AOGD BULLETIN

Volume 20 I December 2020 I Monthly Issue 8

Price ₹30 Only

CARING FOR WOMEN'S HEALTH : EVIDENCE, ATTITUDE & PRACTICE

Dedicated Issue:
High Risk Pregnancy

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AOGD Bulletin

Volume 20 • Monthly Issue 8 • December 2020

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Contents

Publisher/Printer/Editor
Dr Geeta Mediratta and Dr Chandra Mansukhani on behalf of Association of Obstetricians & Gynecologists of Delhi.

Printed at
Process & Spot C-112/3, Naraina Industrial Area, Phase-1, New Delhi 110 028

Published from
Institute of Obstetrics & Gynaecology
Sir Ganga Ram Hospital, Sarhadi Gandhi Marg, Old Rajinder Nagar, New Delhi-110 060

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From the President's Pen

Greetings from AOGD Secretariat.

The corona crisis continues with greater waves touching our city. I thank each and every AOGD member for the great success of the annual conference. It was the hard work of the team and the co-operation of the AOGD members that was responsible for the success of the first virtual conference of AOGD 2020.

The e-election for the post of President of AOGD 2021-2022 also held. It was another challenge for our AOGD team to make the data base, co-ordinate with virtual platform consultants and get the proceedings going to the satisfaction of the members of AOGD. We are happy that e-elections went on smoothly. We thank our returning officers Dr. Kiran Guleria, Dr. K. Gujral and Dr. Surveen Ghuman under the overall leadership of Dr. Reva Tripathi for such an excellent and successful e-elections. We were happy that most of our AOGD members did exercise their votes. I thank to all of them.

I also congratulate Dr. Achla Batra and Dr. Jyostna Suri for being the President elect and the Vice- President elect of AOGD for the year 2021-2022. Hopefully they will be able to take over the Secretariat physically.

The position for the chairpersons of sub-committees of AOGD are falling vacant from 01/04/2021. We are inviting applications for the posts till 31/01/2021. We are also proposing an Executive meeting and General Body Meeting in the month of February 2021.

Hope we are able to streamline these important activities and do live up to the expectations of all our members. At every step we solicit co-operation and assistance from all our members.

This edition of bulletin is on high risk pregnancy. The topics touched are recurrent pregnancy loss, newer screening aspects for GDM and Pre-Eclampsia, IUGR and perinatal outcome together with criteria for PAS and prediction of still birth. We have been lucky to have inputs from our neonatologists and they have penned down rational use of antenatal corticosteroids and antenatal Magnesium Sulphate for fetal neuroprotection.

Hope these corona times goes away and we have the luxury of meeting everyone physically.

Long Live AOGD.

Dr Mala Srivastava
President, AOGD

From the Vice President's Pen

Greetings to all members of the association !

As we are into the last month of this much eventful and challenging year 2020, we are seeing a **tremendous upsurge in the number of CORONA positive cases in our city**. But all this has not deterred our medical fraternity, rescue and relief agencies to perform their duties.

I hope we, at the AOGD Secretariat have been able to live up-to the expectations of all AOGDians. We've tried to put our best efforts possible in the current challenging Scenario to continue our journey of Learning. As the challenges posed in front of us were new and unexplored, we used Technology based innovative ideas to fulfil our objectives of continuing medical education in the field of Obstetrics and Gynaecology.

Our **expert Editorial team** has brought out this **December's E-Bulletin** dedicated to **'High Risk Pregnancy'**. I'm sure this exclusive Bulletin with expert write-ups from senior Obstetricians and Neonatologists would be of great interest to the readers.

'The strength of our Association is Unity'. It was decided unanimously in the Executive Committee meeting to hold **E-Elections for the post of President AOGD 2021-22 for the first time** since the inception of the Association. They were **very successfully and graciously conducted** by Electronic Voting on a Virtual platform **from 5th to 10th December** under the supervision of **Dr Reva Tripathi**, jointly by the Returning Officers **Dr Kiran Guleria, Dr K. Gujral, Dr Surveen Ghumman and AOGD secretariat.**

We congratulate **Dr Achla Batra and Dr Jyotsna Suri** on being chosen to be the **President and Vice President Elect AOGD 2021-22** respectively.

Here I would like to quote: ***'Individually we are a drop, but together we are an Ocean'*** **–** *Ryunosuke Satoro*

I wish all our members a **"Merry Christmas and A very Happy New Year"**

Regards,

Dr Kanika Jain
Vice President, AOGD

From the Secretary's Desk

Greetings to all ! Hope you all are keeping safe and healthy.

As we are now towards the end of year 2020, we wish the coming year helps the global efforts to vanquish the CORONA virus.

AOGD E-elections for the post of President AOGD were successfully conducted from 5 to 10 December 2020. Heartiest Congratulation to Dr. Achla Batra and Dr. Jyotsna Suri from Safdarjung Hospital for being elect President and Vice President AOGD for the year 2021-22.

The academic activities in the month of November-December continued on the virtual platform as webinars and e-CMEs post 42nd AOGD Annual Conference.

Our editorial team has brought the AOGD E-bulletin December version dedicated to **High Risk Pregnancy**, which should be of great interest and immense use to our readers.

Looking forward to your continued support.

IN ORDER TO CARRY A POSITIVE ACTION, WE MUST DEVELOP HERE A POSITIVE VISION- **Dalai Lama**

Warm Regards

Dr Mamta Dagar
Hon. Secretary

Monthly Clinical Meeting

AOGD Monthly Virtual Clinical Meet will be organised by Sir Ganga Ram Hospital, New Delhi on 18th December, 2020 from 04:00pm to 05:00pm.

From the Guest Editor's Desk

Dr Kanwal Gujral
Guest Editor

Dr Geeta Mediratta
Chief Editor

Dr Chandra Mansukhani
Co-Editor

Dear Friends,

Greetings from AOGD Secretariat!!!

We end the eventful year 2020 with a bulletin on High Risk Pregnancy.

As you are aware that pregnancies with risk factors are increasing day by day mainly because of advanced maternal age, obesity, hypertension, diabetes mellitus, other medical disorders and placental problems, all leading to abortions, preterm births, growth restriction and stillbirths. We have selected some common risk situations starting with recurrent pregnancy losses. Dr. Mala Arora has given a detailed account of its etiology and a very practical management approach.

India is the Diabetic Capital of the world. Screening for Gestational Diabetes Mellitus lacks consensus. Dr. Pikee Saxena has dealt with various screening strategies, their efficacy and what best suits to Indian scenario.

Pre-eclampsia is one of the top three causes of maternal mortality besides being a major contributor to perinatal mortality and morbidity. While the western world has accepted universal screening at the end of first trimester and Asprin prophylaxis for screen positive women, we are still far from it. Dr. Sakshi Nayar has given an in-depth review of screening strategies through each trimester.

Fetal growth restriction complicates 10% of pregnancies. Dr. Chanchal in her article has detailed diagnosis, surveillance methods and timing of delivery to optimize the perinatal outcome.

Accurate pre-operative diagnosis and multidisciplinary management approach is the key to successful outcome in pregnancies with Placenta Accreta Spectrum. Standardization of ultrasound terminology and various scoring systems additionally help to diagnose and plan the management. Dr. Divya Pandey has beautifully summarized all this in her article.

India with its 1.32 billion population has been ranked first in absolute numbers in stillbirths. Dr. Sangeeta Gupta has given an excellent account of not only how to predict, but also how to prevent stillbirths.

Antenatal corticosteroids for decreasing respiratory distress syndrome and related morbidities and Magnesium Sulphate for fetal neuroprotection in women who are likely to deliver preterm have been extensively studied in the last three decades. However, there are some recent controversies regarding their fetal safety. Dr. Pankaj Garg & Dr. Nikhil Tenetti have run through the evidence brilliantly in their articles.

We sincerely hope you enjoy reading this bulletin on High Risk Pregnancy.

Wishing all the AOGDIANS a Happy, Healthy, Prosperous and Corona Free 2021.

Dr Kanwal Gujral
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Recurrent Pregnancy Loss

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Recurrent Pregnancy Loss (RPL) was earlier defined as three or more consecutive pregnancy losses at 20 weeks or less or with fetal weight of less than 500 grams[1,2]. The American College changed it to two or more spontaneous miscarriages for clinical purposes[3]. American Society of Reproductive Medicine (ASRM) defines recurrent pregnancy loss as two or more failed clinical pregnancies, which should be documented by either ultrasound or histo-pathological examination. None of the definitions include biochemical pregnancies, ectopic pregnancies or pregnancy of uncertain location.

The causes of Recurrent miscarriages are listed below:-

1. **Immunological – Auto immune**
   - Primary antiphospholipid syndrome (PAPS)
   - Secondary antiphospholipid syndrome (SAPS)– SLE, Autoimmune conditions
   - Any systemic autoimmune disorder e.g Rheumatoid arthritis, may lead to abnormal immunological response to pregnancy.
2. **Immunological – Alloimmune (Currently classified as Unexplained)**
   - Normally the maternal immune system tolerates the fetal allograft which is foriegn. Lack of this immunotolerance leads to miscarriage. This may be manifest in the endometrium as:-
   - Abnormalities of cytokine production- lack of shift of Th1 to Th 2 response
   - Lack of alpha V beta 3 integrin
   - Increased levels of tumour necrosis factor alpha (TNF) in the endometrium
   - Increased Uterine Natural Killer cells
   - Low concentration of Macrophage Inhibitory Cytokines (MIC)
   - Asynchronous timing of Ovulation and Implantation window as seen in PCOD also leads to poor implantation and miscarriage
3. **Genetic**
   - Fetal Aneuploidy- trisomy/ monosomy & polyploidies
   - Parental balanced translocations, inversions, deletions, duplications
   - Skewed inactivation of X chromosome, Fragile X syndrome
   - Single gene defects e.g Alpha thalassemia major, Retts syndrome etc
4. **Hormonal**
   - Polycystic ovarian syndrome
   - Progesterone receptor gene polymorphism & Luteal phase defects
   - Hyperandrogenism
   - Hypothyroidism/hyperthyroidism
   - Hyperprolactinaemia
   - Low AMH / Poor Ovarian Reserve
   - Adrenal hyperplasia/Addison's disease
   - Defeciency of Vitamin D
   - Uncontrolled diabetes mellitus
5. **Anatomical**
   - Müllerian abnormalities, septate uterus
   - Myomas– submucous, intramural
   - Uterine synechiae & polyps
   - T-shaped uterus
   - Cervical incompetence
6. **Inherited thrombophilia**
   - Antithrombin III deficiency
   - Deficiency of protein C and protein S
   - Activated Protein C resistance
   - Factor V Leiden mutation
   - Methyl tetrahydrofolate gene homozygosity& Hyperhomocysteinaemia
   - Prothrombin gene mutation
   - Plaminogen Activator Inhibitor
7. **Semen Factors**
   - High Sperm DNA fragmentation index
   - Male urogenital infections
8. **Infections**
   - Genital bacterial vaginosis, chlamydia, latent tuberculosis
   - Subclinical chronic Endometritis diagnosed by

increased plasma cells in the endometrium.

- Abnormal Uterine microbiome –Non lactobacilli dominated microbiome.
- Systemic syphilis, Lyme's disease, toxoplasmosis, brucellosis

9. **Systemic conditions**
   - Hypertension
   - Chronic renal disease
   - Chronic pulmonary disease
   - Heart disease
   - Severe rhesus sensitisation
   - Other diseases associated with RPL are Sickle cell anemia, Myotonic dystrophy, Marfan's syndrome, Homocystinuria, factor VIII deficiency, dysfibrinogenemia and Ehler's Danlos syndrome.
10. **Life Style factors**
    - Maternal Age > 35 years
    - Maternal Obesity BMI > 30
    - Paternal Age
11. **Environmental**
    - Endocrine disrupters
    - Smoking, alcohol, drugs
    - Exposure to irradiation
    - Exposure to environmental toxins, pesticides, DDT, Drycleaning chemicals
    - Exposure to anaesthetic gases

Chemicals which have been associated with RPL include nitrous oxide, arsenic, aniline dyes, benzene, ethylene oxide, lead, pesticides, mercury and cadmium.

Although an exhaustive list of causes exists, we still have 40-50% patients that fall in the unexplained category. In many patients more than one factor may lead to miscarriage and in some each miscarriage may have a different etiology. This poses a diagnostic difficulty to the physician.

Life Style & Environmental Factors

Maternal age has a very positive corelation with recurrent pregnancy loss.[4] Over the age of 40 years majority of pregnancies are lost with autologous oocytes. Hence reproduction should be encouraged before the age of 35 years.

Parental obesity should be addressed positively[5] and parental smoking, alcohol & drug exposure should be strongly discouraged. Exposure to environmental toxins like pesticides, anaesthetic gases, dry cleaning chemicals and endocrine disruptors released from plastic should be avoided.

