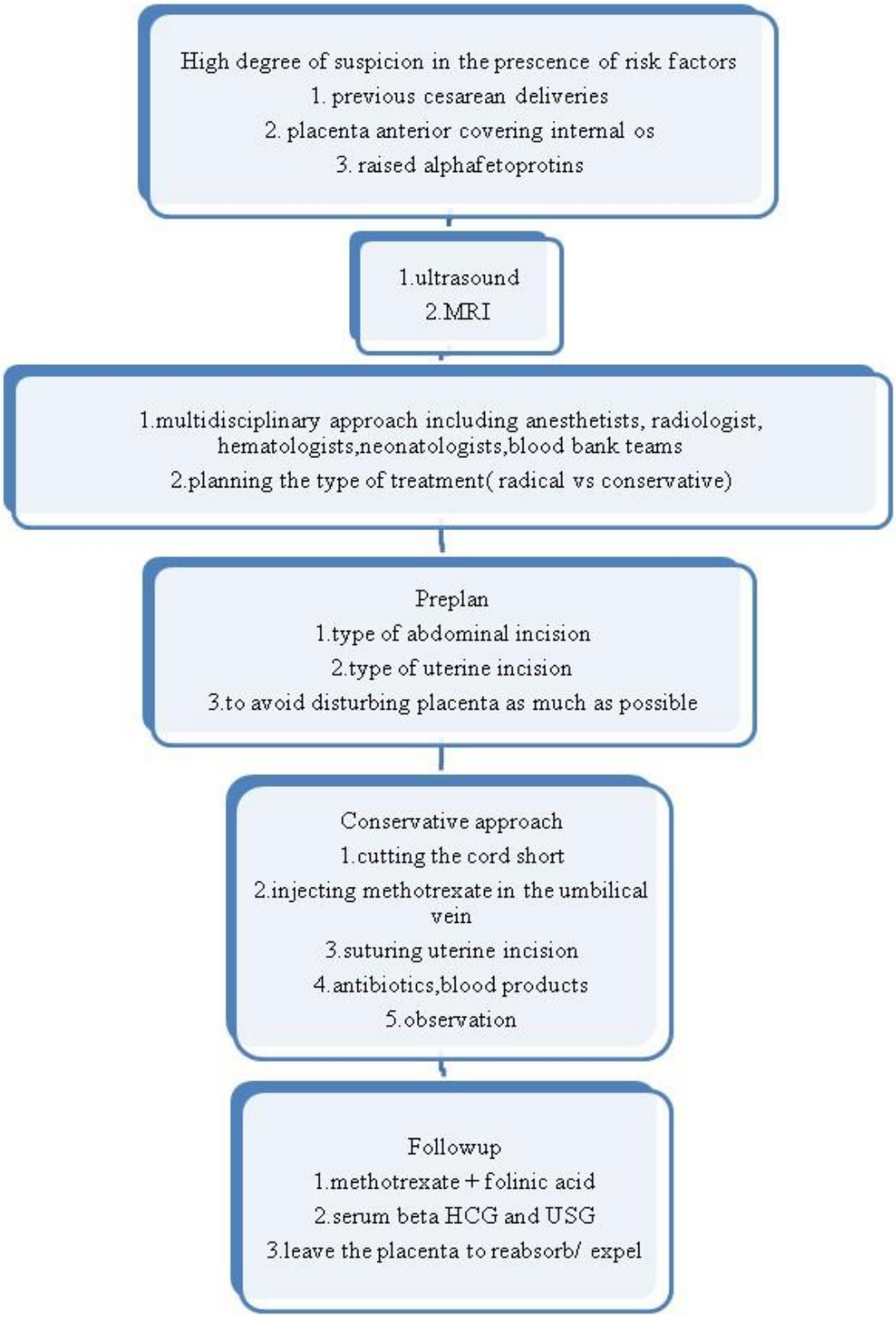

serum potassium
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
day0
day2
day5
day12
day14
day 16
day 23
day26
day35
day 50
serum potassium

- Figure 8


High degree of suspicion in the prescence of risk factors
1. previous cesarean deliveries
2. placenta anterior covering internal os
3. raised alphafetoprotins
1.ultrasound
2.MRI
1.multidisciplinary approach including anesthetists, radiologist, hematologists,neonatologists,blood bank teams
2.planning the type of treatment(radical vs conservative)
Preplan
1.type of abdominal incision
2.type of uterine incision
3.to avoid disturbing placenta as much as possible
Conservative approach
1.cutting the cord short
2.injecting methotrexate in the umbilical vein
3.suturing uterine incision
4.antibiotics,blood products
5.observation
Followup
1.methotrexate + folinic acid
2.serum beta HCG and USG
3.leave the placenta to reabsorb/ expel