FIRST TRIMESTER PREGNANCY LOSS MANAGEMENT

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1. INTRODUCTION

First trimester pregnancy loss, often referred to as miscarriage or early pregnancy loss, is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or foetus without foetal heart activity within the first 12 weeks of gestation. It's a common condition that affects 10-20% of all pregnancies.

Most of the early pregnancy losses occur before 10 weeks of gestation (2/3 of them occur in the preimplantation period), being less frequent once a viable embryo with foetal heart activity has been observed.

Approximately 65-70% of cases are due to chromosomal abnormalities, being the most frequent cause of early pregnancy loss. Other less frequent causes are uterine anomalies, such as submucosal fibroids or uterine septum; immunological diseases (i.e. antiphospholipid syndrome) or toxic substances (tobacco, alcohol or drugs).

The most common risk factors identified among women who have experienced early pregnancy loss are advanced maternal age (>40 years old) and a prior early pregnancy loss.

1.1. **NOMENCLATURE AND DEFINITIONS:**

Pre-implantation or peri-implantation loss: occurs before 5 weeks of pregnancy and is detected by a poor progression of β-hCG without having observed a gestational sac by ultrasound.

Pre-embryonic loss: occurs between 5.0 – 5.6 weeks of pregnancy, observing a gestational sac (with or without yolk sac) with no visible embryo by ultrasound.

Embryonic loss: occurs between 6.0 – 9.6 weeks of pregnancy, with a visible embryo with no foetal heart activity and a crown-rump length (CRL) < 30 mm.

Early pregnancy loss: occurs between 10 – 12 weeks of pregnancy, with a visible embryo with no foetal heart activity and a CRL > 30 mm.

Second trimester pregnancy loss: occurs between 12.0 – 21.6 weeks of pregnancy.

Early incomplete miscarriage: persisting retained products of conception (RPOC) defined as an endometrial thickness >15 mm by ultrasound.

Complete miscarriage: when all the products of conception have been expelled from the uterus and the endometrial thickness is <15 mm. Serum β-hCG testing is not required for its diagnose since it will not be completely negativized until two weeks of complete miscarriage. Positive β-hCG levels after two weeks require further study to exclude RPOC, ectopic pregnancy and gestational trophoblastic disease.

Pregnancy of unknown location (PUL): used to describe a situation in which a positive pregnancy test occurs, but a transvaginal ultrasound does not show intrauterine or extrauterine gestation, nor does it show the retention of conception products.

2. DIAGNOSIS

The diagnosis of early pregnancy loss must be made in a timely manner and it is necessary to be strict in the diagnosis to confirm that the diagnostic criteria are met to avoid interrupting an ongoing pregnancy. When in doubt, expectant management for a short period of time to allow for further evaluation carries little risk.

These are the diagnostic criteria for nonviable pregnancy early in the first trimester.

Findings diagnostic of pregnancy loss:

- Crown-rump length (CRL) of 7 mm or greater and no heartbeat.
- Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac.
- Mean sac diameter of 25 mm or greater with no visible embryo.

Findings suggestive but not diagnostic of pregnancy loss:

- Crown-rump length (CRL) of less than 7 mm and no heartbeat.
- Mean sac diameter of 16-24 mm and no embryo.
- Absence of embryo with heartbeat 7-13 days after a scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat 7-10 days after a scan that showed a gestational sac with a yolk sac.
- Absence of embryo for 6 weeks or longer after last menstrual period.
- Empty amnion (amnion seen adjacent to yolk sac, with no visible embryo).
- Enlarged yolk sac (greater than 7 mm).
- Small gestational sac in relation to the size of the embryo (less than 5 mm difference between sac diameter and crown-rump length).
- Foetal heartbeat less than 100 beats per minute.
- Presence of subchorionic hematoma.