Systemic Conditions

Maternal Co morbidities like chronic kidney, liver, cardiac or respiratory illness can result in pregnancy loss. Such mothers need to be counseled regarding surrogacy to safe guard their health and fulfill their reproductive desires. Women with true rhesus sensitization are managed with intrauterine blood transfusions and early delivery.

Infections

Genital tract infections often result in Infertility. However milder forms may result in recurrent pregnancy loss e.g bacterial vaginosis,[6] latent genital tuberculosis[7] and non specific bacterial endometritis post intrauterine procedures like dilatation & curettage. There is growing evidence that alteration of the microbiome of the vagina and endometrial cavity will lead to implantation failure and miscarriages.[8] Although microbiome testing is still a research tool and not available in the clinical setting, probiotics like lactobacilli may play a role in correcting the uterine microbiome.

Certain systemic infections like brucellosis, Lymes disease and toxoplasmosis are also associated with sporadic miscarriages.[9] These are rare and may be diagnosed by positive serology if suspected.

Semen Factors

An unhealthy paternal life style, exposure to alcohol and smoking are associated with increased sperm DNA fragmentation, which in turn, can lead to poor embryo quality and recurrent pregnancy loss.[10] These patients need life style modification and long-term (i.e. 3 months or longer) treatment with antioxidants to reverse the damage

Male accessory gland infections (MAGI) e.g. seminal vesiculitis and prostatitis will coat the sperm with bacteria prior to ejaculation. This in turn may cause chronic endometritis and recurrent pregnancy loss.

Inherited Thrombophilia

These are most commonly associated with second & third trimester pregnancy loss. However some

disorders like prothrombin gene and factor V leiden mutation may be associated with recurrent pregnancy loss.[11]

Anatomical

An estimated 15% of couples (one in six) with recurrent miscarriage have an anatomic abnormality of the uterus as the primary cause.[12] These abnormalities include the following.

- Defects of Müllerian fusion, which include septate uterus, unicornuate uterus and bicornuate uterus with unequal uterine horns.
- Acquired anatomical defects, such as, submucous or intramural myomas, endometrial polyps and uterine synechae.
- Small tubular uterine cavity: this may be congenital, secondary to diethyl stilboestrol exposure *in utero* or genital tuberculosis.
- Cervical incompetence, which is diagnosed by visualizing the cervix with an empty bladder on transvaginal ultrasound scan and assessing the width at the internal os as well as the cervical length from internal to external os.[13] It maybe a congenital weakness or secondary to repeated cervical dilatation. It is also associated with unicornuate or bicornuate uteri.

Hormonal

A multitude of endocrinal disorders can cause recurrent miscarriage.

Polycystic ovarian syndrome is one of the commonest endocrinal abnormality affecting female reproductive performance. Besides infertility, it presents higher risks of first and second-trimester miscarriages.[14]

Factors associated with a high miscarriage rate are *hyperandrogenism*, *hyperinsulinemia* and/or *ovulatory dysfunction* that accompanies high levels of luteinising hormone and low levels of progesterone.

Women with poorly controlled *type 1 (insulin-dependent) diabetes mellitus* with glycosylated (HbA1C) haemoglobin levels greater than four standard deviations above the mean had a higher pregnancy loss rate. Well-controlled diabetes had pregnancy loss rates similar to those of non-diabetics. Apart from frank diabetes, syndrome X,[15] which comprises of impaired glucose tolerance test (GTT), hypertension, hypertriglyceridaemia and a procoagulant state with increased coronary heart disease, could also potentially cause recurrent pregnancy loss

Abnormal maternal thyroid functions have been implicated as a cause of recurrent miscarriage.[16] However, mild or subclinical thyroid dysfunction is not associated with recurrent miscarriage, as it more often leads to infertility, but increased levels of thyroid peroxidase and/or microsomal antibodies have been associated with recurrent miscarriage.[17] In Autoimmune thyroid disease (AITD), the risk of miscarriage was the same whether the status was hypothyroid or euthyroid, indicating that AITD negatively affects fetal implantation. Hence all women with positive thyroid antibodies should be treated with a low dose of thyroxine replacement to suppress thyroid autoimmunity and achieve a favourable maternal and perinatal outcome.[17]

Hyperprolactinaemia usually causes infertility due to luteolysis; however, in partially treated cases, the picture may change to early pregnancy loss due to corpus luteum defeciency.

Although rare, the patient with an untreated late onset *congenital adrenal hyperplasia* may have an increased chance of recurrent miscarriage owing to hyperandrogenism. On the other hand, incipient *Addison's disease* will also cause recurrent miscarriages; the patient often has low blood pressure and hyperpigmentation.

Poor Ovarian reserve, diagnosed by low levels of Anti mullerian hormone (AMH) and a poor antral follicle count, remains an important factor responsible for recurrent miscarriage, owing to increased rate of aneuploidy in oocytes. Women with AMH levels below 1ng/ml not only experience difficulty in conceiving but also have a higher rate of pregnancy loss due to a higher rate of aneuploidy in the embryo.[18] Therapy with Dehydroepianrostenedione sulphate (DHEAS) andCo enzyme Q 10 (CoQ 10) has been tried but there is no robust evidence to support it.

Genetic

Genetic Abnormalities in Karyotypically Normal Parents

Various studies demonstrate that at least 50 percent of clinically recognised pregnancy loss results from a cytogenetic abnormality,[19] of which 51% show

autosomal trisomies, 22% show polyploidy, 19% show monosomy, 4% show translocations, and the rest are unclassified genetic defects. The autosomal trisomies commonly encountered are those of chromosomes 3, 4, 9, 13–16, 19, 21 and 22.[12]

Products of conception (POC) should be routinely submitted for genetic testing preferably with Array CGH and couples with abnormal genetic testing should have parental karyotyping.[20] If POC results show an aneuploidy, and parental karyotype is normal, the couple should be counseled regarding an optimistic outcome in future pregnancies.

Genetic Abnormalities in Karyotypically Abnormal Parents

Women may have structural chromosomal abnormality in the following forms.

- Deletions and duplications produce large chromosomal defects, which may cause severe phenotypic anomalies, thus individuals with these anomalies rarely reproduce.
- Dicentric and ring chromosomes are mitotically unstable, so the chances of offspring acquiring these anomalies are very small.
- In balanced translocations in men, the reproductive fitness is only slightly diminished. In spite of their good reproductive performance, these individuals show a significant decrease in live births, and a significant increase in both fetal death and interval infertility; hence they will present with recurrent miscarriage.
- In unbalanced translocations in men, not only is there productive fitness greatly decreased but the riskof abnormal offspring is also increased.
- In single gene defects, diagnosis can only be made by a detailed family history coupled with Array complete genomic hybridization (CGH) testing. Alternatively if the gene locus is well identified PCR testing or SNP will help in diagnosis.

Immunological Causes

Antiphospholipid antibody syndrome (APS) is the commonest immunological cause of recurrent miscarriage. It is the most rewarding as far as the treatment is concerned. Antibodies are directed against negatively charged phospholipids, which are the major constituents of trophoblast. These antibodies can cause impaired trophoblastic function, abnormal placentation, and placental thrombosis / infarction. This may lead to pregnancy-induced hypertension, intrauterine growth retardation (IUGR), intrauterine fetal death and recurrent miscarriage. Both early first-trimester losses and late third-trimester losses can occur. There is usually an ultrasound confirmation of a viable pregnancy prior to the pregnancy loss in most first trimester losses.

The diagnosis of APS is made by the presence of *one clinical criterion and one-laboratory criterion, which must be positive on two occasions 3months (12 weeks) apart.*

Clinical Criteria Include The Following[21,22]

- one or more unexplained deaths of a morphologically normal fetus of more than 10 weeks' gestation documented by ultrasonography or direct examination;
- one or more preterm births at or before 34 weeks'gestation due to severe pre-eclampsia or placental insufficiency with evidence of IUGR;
- three or more consecutive miscarriages before 10 weeks' gestation with no maternal hormonal, anatomic abnormalities, normal fetal genetic testing and other causes of recurrent losses being ruled out.

Laboratory criteria include detection of any of the following

1. Lupus anticoagulant by DRVVT, APTT or PTT
2. Anticardiolipin antibodies
3. Anti phospholipid antibodies
4. Anti beta 2 glycoprotein antibodies
5. Antiphosphatidylserine antibodies

Autoimmune disorders, such as systemic lupus erythematosus, systemic sclerosis, and autoimmune thrombocytopenia are associated with recurrent miscarriage, and are often classified as secondary antiphospholipid syndrome (or SAPS). The mechanism of loss and the treatment are the same as those for primary APS.

Treatment with steroids is not recommended based on current evidence. A combination of low dose aspirin and unfractionated /low molecular weight heparin currently gives the best pregnancy outcome. Heparin is not only an anticoagulant, it has a potent complement inhibitory action which

is beneficial in preventing complement mediated damage in APS syndrome. Aspirin should be started pre-conceptually and heparin after a positive pregnancy test and continued until the time of delivery. Post partum thromboprophylaxis is recommended for 2 weeks to prevent deep vein thrombosis.

In cases of SAPS due to systemic Lupus erythematosis, hydroxychloroquine (HCQ) has been used with good success rates during pregnancy. It is started in the preconception period and continued throughout pregnancy in a dose of 400 mg once or twice daily after meals. It is a pregnancy category C drug and it controls both disease activity and flares during pregnancy. It also prevents heart block in the fetus.[23]

Intravenous Immunoglobulins (IVIG) therapy is indicated in women with secondary recurrent miscarriages, very high titres of antibodies where treatment with aspirin and low molecular weight heparin fails to prevent a pregnancy loss.[24]

Autoimmunity

Women with any autoimmune disorder are prone to miscarriage due to alteration of the T regulator cells and Natural killer cells in the endometrium. Hence the autoimmune conditions need to be well controlled prior to planning a pregnancy.

A recent meta-analysis by Chen[25] et al shows that women with positive ANA titres (>1 in 160) have a higher incidence of miscarriage. As a corollary there are a higher number of ANA positive individuals in the ANA positive group as compared to controls.[26]

Hence it may be prudent to include ANA testing as part of the RPL work up.

Unexplained

Almost 50% of recurrent miscarriages remained unexplained by standard work up, which was very frustrating for both the patient and the Obstetrician. However, if we analyze all POC with CGH microarray, we will find a reason for miscarriage in >90% of patients.[27] Then again sperm DNA fragmentation index and semen culture will identify paternal factors. Testing for beta 2 glycoprotein 1, antithyroid and antinuclear antibodies helps to identify autoimmune causes to a greater extent. With the routine performance of these tests the unexplained group shrinks to much less than half. With future research we believe we will be able to find an explanation for all causes of recurrent pregnancy loss, thereby reducing the percentage of unexplained miscarriages to almost extinction.

Summary

All women presenting with two or more miscarriages need to be worked up to identify the cause of miscarriages. All women should have the following

- ◊ Uterine cavity evaluation by 3D ulltrasound scan/ sonohysterogram for cavity lesions like polyps/ myoma. Alternatively a Hysterosalpingogram may be done and in positive cases hysteroscopy is both a confirmatory and therapeutic option.
- ◊ Hormonal profile –Thyroid function test and anti-thyroid antibodies. HbA1C and in women with galactorrhea serum prolactin levels. In women over 35 years serum AMH
- ◊ Autoimmune Screening for APLA syndrome. Antinuclear antibodies (ANA) testing could be considered .[28]
- ◊ Infection Screening – for bacterial vaginosis, cervicitis and endometritis
- ◊ Semen Analysis and Culture and Sperm DNA fragmentation index if indicated.

If all above investigations are normal, a diagnosis of Unexplained RPL should be made. Any subsequent pregnancy losses should have genetic screening of products of conception by Array CGH for genetic abnormalities. In women with recurrent aneuploidy miscarriages, IVF with PGD or Oocyte donation have been suggested.

Treatment of specific causes has been discussed in each section, however treatment in unexplained RPL is largely empirical. Evidence for use of empirical therapy with the following is lacking :-

- ◊ heparin or low dose aspirin
- ◊ Vaginal progesterone supplementation[29]
- ◊ IVIg
- ◊ Glucocorticoids
- ◊ Intralipid therapy

Vitamin D3 deficiency should be corrected and they should receive a maintenance dose of 60,000 units of vitamin D3 weekly during pregnancy.

Probiotics are helpful in subclinical endometritis as they correct the uterine micobiome and make it lactobacilli dominant, that favors implantation.

Diet A vegan diet helps control autoimmune disorders. Eliminating antigenic foods like gluten, eggs, dairy, soya and meat helps to tone down the autoimmune process.

Progesterone therapy is widely prescribed, although there is evidence that use of vaginal progesterone does not improve pregnancy rates.[29] Immune modulation with dydrogesterone may show some benefit.