Those cases fulfilling the criteria that are considered suggestive, but not diagnostic, of early pregnancy loss warrant further evaluation in 7–14 days to assess the viability of the pregnancy. In addition, women presenting symptoms of threatened miscarriage (vaginal bleeding) should be advised to avoid intense physical exercise and vaginal sexual intercourse. There is not enough evidence to recommend resting in bed in these cases. Additionally, there is not enough evidence to recommend treatment with progesterone in all cases. However, recent studies have shown that treatment with vaginal progesterone 400 mg/12 hours from the onset of symptoms until 16.6 weeks increases the live newborn rate in patients with a history of one or more previous abortions. Therefore, in patients with threatened abortion and with a history of at least one previous pregnancy loss, we will recommend treatment with vaginal progesterone 400 mg/12 h from the start of bleeding until 16.6 weeks.

3. MANAGEMENT AND TREATMENT

Once the early pregnancy loss diagnosis has been established:

- The different possible therapeutic options and the most appropriate for each particular case have to be explained to the patient. *It is recommended to give an informative brochure to the patient if your clinic has one.*

- A blood test should be performed to evaluate complete blood count, coagulation test, blood type and Rh factor in all patients where such information is not available.

- Chorionic villus sampling (CVS) should be offered to analyse if there is any chromosomal alteration that could have caused the pregnancy loss, and to be able to offer genetic advice for future pregnancies.

The therapeutic options available are: expectant management, medical treatment and surgical treatment. Our recommendation will be explained according to the clinical situation and the available treatments, so that the patient can decide which option suits her best after receiving the information about all the alternatives.

Anti-D immunoglobulin administration is indicated in Rh negative patients in case of:

- Medical or surgical treatment.
- Spontaneous miscarriage over 8 weeks of pregnancy.

3.1 EXPECTANT MANAGEMENT

Consists in waiting for the spontaneous resolution of the process. There is a higher probability that complete miscarriage occurs within the first 7 – 14 days after diagnosis, however there is no defined threshold in the literature. It is the option that offers the lowest global efficiency rate, approximately 40 - 70%.

It is recommended in cases of early incomplete miscarriage (persisting retained products of conception defined as an endometrial thickness >15 mm by ultrasound) in absence of heavy metrorrhagia or fever.

The patient should be visited in 7 – 14 days by her reference gynaecologist or in the emergency room for a follow-up.

In the case that complete expulsion does not occur after this time, the patient should be offered the other therapeutic options (medical treatment or surgical treatment). We must keep in mind that the most recommended option in case of an incomplete loss, in terms of efficacy, is surgical treatment.

3.2 MEDICAL TREATMENT

Consists of administering medication (generally misoprostol) to trigger uterine contractions and achieve complete expulsion of all the products of conception from the uterus.

It is recommended in cases of pre-embryonic and embryonic loss with a CRL less than or equal to 23 mm (≤ 9 weeks of pregnancy). It is highly recommended in patients with uterine fibroids, previous myomectomy or previous caesarean section, that are at a higher risk of surgical complications.

Despite the fact that there are several pharmacological treatments with an overall efficacy between 70 – 90%, the one that has demonstrated greater efficacy is the administration of 800 µg of Misoprostol vaginally, single dose, therefore being the treatment of choice.

Alternatively, there is the option of administering Misoprostol orally (introducing the tablets between the lips and the gums, waiting 30 minutes before swallowing), but we must take in consideration that this way of administration causes more systemic side effects.

The misoprostol-based regimen is more effective within the first 48 hours, but the bleeding time can be variable and can last up to 14 – 21 days. It is important to explain to the patient the symptoms she will be presenting, such as vaginal bleeding and menstrual cramps (dysmenorrhea). Analgesic medication should be added to the Misoprostol treatment and warning signs must be explained to the patient, so she knows when to go to the emergency room (more than two pads per hour for more than two hours or persisting pain after the complete miscarriage).

The recommended treatment is: Paracetamol-Codeine 500/30 mg + Ibuprofen 600 mg 30-40 minutes before Misoprostol. Then Misoprostol 800 µg, single dose, vaginally. Painkillers can be administered every 6-8 hours if the pain persists.

Contraindications:

Contraindications for using misoprostol:

- Allergy to prostaglandins
- Confirmed or suspected ectopic or molar pregnancy
- Arterial hypertension
- Inflammatory bowel disease
- Glaucoma
- Hereditary porphyria
- Chronic kidney disease
- Severe asthma
- Infection
- Severe haemorrhage
- Severe anaemia (Hb < 9 g/dL)
- Bleeding disorders
- Well-placed IUD.

Not recommended if:

- Kidney/liver failure
- Body mass index (BMI) < 18.5
- Breastfeeding

Special attention should be taken into account in case of:

- Anaemia
- Cardiovascular diseases
- Long-term corticosteroid use
- Epilepsy

Misoprostol is not contraindicated in cases of: thyroid dysfunction, insulin-dependent diabetes, multiple pregnancies, obesity, smoking, uterine malformations, previous surgery of the uterine cervix (conizations, etc.), mild asthma (occasional asthma attacks and no regular use of bronchodilator treatment).

In the case of breastfeeding, the patient should wait 6 hours from the administration of Misoprostol to breastfeed.

Side effects/complications:

The rate of complications of medical treatment is less than 3% (mainly bleeding and infection). Infectious complications and the need for transfusion do not differ from surgical treatment.

Medication side effects usually appear 4 – 6 hours after administration. These are:

- **Severe bleeding**: it is difficult to quantify the bleeding but we consider it as severe when the patient reports a large pad change every 2 hours or bleeding more than a normal menstruation (more than two pads/hour for more than two hours). In <1% it may require surgical haemostasis and/or transfusion.
- **Abdominal pain** (dysmenorrhea): prescriptions for pain medications should be provided to the patient.
- **Gastrointestinal symptoms**: diarrhoea, nausea and vomiting.
- **Low-grade fever:** this is a fever of central origin up to 38.5ºC (101.3ºF).
- **Rash and itching:** especially in palms and soles.
- **Infection** (<2%). Universal prophylactic antibiotic treatment is not recommended in the medical treatment of miscarriage.

Follow-up:

The patient should be visited in 7 – 14 days by her reference gynaecologist or in the emergency room. The complete evacuation of products of conception should be evaluated by ultrasound. In the event that complete expulsion does not occur after this time, a second dose of Misoprostol (800 µg) can be administered, or we can offer surgical treatment.

3.3 SURGICAL TREATMENT

It consists of performing a suction curettage and is considered the most effective option, with a complete evacuation rate of 97%.

We must explain the procedure in detail to the patient and a specific informed consent should be filled in before performing the curettage.

Indications:

- **Severe haemorrhage** or **hemodynamic instability**.
- Evidence or high suspicion of **infection**. In these cases, curettage must be performed after starting intravenous antibiotic coverage *(see section on septic abortion)*.
- Suspected **gestational trophoblastic disease**.
- Embryonic loss between **9 and 12 weeks of pregnancy** (CRL >23 mm and <55 mm and/or femur length <12 mm).
- It is the most effective option in **cases of RPOC** when comparing to expectant management or medical treatment.

- **Contraindication for using Misoprostol**.

Cervical ripening is recommended in all cases prior to the curettage to facilitate cervical dilation, and reduce the risk of haemorrhage and the risk of cervical and uterine trauma. The treatment of choice is Misoprostol (400 µg vaginally 2 – 4 hours before the procedure). In case of contraindication, allergy or intolerance to Misoprostol, Mifepristone 200 mcg orally 36 – 48 hours before the procedure can be used. As an alternative mechanical dilation with Dilapan-S® (4-6 hours before the procedure) can be performed.

It is recommended to perform a transvaginal ultrasound prior to the curettage to assess the uterine position, presence of fibroids or uterine abnormalities that may difficult the procedure.

Side effects/complications:

- Delay in the procedure.
- Need for anaesthesia (local vs sedation according to associated risk factors).
- Risk of serious complications (9.5% vs 5% in expectant management): uterine perforation, cervical laceration, Asherman syndrome, slightly increased risk of pelvic inflammatory disease, infertility, and preterm labour in later gestation.