Tender loving care with reassurance scans in early pregnancy is effective in reducing stress levels. In a study Brigham et al reported that seeing a heart beat at 6 weeks of pregnancy resulted in 78% of the pregnancy to continue and then again seeing a heart beat at 8 weeks resulted in 98% of the pregnancies to continue.[30] This favors the right cytokine balance in the endometrium and prevents a miscarriage.

Complimentary therapies Acupuncture, reflexology and other stress relieving therapies can also be tried.

Since the diagnostic workup is extensive and the treatment options varied, stratification of RPL patients with Machine learning has also been attempted.[31]

The machine learning is based on ESHRE guidelines[28] and provides an evidence based management plan for patients with RPL.

There is an 80% chance that these women will achieve a live birth, however they may have an increased incidence of pregnancy complications like gestational diabetes, preterm deliveries and hepatic cholestasis.[32]

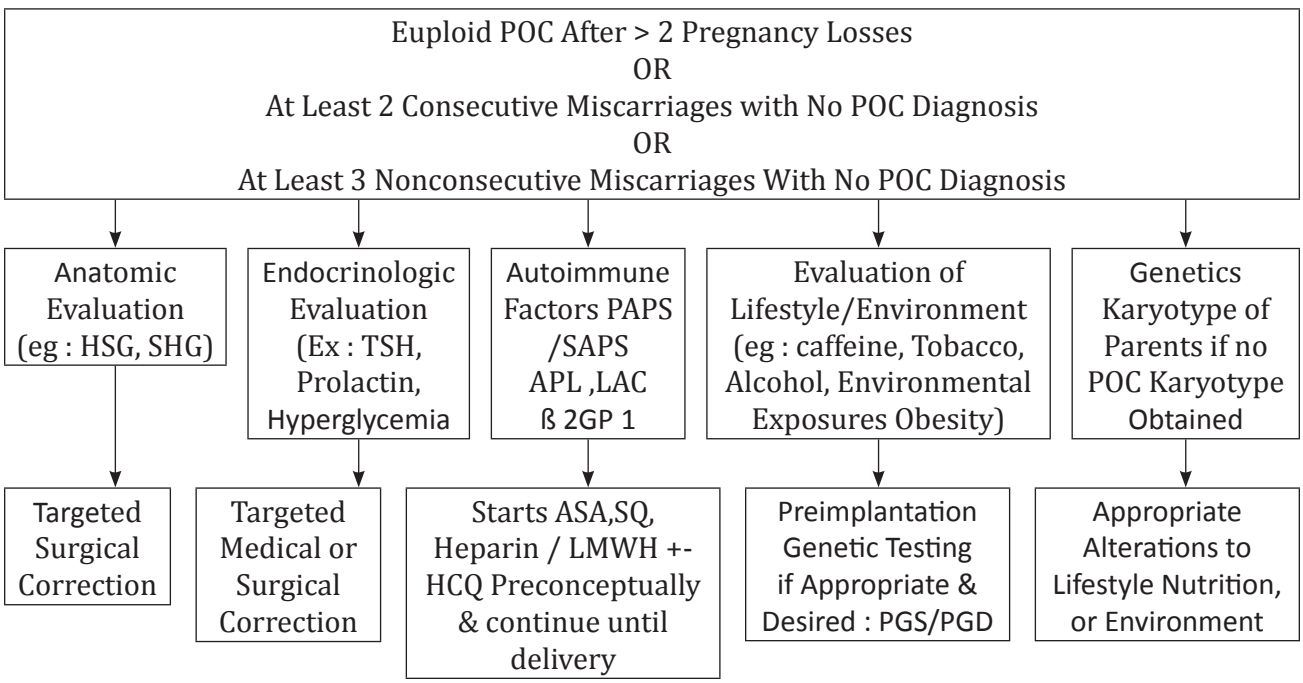
The following algorhithms summarize clinicians approach to a patient with RPL.

For a full workup all the possible causes have to be looked into.[33]

ANA Testing may soon be a part of the work up of RPL.

References

1. Royal College of Obstetricians and Gynecologists. The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage.Green-top Guideline No.17;April 2011.www.rcog.org.uk
2. Bhattacharya S Recurrent miscarriage: should the definition be revised ? In World Clinics Obstetrics & Gynecology vol 1 no 1 Jun 2011 Jaypee ed Mala Arora
3. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. Fertil Steril 2008;89:1603.
4. Practice Committee of the American Society for Reproductive Medicine. Aging and infertility in women. Fertil Steril 2006; 86(5 Suppl) :S248-52
5. Pandey S & Bhattacharya S Obesity and miscarriage in



World Clinic Obstetrics & gynecology vol1 no1 2011 Jaypee ed Mala Arora

6. Kuppusamy R, Visvanathan D, Hollingworth T Pregnancy loss and bacterial vaginosis in World Clincs in Obstetrics & gynecology vol1 no1 2011 Jaypee ed Mala Arora
7. JaiswarSP, Gautam S Latent genital infections & subclinical endometritis. In Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
8. Moreno I Codoner FM,Vilella F et al Evidence that the endometrial microbiota has an effect on implantation success or failure Am J Obstet Gynecol 2016 Dec 215(6) 684-703
9. Pal N Thyroid and medical disorders In Recurrent Pregnancy Loss second edition 2007 Jaypee ed Arora & Konje
10. Sperm DNA fragmentation Index Opuwari CS, Henkel RR, Agarwal A in Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
11. Mishra S Inherited Thrombophilia In Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
12. Basiri A, Kabessa M, Gvenetadze A et al Anatomical factors In Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
13. John O'Brien Cervical causes of Preterm labor In World Clinics Obstetrics & Gynecology Jun 2012 vol 2 no 1 Jaypee ed Mala Arora
14. Venkataraman M & Thanawala U Pregnancy complication in Polycystic ovaries In World Clinics in Obstetrics & Gynecology 2017 vol 6 no 1 Jaypee ed Mala Arora
15. Zaveroni I, Bonini L, Fantuzzi M, et al. Hyperinsulinemia, obesity and AQ Syndrome X. J Intern Med 1994;235: 51–6
16. Alexander EK et al American Thyroid association guidelines for thyroid disease in pregnancy 2017 Thyroid vol 27(3)
17. Lata K, Dutta P, Sridhar S et al Thyroid autoimmunity and obstetric outcomes in women with recurrent miscarriage: a case control study. Endocrine connect 2013Jun 1;2(2):118-124
18. Atasever M, Soyman Z, Demirel E et al Diminished ovarian reserve : is it a neglected cause in the assessment of recurrent miscarriage ? a cohort study Fertil Steril 2016;105(5):1236-40
19. Boui J, Boui A, Lazar P. Retrospective and prospective epidemiological studies of 1500 karyotyped spontaneous human abortions. Teratology 1975; 12: 11.
20. Kasak L, Rull K, Laan M Overview of Genetic Causes In Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
21. Rai RS. Antiphospholipid syndrome and recurrent miscarriages J Post grad Med 2002;48:3-4
22. Ernest JM, Marshburn PB, Kutteh WH. Obstetric antiphospholipid antibody syndrome- an update on pathophysiology and management. Semin reprod Med 2011;29522-39
23. Autoimmune disorders Pal N Arora S In Recurrent Pregnancy Loss third edition 2019 Jaypee ed Arora & Mukhopadhaya
24. Christiansen OB, Larsen EC, Egerup P et al Intravenous Immunoglobulin treatment for secondary recurrent miscarriage : a randomized double blind placebo controlled trial BJOG 2015; 122:500-8
25. Chen S et al Antinuclear antibodies positivity is a risk factor of recurrent pregnancy loss :a meta analysis. Seminars in Arthritis & rheumatism 2020 Aug;50(4):534-43
26. Cavalcante MB, de Melo Bezerra CT Antinuclear antibodies and recurrent miscarriage: Systematic review and meta-analysis. Am J Reprod Immunol 2019 Dec; 83(3):e13215
27. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24 chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Human reproduction 2018 April.vol 33(4):579-87
28. ESHRE guidelines for recurrent pregnancy Human Reproduction Open, Volume 2018, Issue 2, 2018
29. Coomarasamy A, Helen Williams, Ewa Truchanowicz, Paul T. Seed, Rachel Small, Siobhan Quenby, Pratima Gupta et al A randomized trial of progesterone in women with Recurrent miscarriages. Promise study N Engl J Med 2015; 373:2141-2148 DOI: 10.1056/NEJMoa1504927
30. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999;14(11):2868-71
31. Bruno V, D'Orazio M, Ticconi C et al Machine learning (ML) based method applied in recurrent pregnancy loss (RPL) patients diagnostic work up: a potential innovation in common clinical practice. Sci Rep 10,7970 (2020) ;64512-4
32. Cozzolino M, Rizzello F, Riviello C, Romanelli C, Coccia Elisabetta M. Ongoing pregnancies in patients with unexplained recurrent pregnancy loss: adverse obstetric outcomes. *Hum Fertil (Camb)*. 2019;22(3):219-225. doi:10.1080/14647273.2018.1475754
33. Brezina PR, Ke RW, Kutteh WH Preimplantation genetic screening: a practical guide. Clinical Medicine insights in Reproductive health. Jan 2013 p 197-208

GDM Screening: What's new?

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Introduction

Prevalence of GDM varies in India from 4.5% to 18.9% depending on the screening test used, urban or rural population screened, genetic, ethnic and socioeconomic variations. It has been observed that prevalence of GDM is directly proportional to the women with impaired glucose tolerance and Type 2 diabetes in non-pregnant women.

Terminologies for Hyperglycemia in Pregnancy

Traditionally, gestational diabetes mellitus is defined as onset or first recognition of abnormal glucose tolerance during pregnancy. In 2015, International Federation of Gynecology and Obstetrics (FIGO) has given the following terminologies[1] (Figure 1):

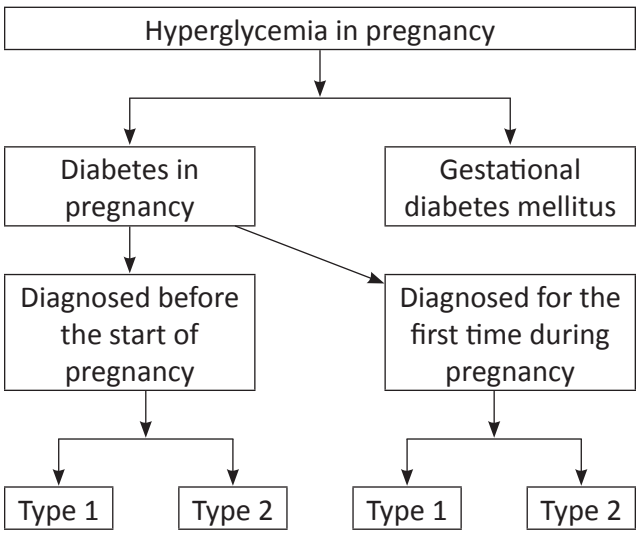


Figure 1: Types of hyperglycemia in pregnancy

Diabetes in pregnancy is also known as "overt diabetes" or "prediabetes". It may be Type1 DM / IDDM or Type 2 DM /NIDDM. It may be diagnosed before pregnancy or during pregnancy if fasting plasma glucose level is ≥126mg/dl or if random, post glucose load or post prandial plasma glucose level anytime is ≥200 mg/dl or if HbA1c ≥6.5%. Difference between diabetes in pregnancy and gestational diabetes mellitus is depicted [1]below in Fig 2.

Diabetes in Pregnancy	Gestational Diabetes Mellitus
Pregnancy in previously known diabetes	Hyperglycemia during pregnancy that is not diabetes
OR Hyperglycemia diagnosed for the first time during pregnancy that meets WHO criterion for diabetes mellitus in the non–pregnant state	Hyperglycemia diagnosed for the first time during pregnancy
May occur anytime during pregnancy including the first trimester	May occur anytime during pregnancy but most likely after 24 weeks

Figure 2: Difference between diabetes in pregnancy and gestational diabetes mellitus.

Perpetual Controversy – Screening and diagnosis of GDM

Multiple guidelines have been given regarding screening of GDM by reputed authorities after taking into consideration their local population, risks prevalence and cost implications. These appear apt for their own set up, but they vary widely and do not provide uniform consensus regarding the best approach.

It appears that the screening strategy should be locally developed; taking in stock the prevalence of GDM in their population, available infrastructure, expertise for conducting the test, economic consideration, practical ease of testing and validity of the test till an ideal screening test is discovered.

What is the Significance of Screening?

Diabetes in pregnancy is associated with several

adverse outcomes for the mother and the fetus. Approximately 2/3rd will develop GDM in subsequent pregnancy and 50% develop type 2 DM within 20-28 years of delivery. GDM offers a unique opportunity for initiation of strategies for prevention of not only immediate pregnancy complications but also diabetes prevention later in life. Hence there is a need for screening and early diagnosis.