Follow-up:

The patient should be visited in 6 weeks by her reference gynaecologist.

4. ANATOMOPATHOLOGICAL STUDY OF RETAINED PRODUCTS OF CONCEPTION

The anatomopathological study of the material obtained by uterine suction curettage should be carried out in any of the following cases:

- No previous evidence of gestational sac, yolk sac or embryo.
- Clinical, analytical or ultrasound suspicion of molar pregnancy (history of mole, enlarged uterus, theca lutein cysts, hyperemesis, clinical hyperthyroidism, expulsion of vesicular material, de novo hypertension...).
- Serum β-hCG >150.000 UI/L.

In all these cases where an anatomopathological study has been requested we must make an appointment with the patient for the result at the specific clinic in 4 – 6 weeks.

5. RECOMMENDATIONS AFTER AN EARLY PREGNANCY LOSS

- No use of tampons, vaginal sexual intercourse or baths for 1 – 2 weeks.
- Once abortion is completed, we can inform the patient about contraceptive methods if desired. Hormonal contraception can be started at the start of the next menstruation. There are no contraindications for IUD placement after abortion by curettage, as long as there is no suspicion of infection.

6. ABNORMAL EVOLUTION AFTER MISCARRIAGE

In the case that the patient explains abnormal bleeding, an ultrasound should be performed:

- When transvaginal ultrasound image is compatible with retained products of conception (heterogenous ultrasound pattern and/or endometrial thickness >15 mm) the treatment of choice should be expectant management (as long as the vaginal bleeding is controlled) with a success rate of 90% at 4 – 6 weeks and with a very low rate of complications. It is important to inform about the diagnostic suspicion and the warning signs and symptoms to go to the emergency room (significant vaginal bleeding, fever, etc.). A follow-up visit should be scheduled 6 weeks after the abortion. In the event that retained products of conception persist during this visit, it should be scheduled a gynaecological ultrasound + hysteroscopy in 2 – 4 weeks. You can also opt for medical treatment with 800 mcg of Misoprostol
- In case the vaginal bleeding is profuse or requires urgent action (hemodynamic instability), a blood analysis with complete blood count and coagulation should be requested, and an ultrasound-guided aspiration curettage should be performed limited to the area of placental remnants. An ultrasound control should be scheduled in 4 – 6 weeks. Aspiration curettage was the classic treatment for retained products of conception but we must take into account complications such as bleeding, uterine perforation, incomplete evacuation (30-40%), post-procedure intrauterine adhesions (30%) and secondary infertility.

- In all other cases (endometrial thickness ≤15 mm and no heterogeneous ultrasound pattern suggesting retained products of conception) the recommendation is also to follow an expectant management.

7. SEPTIC ABORTION

We consider a septic abortion when the abortion is concomitant to an intrauterine infection. It is more common in women with induced abortion than those having a spontaneous abortion. Initially intrauterine infection may progress to salpingitis, generalized peritonitis, and sepsis. A quick diagnosis is important since it can be a serious life-threatening disease if it is not treated properly.

7.1 CLINICAL FINDINGS

The most common symptoms are: fever, malaise, abdominal pain, vaginal bleeding and discharge of purulent material through the external cervical orifice. A small proportion of cases show a septic shock with hypotension, tachycardia and tachypnoea. Analytically it is expected to find leucocytosis (>15,000).

7.2 AETIOLOGY

The most common causes are Staphylococcus aureus, Gram-negative bacilli, or Gram-positive cocci. Multiple infections with anaerobic microorganisms and fungi are not uncommon.

7.3 TREATMENT

- Patient stabilization with intravenous fluids.
- Obtain a sample for endometrial culture (Cornier). In cases of late clinical appearance (>1 week post-abortion) Chlamydia PCR should also be performed.