In the landmark HAPO study[3], 25,505 pregnant women at 15 centers in 9 countries underwent 75-g oral glucose-tolerance testing at 24-32week gestation. Primary outcomes parameters were birthweight > 90th percentile, primary cesarean section, clinically diagnosed hypoglycemia and cord-blood C-peptide > 90th percentile (fetal hyperinsulinemia). It was observed that with increasing maternal glucose levels, the frequency of each primary outcome increased. Secondary outcomes of preeclampsia, shoulder dystocia or birth injury, premature delivery, NICU admission and hyperbilirubinemia also showed significant positive associations with maternal glycaemia.

Whom to Screen?

High risk or selective screening: Should be conducted in low risk populations; National Institute for Health and Care Excellence (NICE, 2015)[3] recommends assessment of risk factors during the first visit and selective screening.

Risk Factors

- Body mass index (BMI)> 30kg/m^2
- Previous macrosomic baby weighing ≥4.5 kg
- Previous still birth or anomalous baby
- Previous history of gestational diabetes
- Family history of diabetes (first degree relative)
- High risk ethnic population for DM- African, Asians and Non-Caucasians
- History of polycystic ovarian syndrome (PCOS)

Table 1: Maternal and fetal adverse effects of gestational diabetes mellitus.

Maternal morbidity	**Fetal/neonatal/child morbidity**
Early pregnancy	Stillbirth
Spontaneous abortions	Neonatal death
Pregnancy	Nonchromosomal congenital malformations
Pre-eclampsia	Prematurity
Gestational hypertension	Fetal growth restriction
Excessive fetal growth (macrosomia, large for gestational age)	Macrosomia
Hydramnios	Birth Injury
Urinary tract infections	Shoulder dystocia
Delivery	**Neonatal**
Preterm labor	Neonatal hypoglycemia
Traumatic labor	Respiratory distress syndrome
Instrumental delivery	Neonatal polycythemia
Cesarean delivery	Neonatal hyperbilirubinemia
Postoperative/postpartum infection	Neonatal hypocalcemia
Postoperative/postpartum hemorrhage	Neonatal hypothermia
Thromboembolism	Hyperviscosity Syndrome
Maternal morbidity and mortality	Neonatal hypomagnesemia
Hemorrhage	**Childhood**
Puerperium	Obesity
Failure to initiate and/or maintain breastfeeding	Impaired glucose tolerance
Infection	**Adulthood**
Long-term postpartum	Hypertension
Weight retention	Diabetes
GDM in subsequent pregnancy	Coronary Artery Disease
Future overt diabetes	Metabolic Syndrome
Future cardiovascular disease	CVA

Universal screening: Implies screening of the entire population or sub group irrespective of the risk factors. ACOG[4], American Diabetes Association (ADA)[5], International Association of Diabetes and Pregnancy Study Group (IADPSG)[6] and Diabetes In Pregnancy Study group India (DIPSI)[7] support universal screening. It has been suggested that selective screening would miss 20% of GDM cases as compared to universal screening. In India, universal screening is essential, as Indian women have 11 fold increased risk of developing glucose intolerance in pregnancy as compared to Caucasian women.

When to Screen?

It is now known that several adulthood diseases like diabetes, hypertension, coronary artery disease, obesity, metabolic syndrome originate in fetal life. Adverse intrauterine events permanently "program" the fetus through a process known as early metabolic imprinting.[8] Hence, screening in the first trimester helps us to identify those women who already have pre-existing diabetes and helps to control the sugar levels to avoid the complications in the offspring by modifying the treatment at an early gestation.

- **NICE[3]**: 24 – 28 weeks in high risk population
- **ACOG[4]**: 24 – 28 weeks, except, women with high risk factors who are screened at first visit.
- **ADA and IADPSG[6]**: First ANC visit and then at 24 – 32 weeks in previously undiagnosed GDM
- **DIPSI[7]**: First visit, if normal then at 24-28 weeks and repeat at 30-32 weeks
- **National Guidelines of India[8]:** First visit, if normal then repeat at 24-28 weeks

How to Screen and Diagnose?

A universal guideline for the ideal screening and diagnosis method is lacking. A number of methods have been suggested on the basis of population risks, cost effectiveness and lack of large national screening programmes.

ACOG 2017[4]

Continues to recommend two step procedure:

Step 1: Glucose Challenge Test (GCT)/ Glucose Loading Test (GLT)

- 50gram oral glucose load irrespective of last meal.
- If after one hour, venous plasma glucose >140mg/dl, proceed to second step.
- If one-hour venous plasma glucose is ≥ 200mg/dl, then a diagnosis of pregestational diabetes is made.

Step 2: Glucose Tolerance Test (GTT) -2nd visit

- After an overnight fast of 8-10 hours and three days of unrestricted diet, measure fasting plasma glucose.
- Give 100 gram of glucose load
- Blood is then drawn at hourly intervals (3 samples)

Time	Carpenter & Coustan	NDDG
FASTING	95mg/dl	105mg/dl
ONE HOUR	180mg/dl	190mg/dl
TWO HOUR	155mg/dl	165mg/dl
THREE HOUR	140mg/dl	145mg/dl

If any two or more of the above mentioned values are deranged, woman is diagnosed to be having gestational diabetes mellitus. ACOG criteria is based on the risk of development of overt diabetes mellitus and not on the fetal and maternal outcome. Both Carpenter and Coustan and National Diabetes Data Group (NDDG) criteria are considered in ACOG. Advantage of 2 step screening is that not all women have to undergo intensive 3 hour OGTT, where 5 blood samples are drawn.

Disadvantage of this test is that patient has to come for a second visit in a fasting state and therefore may be lost to follow up especially in developing countries, where 50-60% women receive antenatal care and about one third are lost to follow up. It is costly, inconvenient and time consuming as five samples are required.

NICE[3]

A woman is diagnosed as having gestational diabetes mellitus if she has either:

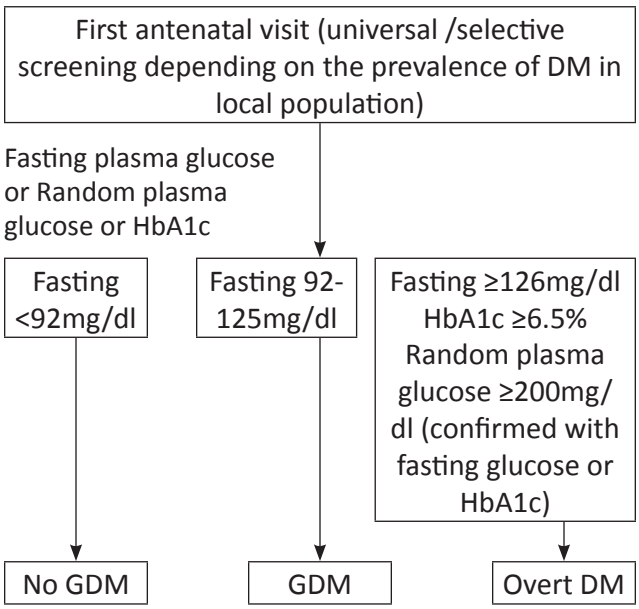
- Fasting plasma glucose ≥ 5.6mmol/l or 100mg/dl.
- 2-hour plasma glucose ≥ 7.8mmol/l or 140mg/dl after 75g of glucose intake.

Although it is a one-step screening test, disadvantage is that the patient has to come for a second visit in a fasting state and may be lost to follow up.

International Association of Diabetes and Pregnancy Study Group (IADPSG)[6]

The IADPSG criteria has been adopted by ADA in 2010 and by WHO in 2013. It is the only criteria based on adverse pregnancy outcomes. In the hyperglycemia and adverse pregnancy outcome (HAPO) study, cut off levels for diagnosis of GDM were lowered to give an odd's ratio of 1.75 times the likelihood of adverse outcomes at mean glucose levels of HAPO study. It was observed in this study that adverse pregnancy outcomes were noted even below the threshold of diagnostic criteria of GDM (<95mg/dl).

IADPSG recommend screening at first visit and one step, diagnostic two hours 75-gram oral glucose tolerance test at 24- 28 weeks.



At 24-28 Weeks

At 24 to 28week gestation, plasma glucose is estimated in the fasting state and again at 1 and 2 hours after glucose load of 75 gm.

Time	Plasma Glucose (mg/dl)
FASTING	≥92
1 HOUR	≥180
2 HOUR	≥153

If any one or more value is deranged, then GDM is diagnosed.

ACOG stated that lowering the thresholds of diagnosis of GDM would result in increasing the prevalence and hence, the cost of care.[2]

Seshiah et al[7] opined that IADPSG had the following shortcomings:

- HAPO study was not done on South East Asian population
- The Asians have higher insulin resistance in pregnancy and hence increased blood glucose levels, unlike Caucasians on whom HAPO study was conducted
- Mostly, pregnant women do not come fasting to the hospital and if asked to come back in a fasting state, the dropout rate is very high, especially in developing countries.
- HbA1c is an expensive test and is not possible in low resource setting.

Diabetes in Pregnancy Study Group, India (DIPSI)[7]

Diabetes in pregnancy study group, India have suggested a universal, one step screening and diagnostic procedure keeping in mind the high prevalence of diabetes in India. Plasma glucose is estimated 2 hours after 75gm of oral glucose load given to the pregnant woman at the first ANC visit, irrespective of the last meal. This single step procedure is convenient, economical and evidence based [9,10]. Patient need not be fasting and there is no issue of loss to follow up as patient is screened at the first visit. This method has been approved and recommended by the National Guideline of India for diagnosis of GDM and also accepted by FIGO for resource constraint countries.

Interpretation of DIPSI

Plasma Glucose level (mg/dl)	Diagnosis in Pregnancy	Diagnosis Outside Pregnancy
≥140-200	Gestational Diabetes Mellitus	Impaired Glucose Tolerance
≥ 200	Pre- existing Diabetes	Diabetes Mellitus

WHO 1999

Hyperglycaemia first detected at any time during pregnancy should be classified as either as diabetes mellitus in pregnancy or gestational diabetes mellitus.

- Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/ dl)
- 2-hour plasma glucose ≥ 11.1 mmol/l (200 mg/dl) following a 75g oral glucose load
- Random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl) in the presence of diabetes symptoms.

Summary

Organization	Year	Screening mode	Approach	Glucose load	Diagnostic criteria(mg/dl)				Remarks
					F	1hr	2hr	3hr	
ACOG	2017	Universal	Two step	100gm	95	180	155	140	Carpenter & Coustan; ≥ 2 value abnormal
					105	190	165	145	NDDG; ≥ 2 value abnormal
NICE	2015	Selective	One step	75gm	100	-	140	-	≥ 1 value abnormal
WHO	2013	Universal	One step	75gm	92	180	153	-	≥ 1 value abnormal
ADA & IADPSG	2010	Universal	One step	75gm	92	180	153	-	≥ 1 value abnormal
DIPSI	2006	Universal	One step	75gm	-	-	140	-	1 value
MOHFW National Guidelines	2018	Universal	One step	75gm	-	-	140	-	1 value

- 2-hour plasma glucose ≥ 7.8 mmol/l (140 mg/dl) following a 75g oral glucose load- diagnosis of GDM is made

WHO has recently adopted the IADPSG Criteria for diagnosing diabetes in pregnancy in 2013.

Challenges in GDM Screening in Low Resource Settings

Health System Barriers- Lack of healthcare professionals/ sampling & diagnostic facilities Patient related barrier- Coming back for a 2nd visit in fasting state, economic, social & accessibility barriers.

Conclusion

- There is insufficient evidence to suggest which strategy is best for diagnosing GDM. Indian population is diverse and variable, hence judging international criteria on Indian population may not be conclusive.
- Clinician should understand the evidence but individualize decision making to the specific patient or set up.
- For low and middle income countries like India, with high diabetic burden, universal, early screening with single step, DIPSI criteria appears to be convenient, practical and evidence based.
- DIPSI test is cost effective- even if repeated in each trimester- 66% lesser than IADPSG
- For India, DIPSI criteria is most appropriate and has also been advocated by the National Guidelines and accepted by FIGO.

References

1. Hod M,Kapur A, Sacks DA et al. The International Federation of Gynecology and Obstetrics (FIGO) Initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management and care. Int J Gynaecol Obstet 2015; 131 Suppl 3:S173
2. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Eng J Med 2008; 358:1991-2002
3. NICE clinical guideline, February 2015. Diabetes in pregnancy: management from preconception to the postnatal period.
4. ACOG Practice Bulletin No. 180: Gestational Diabetes Mellitus .Obstet Gynecol. 2017 Jul;130(1):e17-e37. doi: 10.1097/AOG.0000000000002159.PMID:2864433
5. Classification and Diagnosis of Diabetes, American Diabetes Association, Diabetes Care 2017 Jan; 40(Supplement 1): S11-S24. https://doi.org/10.2337/dc17-S005
6. Metzger BE, Gabbe SG, Perrson B et al. International association of diabetes and pregnancy study group recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33:676-682
7. Seshiah V, BK, Das AK et al. Diagnosis and Management of Gestational Diabetes mellitus: Indian guidelines. Diabetology.2013;44(5):201-204.
8. Waterland Robert A, Garza Cutberto. Potential mechanisms of metabolic imprinting that lead to chronic disease 1,2,3. Am J Clin Nutr, February 1999, vol.69 no.2 179-197
9. Saxena, P., Verma, P. & Goswami, B. J Obstet Gynecol India (2017) 67: 337. https://doi.org/10.1007/s13224-017-0962-y
10. Pikee Saxena, Aruna Nigam. Screening and diagnosis of hyperglycemia in pregnancy. Challenges and controversies. In: Pikee Saxena, Alka Pandey, Anupam Prakash (Eds). (2018). Clinical guidelines for management of diabetes in pregnancy.1st Edition. New Delhi: FOGSI Publication, Jaypee Publishers; 2018. p.32-41

Screening for Pre Eclampsia- An update

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Pre-eclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality affecting 2-5% of pregnancies worldwide.[1,2] It is defined as early onset pre-eclampsia (EOPE) when it leads to delivery < 34 weeks and late onset pre-eclampsia (LOPE) when delivery happens after 34 weeks. It is also sub-classified as preterm PE or term PE depending upon whether the onset occurs <37 weeks or >37 weeks respectively.

EOPE is because of a defective placentation i.e. failure of trophoblasts to migrate, invade the spiral arterioles and convert them into wide flaccid channels from narrow contractile ones. When this remodelling is incomplete, there is an increase in resistance to the blood flow within uterine arteries as reflected by measurement of uterine artery doppler. Because of reduced utero-placental perfusion and resultant ischemia, there is release of various analytes, angiogenic and anti-angiogenic factors, which can be measured in maternal serum. These resulting ischemic products subsequently cause multiorgan dysfunction. Also it is a known fact that certain women are at risk of development of PE as indicated by NICE and ACOG.[3,4] Therefore, a combination of maternal factors, uterine artery doppler and serum biomarkers form the basis of first trimester screening of PE.

LOPE is because of aging of normal placenta and / or increased maternal predisposition.

Screening for PE in early pregnancy is fully justified as ASPRE Study has firmly established that 150mg of Asprin from 14 – 36 weeks of pregnancy in women at high risk for developing preterm PE led to 62% reduction in PE < 34 weeks, 78% < 32 weeks.[5]

First Trimester Screening of PE

Risk factors based screening – Identification of women at risk of developing PE at first antenatal visit allows focused and timely prophylaxis (Risk factors as indicated by NICE & ACOG are as below)

Table 1:

NICE	ACOG
High Risk Factors: • Hypertensive disease in previous pregnancy • CH, CKD, DM, Autoimmune disease **Moderate Risk Factors:** • Nulliparity • Age≥ 40 years • BMI≥ 35Kg/m^2 • Family history of PE • Interpregnancy interval >10 yrs	• Previous pregnancy PE • Chronic Hypertension • Chronic renal disease • Diabetes mellitus • SLE or thrombophilia • Nulliparity • Age> 40 years • BMI≥ 30Kg/m^2 • Family history of PE • Conception by In-vitro fertilization
CH-Chronic Hypertension, CKD-Chronic Kidney Disease, DM-Diabetes Mellitus, SLE-Systemic Lupus Erythematoasis	

Risk factors based screening has moderate performance for PE prediction and inclusion of factors like nulliparity, obesity etc. increases sensitivity, but lowers specificity.

A. **Uterine Artery Doppler**- Harrington in 1997, first published a prospective study correlating abnormal uterine artery Doppler with PE. This was followed by many studies through years each using different criteria and cut-off values. (Table-2)[6]
Inference from these studies is that screening has greater accuracy for EOPE and accuracy increases with inclusion of maternal risk factors. A recent large meta-analysis on 55974 women has further validated the use of uterine artery Doppler for PE screening (sensitivity 47.8%, specificity 92.1% for early PE, 26.4% and 93.4% for any PE respectively).[12]

B. **Maternal Serum Analytes**: Many biomarkers have been associated with risk of developing PE. Detection rate (DR) of 7 biomarkers at a fixed false positive rate (FPR) of 10% is depicted below. - Not very promising.[13]

Angiogenic & Anti-Angiogenic Markers
Angiogenic marker PIGF is decreased and anti-angiogenic markers sFLT and sENG are increased in women who are destined to develop PE. Also, there is plausible hypothesis that an imbalance between the two i.e. an altered ratio can predict PE with greater accuracy. Following tables depict their performance (Table 4 & 5).

Table 2: 1st Trimester Uterine Artery Doppler Velocimetry & the Prediction of PE

Author/ year	Prevalence of PE	Doppler Criteria	Sen.	Spec.	PPV	NPV
Martin (2001)[7] 63/3045 (2.1%)		Mean PI>2.35	27	95.4	11	98.4
Martin (2001)[7] Early PE	14/3045 (0.46%)	Mean PI>2.35	50	95.1	4.5	99.8
Gomez (2005)[8]	22/999 (2.2%)	Mean PI>95th percentile	24	95.1	11.3	97.9
Melchiorre (2008)[9]	90/3058 (2.9%)	Mean UtA-RI>90th centile	48.5	91.8	6.2	99.4
Plasencia (2008)[10] Early PE	22/3107 (0.71%)	Mean PI>95th percentile + history	90.9	90	6	99.9
Plasencia (2008)[10] Late PE	71/3107 (2.3%)	Mean PI>95th percentile + history	40.8	90	8.7	98.4
Poon (2009)[11] Early PE	37/8366 (0.44%)	Lowest UtA-PI MOM+ history	81.1	90	3.1	99.9
Poon (2009)[11] Late PE	128/8366 (1.5%)	Lowest UtA-PI MOM + history	45.3	90	10.1	99

Table 3: Detection rate (DR) of 7 biomarkers

Marker	No. of Studies	Detection Rates
PP13	5	36 – 80% for early PE
PAPP A	8	22 – 43% for early PE
PIGF	4	41 – 59% for early PE, 33% for late PE
ADAM 12	5	37% unspecified PE
Inhibin A	2	35% unspecified PE
Activin	1	20% unspecified PE
fbHCG	1	22% unspecified PE

Table 4: Systematic Rev 22 case control and 12 cohort studies PIGF (27), VEGF (3), sFLT 1[14]

PIGF ⇩	Diag OR 9.0 (95% CI 5.6-14.5) FPR 5%	Sens 32%
sFLT 1⇧	Diag OR 6.6 (95% CI 3.1-13.7) FPR 5%	Sens 26%
sENG ⇧	Diag OR 4.2 (95% CI 2.4-7.2) FPR 5%	Sens 18%

Table 5: sFlt-1/PIGF ratio – Screening for PE[15]

Study	Number of patients with PE (control)	Patients	Sensitivity (%)	Specificity (%)
Before onset of PE				
Stepan et al. (2007)	12 (38)	All patients	62	51
	9 (38)	Early-onset PE	67	51
Kim et al. (2007)	46 (100)	All patients	80.4	78
Crispi et al. (2008)	38 (76)	Early-onset PE	84.2	90
Diab et al. (2008)	33 (108)	All PEs	100	85
	8 (108)	Early-onset PE	90	90
De Vivo A. et al. (2008)	52 (52)	All patients	88.5	88.5
Kusanovic et al. (2009)	62 (1560)	All patients	40.3	78.5
	9 (1613)	Early-onset PE	100	89.1

Two studies have highlighted that concentration of these biomarkers alone or their ratio was predictive of PE but levels do not change significantly until second half of pregnancy specially sFLT/PIGF ratio – a time rather late for aspirin prophylaxis.[16,17]

C. **Ophthalmic Artery Doppler:** Meta-analysis of 3 studies have shown changes in ophthalmic artery for EOPE prediction at a Sensitivity 61.0% & Specificity 73.2 %. More work needs to be done before it can be incorporated in clinical practice.[18]

PE Screening Models

Maternal risk factors are used by NICE & ACOG[3,4] for PE prediction whereas Fetal Medicine Foundation (FMF) algorithm uses a combination of maternal factors, mean arterial pressure (MAP), uterine artery PI, PAPP-A and PIGF[19]. A cut-off of 1 in 100 is taken as screen positive. Screen performance of NICE vs FMF is depicted in the following tables 6 & 7 (THE SPREE STUDY)[20].

Table 6: PE: Screen Performance: NICE vs Combination of Maternal factors & biomarkers

Method of screening	Detection rate %, (95% CI)
All pre-eclampsia (n=473)	
NICE guidelines	30.4%, *(26.3-34.6)*
Maternal factors + MAP+PAPP-A	42.5 %, *(38.0-46.9)*
Preterm pre-eclampsia (n=142)	
NICE guidelines	40.8%, *(32.8-48.9)*
Maternal factors + MAP+PAPP-A	53.5 %, *(45.3-61.7)*
Maternal factors + MAP+PIGF	69.0 %, *(61.4-76.6)*
Maternal factors + MAP+PIGF+ UtA-PI	82.4 %, *(76.1-88.7)*

Table 7: PE Screening: Detection rate, at screen positive rate of 10%, by various combinations of maternal factors (MF) with biomarkers using Bayes' theorem-based method

Method of screening	Detection rate {(%, 95% CI)} PE<34 weeks (n=60)
MF	48.3 %, *(35.2-61.6)*
MF+MAP	65.0 %, *(51.6-76.9)*
MF+UtA-PI	73.3 %, *(60.3-83.9)*
MF+PAPP-A	55.0 %, *(41.6-67.9)*
MF+PIGF	66.7%, *(53.3-78.3)*
MF+ MAP+ UtA-PI	88.3%, *(77.4-95.2)*
MF+ MAP+ PAPP-A	65.0%, *(51.6-76.9)*
MF+ MAP+ PIGF	73.3%, *(60.3-83.9)*
MF+ UtA-PI + PAPP-A	73.3%, *(60.3-83.9)*
MF+ UtA-PI+ PIGF	75.0%, *(62.1-85.3)*
MF+PAPP-A+PIGF	68.3%, *(55.0-79.7)*
MF+ MAP+ UtA-PI + PAPP-A	86.7%, *(75.4-94.1)*
MF+ MAP+ UtA-PI + PIGF	**90.0%,*(79.5-96.2)***
MF+ MAP + PAPP-A+ PIGF	76.7%, *(64.0-86.6)*
MF+UtA-PI+PAPP-A+PIGF	78.3 %, *(65.8-87.9)*
MF+MAP+UtA-PI+-PAPP-A+PIGF	**90.0%, *(79.5-96.2)***

MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PIGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Going a step ahead, Poon et al have reported that women who were screen positive for preterm PE by ACOG or NICE but negative by FMF algorithm, the risk of preterm PE was reduced to within or below background levels.[21]

To summarise, a combination of maternal factors, uterine artery doppler, PIGF is optimal for first trimester screening for all pregnant women. Other screening methods are inferior to FMF algorithm. In the non-availability of PIGF, PAPP-A can be considered for inclusion.

Screening of PE in 2nd and 3rd Trimester

sFLT/PIGF ratio is extensively being evaluated for PE prediction in second and third trimester. PROGNOSIS study has reported a negative predictive value of 99.8% at a level of ≤38 for ruling out PE within one week in women with signs and symptoms suggestive of PE. The PPV value of sFLT/PIGF ratio >38 for ruling in the occurrence of PE within 4 weeks, was 36.7% and for HELLP syndrome it was 65.6%.[22] A post hoc analysis from PROGNOSIS study highlighted that a ratio of sFLT/PIGF at ≤ 38 can rule out PE within 4 weeks at a NPV of 94.3%.[23]

Based on available literature, it is recommended that, after a first trimester screen, a repeat risk stratification for evolving PE in 2nd and 3rd trimester should be carried out. Following model is proposed by Poon et al which is practical and doable.[24]

Key Points

1. PE, especially early onset PE is a disease of high maternal, perinatal mortality & morbidity
2. Aspirin 150mg/day started before 14 weeks of pregnancy significantly reduces incidence of PE, more so preterm PE
3. At the moment, best screen performance is by a combination of maternal factors, MAP, Uterine artery Doppler and serum PIGF (FMF Algorithm).
4. PAPP-A can be considered for inclusion in FMF Algorithm in the event of non-availability of PIGF
5. Screening based on maternal factors only as recommended by ACOG & NICE are inferior to FMF Algorithm regarding detection, false positive and false negative rates
6. After a first trimester screen, repeat risk stratification for evolving PE in 2nd and 3rd trimester is recommended.