- Antibiotic regimen: Piperacillin/Tazobactam 4g/6h IV or Ceftriaxone 1g/12-24h + Metronidazole 500 mg/12h IV.
- In cases of late-onset infection (>1 week post abortion), positive Chlamydia PCR or no response to usual treatment, Azithromycin 1g/week po for 3 weeks should be added. Alternative: Azithromycin 500 mg/24h IV for 2 days. In case of allergy or intolerance: Doxycycline 100 mg/12 h po for 7 days.
- If risk factors for resistant bacteria are met: Ertapenem 1g/24h IV.
- In case of allergy to Penicillin: Tigecycline 100 mg first dose followed by 50 mg/12h IV + Metronidazole 500 mg/12h IV.
- Suction curettage 6 – 12 hours after stating IV antibiotics. The use of drugs for cervical ripening is not indicated. In these cases, Dilapan-S ® or Hegar dilators can be used. It is necessary to take a sample of the curettage products for performing culture studies and another one for anatomopathological study.
- Once the patient has been without fever for 48 hours, empiric antimicrobial therapy can be changed to: Amoxicillin-clavulanate 875-125 mg/8h orally (Clindamycin 300 mg/8h orally in patients allergic to penicillin) until completing 7-10 days. In case the patient has been treated with Doxycycline at the hospital, prescribe Doxycycline 100 mg/12h orally for 14 days. We must adapt the antibiotic treatment as soon as the antibiogram is available.

Finally, it is important to be aware of a serious and lethal complication, the Clostridium toxic shock syndrome (Clostridium sordellii y Clostridium perfringens). This syndrome initially starts with symptoms of nausea, vomiting and pain. The absence of fever is detectable. Subsequently, after 24 – 48 hours, it usually debuts with hypotension, tachycardia, leucocytosis, generalized oedema, haemoconcentration and toxic shock.