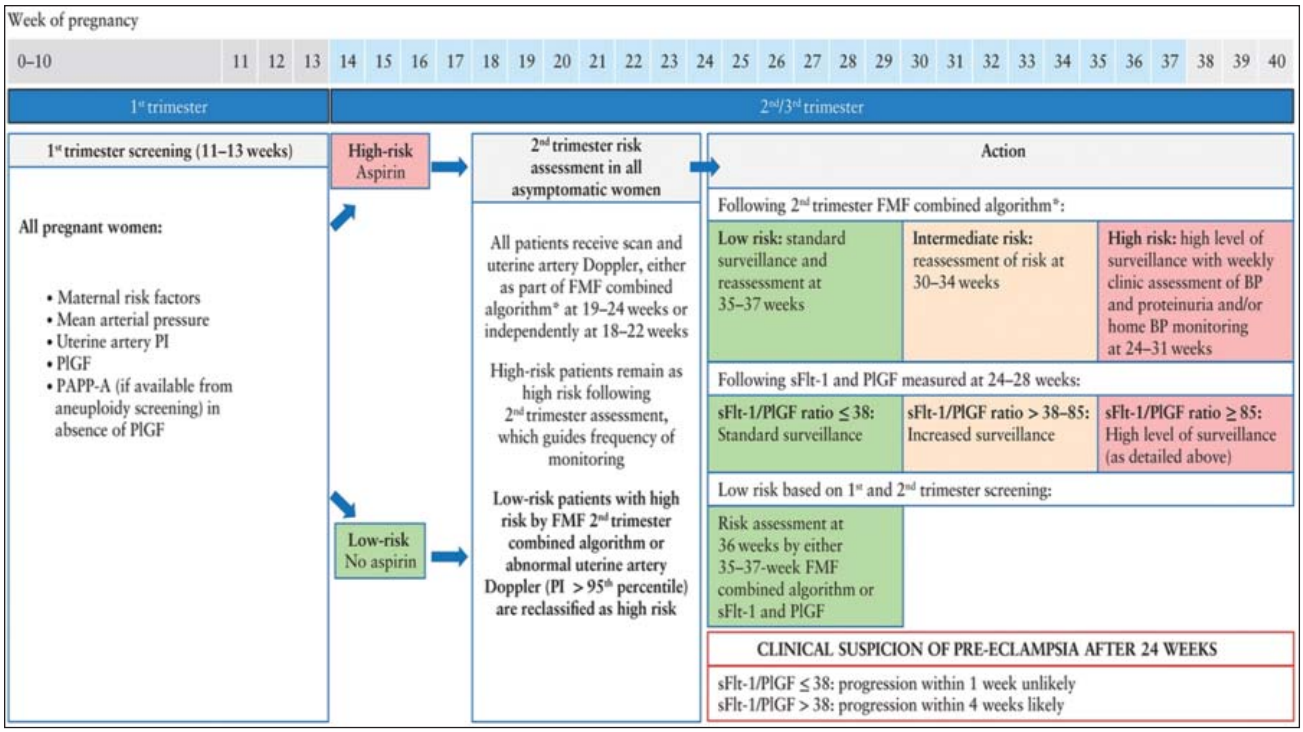

Figure 1: FMF combined algorithm for screening utilizes combination of maternal factors, uterine artery pulsatility index, mean arterial pressure and angiogenic biomarkers. BP, blood pressure; FMF, Fetal Medicine Foundation; PAPP-A, pregnancy-associated plasma protein-A; PI, pulsatility index; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

References

1. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, Souza JP. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG 2014; 121 (Suppl 1): 14 – 24.
2. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol 2009; 33: 130–137.
3. National Collaborating Centre for Women's and Children's Health (UK). Hypertension in Pregnancy: The management of Hypertensive Disorders during pregnancy. London: RCOG Press 2010.
4. ACOG Committee Opinion No. 638: First-trimester risk assessment for early-onset preeclampsia. Obstet Gynecol 2015; 126: e25– e27.
5. Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med 2017; 377: 613– 622.
6. Harrington K, Goldfrad C, Carpenter RG, Campbell S. Transvaginal uterine and umbilical artery Doppler examination of 12–16 weeks and the subsequent development of pre-eclampsia and intrauterine growth retardation. Ultrasound Obstet Gynecol. 1997;9:94–100.
7. Martin AM, Bindra R, Curcio P. Screening for pre- eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. Ultrasound Obstet Gynecol. 2001;18:583-586.
8. Gomez O, Martinez JM, Figueras F. Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an unselected population. Ultrasound Obstet Gynecol. 2005;26:490-494.
9. Melchiorre K, Wormald B, Leslie K. First trimester uterine artery Doppler indicates in term and preterm pre eclampsia. Ultrasound Obstet Gynecol. 2008;32:133-137.
10. Plasencia W, Maiz N, Poon L. Uterine artery Doppler at 11+0 to 13+6 weeks and 21+0 to 24+6 weeks in the prediction of pre eclampsia. Ultrasound Obstet Gynecol. 2008;32:138-146.
11. Poon LC, Karagiannis G, Leal A. Hypertensive disorders in pregnancy: screening by uterine artery Doppler imaging and blood pressure at 11-13 weeks. Ultrasound Obstet Gynecol. 2009;34:497-502.
12. Velauthar L, Plana MN, Kalidindi M, Zamora J, Thilaganathan B, Illanes SE, Khan KS, Aquilina J, Thangaratinam S. First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55,974 women. Ultrasound Obstet Gynecol. 2014;43(5):500-507.
13. Kuc S, Esther JW, Bas BV, Arie F, Gerard HA, Peter CJ. Evaluation of 7 serum biomarkers and uterine artery Doppler ultrasound for first trimester prediction of pre-eclampsia: a systematic review. Obstet Gynecol Survey. 2011;66(4):225–39.
14. Kleinrouweler CE, Wiegerinck MM, Ris-Stalpers C, Bossuyt PM, van der Post JA, von Dadelszen P, Mol BW, Pajkrt E. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG. 2012;119(7):778–87.

15. Verlohren S, Stepan H, Dechend R. Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia. Clin Sci (Lond). 2012;122(2):43–52.
16. Agrawal S, Cerderia AS, Redman C, Vatish M. Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study. Hypertension: 2018 Feb;71(2):306-316.
17. Kleinrouweler C, Wiegerinck M, Ris-Stalpers C, Bossuyt P, van der Post J, von Dadelszen P, Mol B, Pajkrt E, for the EBM CONNECT Collaboration. Accuracy of circulating placental growth factor, vascular endothelial growth factor, soluble fms-like tyrosine kinase 1 and soluble endoglin in the prediction of pre-eclampsia: a systematic review and meta-analysis. BJOG 2012;119:778–787.
18. Kalafat E, Laoreti A, Khalil A, Costa FDS, Thilaganathan B. Ophthalmic artery Doppler for prediction of pre-eclampsia: systematic review and meta-analysis. Ultrasound Obstet Gynecol 2018 Jun;51(6):731-737.
19. Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH. First-trimester prediction of hypertensive disorders of pregnancy. Hypertension 2009; 53:812-818.
20. Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound Obstet Gynecol 2018; 51: 743–750.
21. Poon LC, Rolnik DL, Tan MY, Delgado JL, Tsokaki T, Akolekar R, Singh M, Andrade W, Efeturk T, Jani JC, Plasencia W, Papaioannou G, Blazquez AR, Carbone IF, Wright D, Nicolaides KH. ASPRE trial: incidence of preterm pre-eclampsia in patients fulfilling ACOG and NICE criteria according to risk by FMF algorithm. Ultrasound Obstet Gynecol 2018; 51: 738– 742.
22. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennstrom M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Dilba P, Schoedl M, Hund M, Verlohren S. Predictive value of the sFlt-1:PIGF ratio in women with suspected preeclampsia. N Engl J Med 2016; 374: 13– 22.
23. Zeisler H, Llurba E, Chantraine FJ, Vatish M, Staff AC, Sennstrom M, Olovsson M, Brennecke SP, Stepan H, Allegranza D, Schoedl M, Grill S, Hund M, Verlohren S. Soluble fms-like tyrosine kinase-1 to placental growth factor ratio: ruling out pre-eclampsia for up to 4 weeks and value of retesting. Ultrasound Obstet Gynecol 2019; 53: 367– 375.
24. Poon, L.C., Galindo, A., Surbek, D., Chantraine, F., Stepan, H., Hyett, J., et al. From first-trimester screening to risk stratification of evolving pre-eclampsia in second and third trimesters of pregnancy: comprehensive approach. Ultrasound Obstet Gynecol, 55: 5-12. doi:10.1002/uog.21869

Calendar of Virtual Monthly Clinical Meetings 2020-21

29th May, 2020	B L Kapoor Hospital
26th June, 2020	VMMC & Safdarjung Hospital
31st July, 2020	AIIMS
14th August,2020	Lady Hardinge Medical College
28th August, 2020	Army Hospital- Research & Referral
11th September,2020	Apollo Hospital
25th September, 2020	DDU Hospital
23rd October to 6th November, 2020	AOGD Annual Conference Activities
27th November, 2020	MAMC & LNJP Hospital
18th December, 2020	Sir Ganga Ram Hospital
1st January, 2020	ESI Hospital
29th January, 2021	Dr RML Hospital
26th February, 2021	UCMS & GTB Hospital
26th March, 2021	Lady Hardinge Medical College
23rd April, 2021	Apollo Hospital

Optimising Perinatal Outcome in Fetal Growth Restriction

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Introduction

Fetal growth restriction (FGR) has been defined as 'a fetus unable to reach its growth potential'.[1] However, since it is difficult to determine the optimal 'growth potential' of any given fetus, ultrasound criteria including estimated fetal weight (EFW), 'plateauing' in fetal growth accompanied by Doppler abnormalities have been suggested to differentiate small for gestational age (SGA) fetuses from those small fetuses that are at risk of adverse perinatal outcomes and thus truly 'growth restricted'.[2] FGR has also been recategorized as 'early' and 'late' fetal growth restriction when diagnosed before or after 32 weeks of gestation. It is important to note at the outset that a 'discrepancy in weeks' in fetal head circumference (HC) and abdominal circumference (AC) on ultrasound is ***no longer*** considered a criteria for defining growth restriction. Also identification of Doppler abnormalities should be based on the Pulsatility index (PI) of the target vessel rather than the traditional 'SD ratio'. Estimated fetal weight should be plotted on a 'growth chart'. Use of growth charts (irrespective of which chart is used) is essential for noting the degree of smallness ('centile') as well as weight gain over a period of time, typically over 2-3 weeks.

Diagnosis

If a fetus is identified to be small on ultrasound, the first step is to rule out wrong dates. Thus dating should be confirmed, preferably from the early first trimester crown to rump length (CRL). The next step is to differentiate small for gestational age (SGA) fetuses from 'growth restricted' fetuses, ie those small fetuses that are at risk of adverse perinatal outcomes. Thus, newer diagnostic criteria that include both fetal as well as maternal Dopplers have been proposed by a Delphi consensus in 2016 and should be used for diagnosing FGR (table 1).[3]

Very small fetuses, i.e., those with an estimated fetal weight (EFW) of less than 3rd centile would be considered growth restricted even if Dopplers are normal. Fetuses with EFW between 3rd to 10th centile should have a Doppler abnormality before being considered pathologically small.

All growth restricted fetuses may not have EFW below the 10th centile. Use of growth chart helps in identifying a 'plateauing' growth or falling of weight centile which is usually accompanied with cerebral redistribution.

Table 1: Diagnostic criteria for Early and Late Fetal growth restriction (in a structurally normal fetus)

Early FGR (diagnosed before 32 weeks)	Late FGR (diagnosed after 32 weeks
AC*/EFW < 3rd centile **OR**	AC/EFW < 3rd centile **OR**
Umbilical artery – A/REDF# **OR**	
AC/EFW < 10th centile **AND** Uterine artery PI > 95th centile **AND/OR** Umbilical artery PI > 95th centile	Any 2 of the following 3 criteria: AC/EFW < 10th centile **OR** AC/EFW crossing centiles >2 quartiles on growth chart **AND** CPR< 5th centile **OR** Umbilical artery PI > 95th centile

**AC: Abdominal circumference, #A/REDF: Absent or reversed end diastolic flow*

Early Fetal Growth Restriction

Early FGR, diagnosed before 32 weeks, accounts for 1/3rd of antenatally diagnosed FGR and is usually associated with hypertensive disorders of pregnancy. It is easily identified on ultrasound and follows a predictable deterioration in fetal Dopplers: increase in umbilical artery Pulsatility index (PI) followed by decrease in middle cerebral artery (MCA) PI followed by venous Doppler abnormalities. The deterioration in umbilical artery Doppler follows a typical and predictable pattern in early FGR (figure 1). The mean uterine artery PI is usually above the 95th centile in these pregnancies.

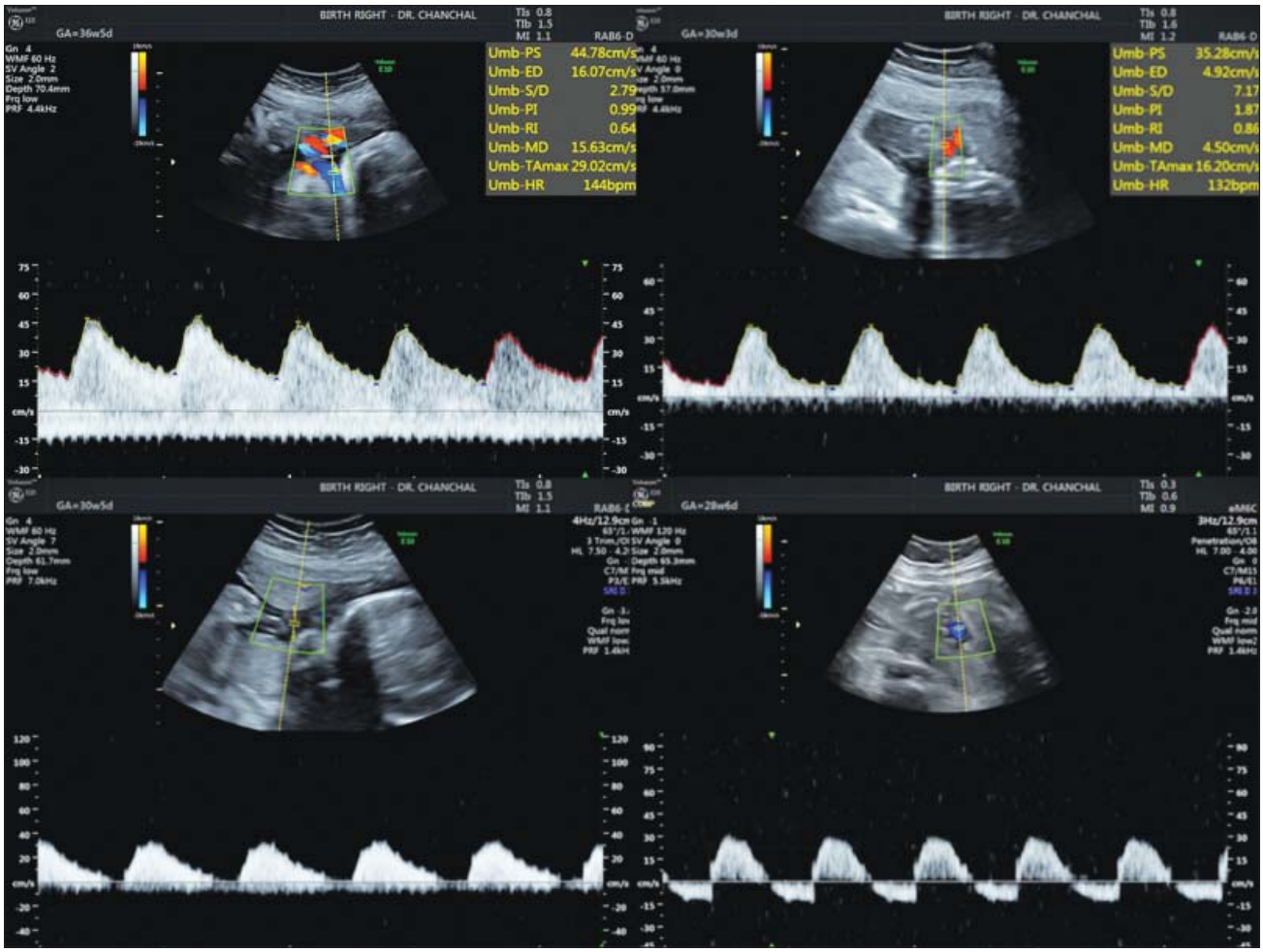

Figure 1: Typical deterioration in umbilical artery Doppler in early FGR (clockwise): normal waveform, increased PI, absent end diastolic flow (AEDF) followed by reversal in end diastolic flow (REDF).

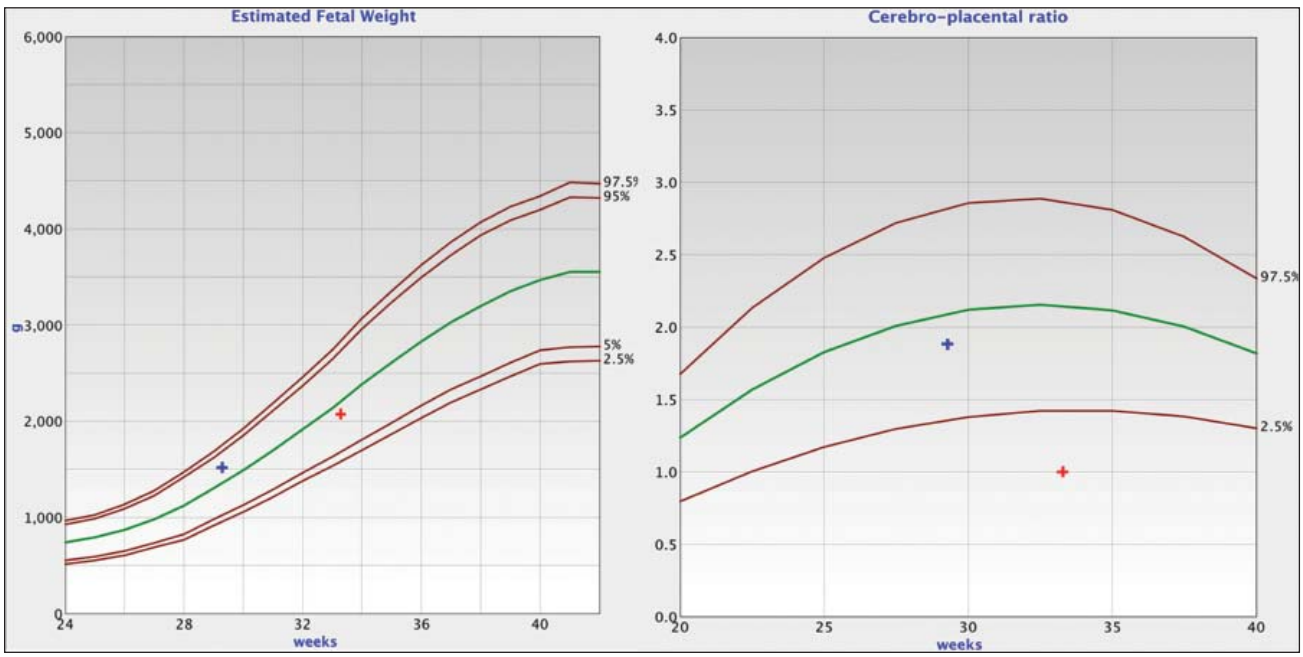

Figure 2: A fall in EFW by 2 quartiles or more than 50 percentile along with a cerebroplacental ratio (CPR) below 5th centile due to cerebral redistribution is typically seen in late FGR.

Early onset FGR especially those presenting before 22-24 weeks warrant detailed evaluation to rule out fetal structural abnormalities, fetal infections and chromosomal and non-chromosomal genetic abnormalities. Amniocentesis for fetal microarray should be considered in FGR presenting in the second trimester.

Although easier to diagnose, early FGR difficult to manage as the only treatment at present is fetal surveillance and optimal timing of delivery. The perinatal mortality remains high for this subgroup of FGR. Since the underlying pathophysiology seems to involve poor placental implantation and spiral artery abnormalities, this is the type that is amenable to antenatal prediction in the first trimester using the Fetal Medicine Foundation (FMF) algorithm. The importance of picking up women at risk is the possibility of primary prevention of early preeclampsia (requiring delivery prior to 34 weeks) by giving 150 mg of aspirin to screen positive women – this strategy is proven to prevent 80% of early preeclampsia as well as preterm SGA.[4,5]

Late Fetal Growth Restriction

Late FGR accounts for 2/3rd of growth restricted fetuses and may be missed as all fetuses may not necessarily be small. In fact the main vessel which is abnormal in early FGR, ie, the umbilical artery waveform may be normal in majority of these fetuses. The main Doppler abnormality in late FGR is cerebral redistribution reflected by a cerebroplacental ratio (CPR) of less than the 5th centile for gestation. Hypertensive disorders are not frequent in this subtype.

Management

There is no known treatment for fetal growth restriction at present. The results of the recent STRIDER trial did not show any benefit of Sildenafil either.[6] Thus, current management of fetal growth restriction remains optimizing the surveillance of these high-risk pregnancies and planning delivery at a gestation that provides the best trade-off between iatrogenic prematurity and intrauterine fetal demise. A proposed protocol for evaluation, frequency of surveillance and timing of delivery of 'small' fetuses is given in figure 1.[1,2] Since early and late FGR are two distinct clinical entities, management is discussed separately for each.

Early FGR

Once a diagnosis of early FGR is made, the patient should be managed in a tertiary care centre with maternal-fetal medicine specialists and NICU facilities. The Trial of Randomized Umbilical and Fetal Flow in Europe (TRUFFLE) trial randomised 503 women with early FGR defined as EFW < 10th centile *and* umbilical artery PI above 95th centile at 26 to 32 weeks' gestation to three arms that would trigger delivery: early DV changes (PI above 95th centile), late DV changes (absent or reversed a wave in DV) and reduced fetal heart rate short term variability (STV) on computerised CTG (cCTG).[7] 82% of children had a normal neurodevelopmental outcome at 2 years – the primary outcome of the trial – which was better than previously reported.[8]

Surveillance

The usual modalities for fetal surveillance of a growth restricted fetus include daily kick count, biophysical profile that includes nonstress test (NST) and assessment of Dopplers. There is no consensus on whether one or all modalities should be used nor how frequently the monitoring should be done. Both would be guided by the gestation at which the diagnosis is made, severity of the condition and presence of maternal preeclampsia. Since cCTG may not be available universally, conventional CTG can be used; however the expected higher baseline fetal heart rate and lower variability of preterm fetuses must be taken into account while interpreting the CTG. 60% of recruited women in TRUFFLE had preeclampsia at study entry; this figure rose to 70% by delivery.[7] Thus, maternal surveillance by BP monitoring, urine protein:creatinine ratio and baseline liver and renal function test is recommended. Fetuses with high PI in umbilical artery with EDF present should be reviewed twice weekly. Fetuses with absent/ reversed EDF should be reviewed daily.

Timing of Delivery

The TRUFFLE trial provided the best evidence to guide timing of delivery in early FGR. Fetuses with absent end diastolic flow (AEDF) in umbilical artery should be delivered by 32-34 weeks. Fetuses with reversed end diastolic flow (REDF) should be delivered by 30-32 weeks. Delivery prior to 30 weeks (and after viability) should be based on late ductus venosus (DV) changes. Conventional CTG may be

used in place of cCTG as a safety net – however only persistent, repetitive decelerations on NST should be considered an indication for delivery. MCA PI and/or cerebroplacental ratio (CPR) should not be used to time iatrogenic preterm delivery in early FGR.

Delivery can be done anytime for maternal indication.

Antenatal Steroids

All available guidelines recommend a single course of corticosteroid prophylaxis to prevent neonatal respiratory distress syndrome if birth is anticipated prior to 34 weeks. The Royal College of Obstetricians and Gynecologists' (RCOG) recommends antenatal steroids can be considered upto 35 weeks and 6 days.[1] Since steroids are most effective when delivery occurs within a week after being given, the single course should be timed judiciously to maximise neonatal benefit. As per Indian guidelines, 4 doses of Dexamethasone 6 mg, 6 hourly is the regime and drug of choice. Administration of steroids may cause a transient improvement in fetal blood flows but it should not affect management as the underlying pathology remains unchanged.

Neuroprotection

Magnesium sulphate for fetal neuroprotection should be given when preterm delivery is anticipated prior to 32 weeks' gestation.[9,10]

Mode of Delivery

Fetal indications for elective Cesarean delivery in early FGR include abnormal venous Dopplers, absent or reversed EDF in umbilical artery, deranged biophysical profile and persistently abnormal CTG.[1,2]

Late FGR

As mentioned earlier, the main Doppler abnormality in late FGR is cerebral redistribution. Umbilical artery and ductus venosus are usually normal in these fetuses. Since these abnormalities may be subtle and fetuses near tern have a lower tolerance to hypoxemia, late FGR remains an important cause of unexpected stillbirth in late gestation.

Surveillance

The optimal frequency of ultrasound surveillance in late FGR is not known. Biophysical profile has a poor role in predicting stillbirth in late FGR and hence should not guide frequency of monitoring. In one study, the median interval between low MCA PI and stillbirth as less than 5 days and almost 90% of stillbirths occurred within one week of normal BPP.[12] Thus weekly to twice weekly Doppler surveillance after 34 weeks has been proposed.

Antenatal Steroids and Magnesium Sulphate for Neuroprotection

There is lack of consensus amongst various guidelines for giving steroids between 34-36 weeks' gestation though the ROG recommends steroid prophylaxis upto 35 weeks and 6 days. There is no role of magnesium sulphate for neuroprotection after 32 weeks.