8. RECURRENT PREGNANCY LOSS

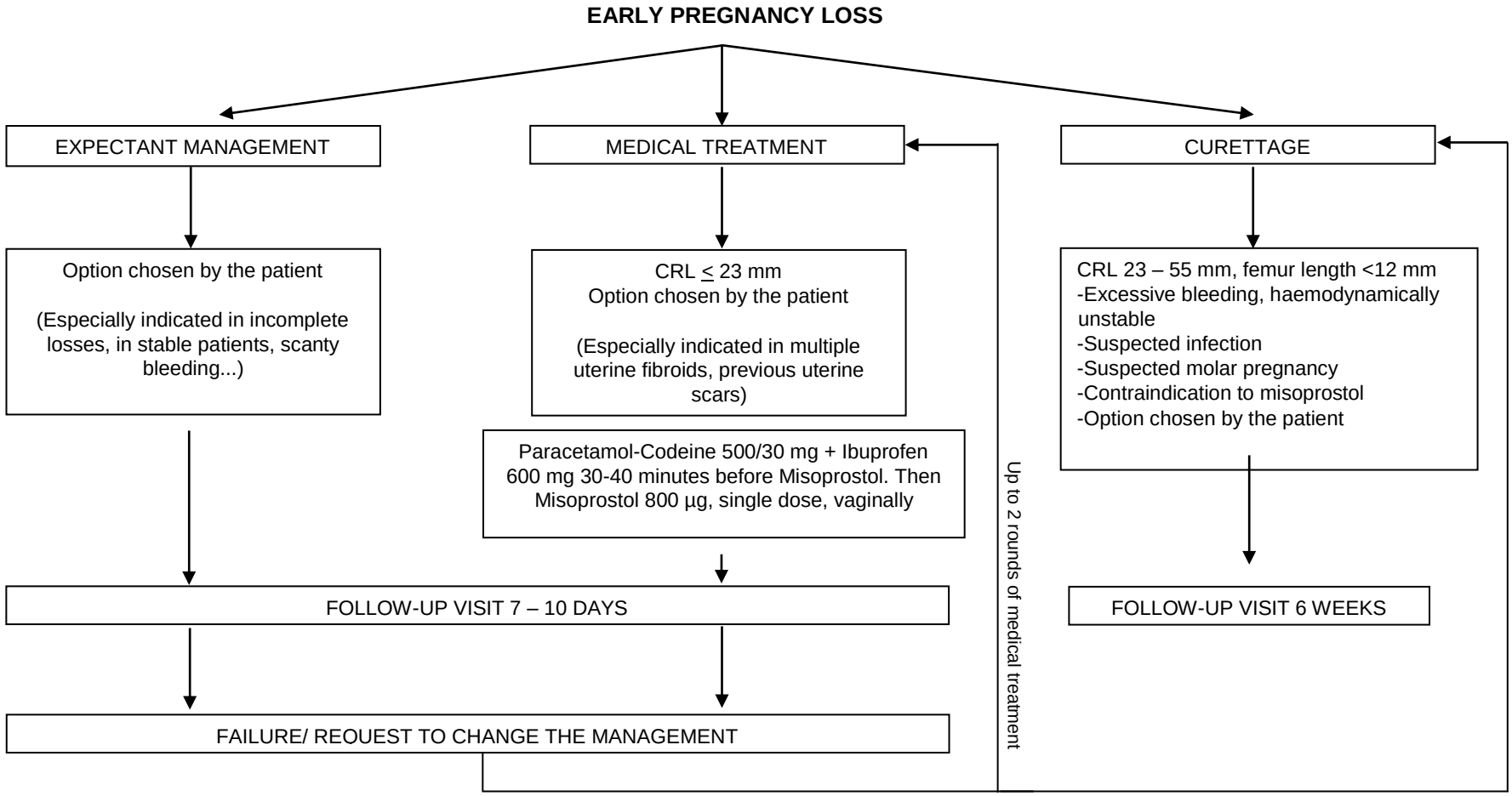
Recurrent pregnancy loss is defined as the loss of two or more pregnancies <10 weeks confirmed by b-HCG in urine or serum, consecutive or not. Biochemical pregnancy losses and miscarriages of uncertain location are included, but not molar or ectopic pregnancies. The prevalence of recurrent pregnancy loss is difficult to determine, but is thought to be <2% of couples. It is very important in these cases to perform a chorionic villus sampling as part of the study.

It is recommended to initiate the study of recurrent pregnancy loss in the following cases:

- 2 pregnancy losses, including at least 1 intrauterine pregnancy loss.
- 3 preclinical pregnancy losses (chemical pregnancy losses or pregnancies of uncertain location).
- In cases of 2 preclinical pregnancy losses, until further scientific evidence is available, the management will be personalized (especially the existence of risk factors for ectopic pregnancy must be assessed, since there is a greater risk in couples with exclusively preclinical pregnancy losses).

When meeting these criteria, the following will be performed:

- 3D Gynaecological ultrasound.
- Karyotype of both parents.
- TSH, T4.
- Antiphospholipid antibodies (anticardiolipin IgG/IgM, lupus anticoagulant, anti-beta-2-glycoprotein IgG/IgM).


EARLY PREGNANCY LOSS
EXPECTANT MANAGEMENT
MEDICAL TREATMENT
CURETTAGE
Option chosen by the patient
(Especially indicated in incomplete losses, in stable patients, scanty bleeding...)
CRL ≤ 23 mm
Option chosen by the patient
(Especially indicated in multiple uterine fibroids, previous uterine scars)
CRL 23 – 55 mm, femur length <12 mm
-Excessive bleeding, haemodynamically unstable
-Suspected infection
-Suspected molar pregnancy
-Contraindication to misoprostol
-Option chosen by the patient
Paracetamol-Codeine 500/30 mg + Ibuprofen 600 mg 30-40 minutes before Misoprostol. Then Misoprostol 800 µg, single dose, vaginally
Up to 2 rounds of medical treatment
FOLLOW-UP VISIT 7 – 10 DAYS
FOLLOW-UP VISIT 6 WEEKS
FAILURE/ REQUEST TO CHANGE THE MANAGEMENT