Timing of Delivery

There is lack of consensus amongst guidelines as to when to offer delivery in late FGR. The RCOG recommends that delivery should be 'offered' after 37 weeks in late FGR.[1] The recent ISUOG guidelines propose that women with late FGR and cerebral redistribution should be delivered at around 38 weeks and not later than 38 weeks and 6 days.[2] If in addition, umbilical artery is above the 95th centile, delivery can be considered after 36 weeks and no later than 37 weeks and 6 days. Fetuses with birth weight below the 3rd centile have the highest risk of stillbirth, hence these pregnancies should not be allowed to continue beyond 37 weeks and 6 days irrespective of fetal Dopplers.

Mode of Delivery

Induction of labour can be done depending on usual obstetric parameters. Continuous intrapartum CTG monitoring is recommended. These fetuses are at higher risk of requiring emergency LSCS for nonreassuring fetal heart rate trace.[2]

Conclusion

Fetal growth restriction should be strictly identified and categorised into early and late on the basis of the revised Delphi consensus. Considering the distinct pathophysiology and clinical phenotypes, management should be tailored to each type as outlined. Since there is no consensus on the modalities and frequency of surveillance, local protocols should be made.

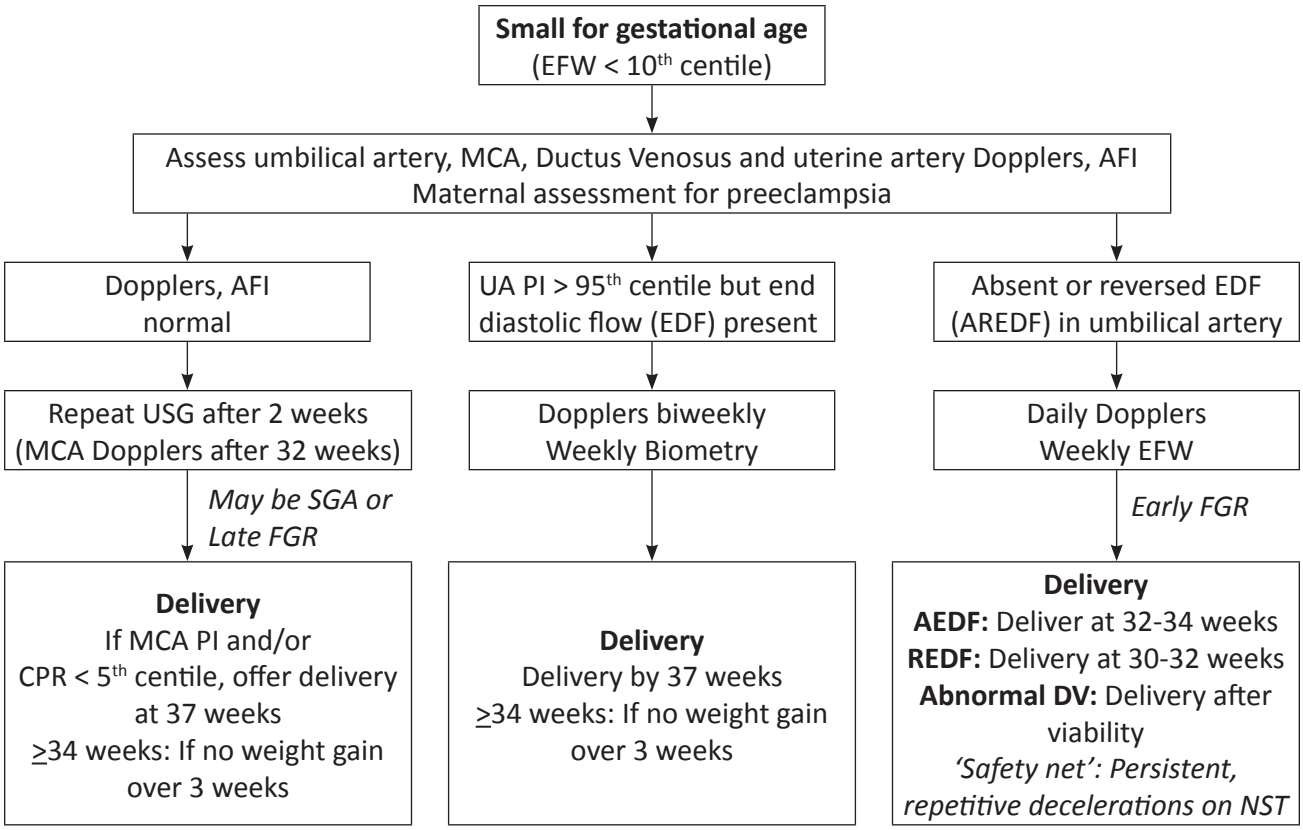

Figure 3: Suggested monitoring and timing of delivery in small fetuses (adapted from RCOG and ISUOG guidelines).

References

1. Royal College of Obstetricians and Gynaecologists. Small-for-Gestational-Age Fetus, Investigation and Management (Green-top Guideline No. 31). 2013. https:// www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf
2. Lees CC, Stampalija T, Baschat A, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020 Aug;56(2):298-312.
3. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016; 48: 333–339.
4. Rolnik DL, Wright D, **Poon LC**, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017 Aug 17;377(7):613-622.
5. Tan MY, Poon LC, Rolnik DL, et al. Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE. Ultrasound Obstet Gynecol. 2018 Jul;52(1):52-59.
6. Pels A, Derks J, Elvan-Taspinar A, van Drongelen J, de Boer M, Duvekot H, et al. Maternal Sildenafil vs Placebo in Pregnant Women With Severe Early-Onset Fetal Growth Restriction: A Randomized Clinical Trial. JAMA Netw Open. 2020 Jun 1;3(6):e205323.
7. Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, et al; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol 2013; 42: 400 – 408.
8. Bilardo CM, Hecher K, Visser GHA, Papageorghiou AT, Marlow N, Thilaganathan B, et al; TRUFFLE Group. Severe fetal growth restriction at 26-32weeks: key messages from the TRUFFLE study. Ultrasound Obstet Gynecol 2017; 50: 285–290.
9. Ting JY, Kingdom JC, Shah PS. Antenatal glucocorticoids, magnesium sulfate, and mode of birth in preterm fetal small for gestational age. Am J Obstet Gynecol 2018; 218: S818–828.
10. Raju TNK, Mercer BM, Burchfield DJ, Joseph GF Jr. Periviable birth: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. Obstet Gynecol 2014; 123: 1083–1096.
11. Torrance HL, Bloemen MC, Mulder EJ, Nikkels PG, Derks JB, de Vries LS, Visser GH. Predictors of outcome at 2 years of age after early intrauterine growth restriction. Ultrasound Obstet Gynecol 2010; 36: 171–177.
12. Crimmins S, Desai A, Block-Abraham D, Berg C, Gembruch U, Baschat AA. A comparison of Doppler and biophysical findings between liveborn and stillborn growth-restricted fetuses. Am J Obstet Gynecol 2014; 211: 669.e1–10.

Newer Diagnostic Criteria for Placenta Accreta Syndrome (PAS)

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Introduction

Placenta Accreta Syndrome (PAS) disorders formerly known as morbidly adherent placenta refers to spectrum of abnormal pathology of placentation ranging from accreta, increta to percreta. Maternal mortality and morbidity remains high due to severe life-threatening hemorrhage requiring massive blood transfusion and even hysterectomy. PAS disorders remain undiagnosed before delivery in half to two-thirds of cases. Maternal mortality and morbidity are reduced when women with PAS disorders, particularly the invasive forms—placenta increta or percreta—deliver at a tertiary centre equipped with a multidisciplinary team which can effectively tackle the surgical challenges and perioperative risks. "Levels of maternal care" have been designated for these disorders. ACOG and Society of Materno-fetal-medicine recommend level III or IV maternal care with multidisciplinary facility for these women before onset of labor or hemorrhage for most optimum outcome. Timely transfer to these tertiary centres is required for females with PAS disorders. This definitely depends largely on both the recognition of the "at risk women" as well as on accurate prenatal diagnosis.[1]

Identification of "at Risk Women"

The most common risk factor is **previous cesarean section (CS)** delivery with the rise of incidence with the number of prior cesarean deliveries. In a systematic review, incidence of PAS rose from 0.3% in one previous CS to 6.74% in women with five or more previous CS. Another major risk factor is **placenta previa (PP)** where PAS disorders are seen in 3% cases of PP without prior CS. In presence of two risk factors i.e. Prior CS as well as PP the risk of PAS increases dramatically. For women with PP, the risk of PAS is 3%, 11%,40%, 61%, 67%for the first, second, third, fourth and fifth or more CS respectively. Other risk factors are advance maternal age (35 years or more) without previous CS, prior uterine surgeries of curettage, post-partum endometritis, h/o myomectomy, manual removal of placenta, Ashermann syndrome and In-Vitro-Fertilisation pregnancy, other uterine pathologies like bicornuate uterus, adenomyosis, submucous fibroids.[1]

How to Diagnose?

Before availability of high resolution USG, the diagnosis was made usually at the time of delivery. But with the advent of gray scale and color Doppler USG, prenatal diagnosis has been possible thereby improving the overall outcome. Since then, there have been many studies on different diagnostic criteria for PAS. The real challenges are precise detection of PAS in the first trimester and prediction of its degree and the extent of invasion of placental villi i.e. the severity of PAS.

Ultrasonography (USG) with grayscale and color Doppler imaging is the recommended **first-line modality** for diagnosing morbidly adherent placenta. Other more promising imaging tools to define the placental topography, such as 3-dimensional Doppler and volume contrast ultrasound are there, yet generalized applicability of technique and validation studies are lacking.

Features of accreta may be seen by ultrasonography ***as early as the first trimester;*** however, most women are diagnosed in the second and third trimesters. Ideally, women with risk factors for PAS, such as placenta previa and previous cesarean delivery, should be evaluated by Obstetricians with experience and expertise in its diagnosis by USG. Perhaps the most important ultrasonographic association of PAS in the second and third trimesters is the presence of placenta previa, which is present in more than 80% of accretas. Other gray-scale abnormalities that are associated with PAS include multiple vascular lacunae within the placenta (figure 1), loss of the normal hypoechoic zone between the placenta and myometrium, decreased retroplacental myometrial thickness (less than 1 mm), abnormalities of the uterine

serosa-bladder interface, and extension of placenta into myometrium, serosa, or bladder. The use of color flow Doppler imaging may facilitate the diagnosis. Turbulent lacunar blood flow (figure 2) is the most common finding of PAS on color flow Doppler imaging. Other Doppler findings of PAS include increased sub-placental vascularity, gaps in myometrial blood flow, and vessels bridging the placenta to the uterine margin.

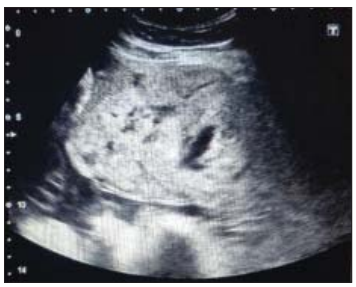

Figure 1: Gray scale USG showing placenta lacunae

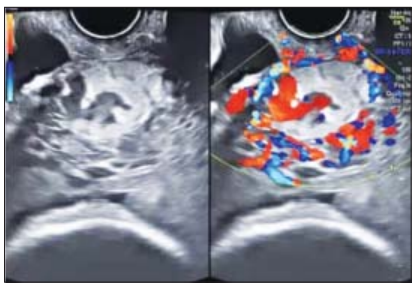

Figure 2: Color doppler USG showing multiple vascular lacunae

Timing of Ultrasound Scan in Women with The Risk of PAS

Though there is no fixed consensus or protocol for USG timing for PAS detection in high risk women. ACOG has suggested a reasonable protocol involving a first trimester scan followed by scan at 18-20 weeks, 28-30 weeks and 32-34 weeks in asymptomatic patients. This permits assessment of previa resolution, placental location to plan the timing of delivery and to rule out possibility of bladder invasion.[1]

First trimester- In women with prior CS.USG done in the early first trimester has been recommended to look for features of Caesarean scar pregnancy (CSP) (figure 3),which is a precursor of PAS in its natural history.[2] Low implantation of the gestational sac within or in close vicinity to a Caesarean scar in the first trimester is associated with an increased incidence of placenta accrete in the third trimester This sign has high diagnostic accuracy with a sensitivity of 93.0% and a specificity of 98.9%. The risk of PAS approaches 100% if pregnancy is allowed till term. Other first trimester USG feature of PAS is presence of gestational sac in lower uterine segment along with presence of multiple irregular vascular spaces within the placental bed. These features can help in timely detection, counselling, successful management and safe referral.

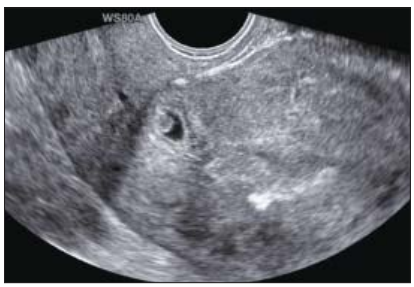

Figure 3: Gray scale USG showing Caesarean scar pregnancy

The classical USG signs of PAS are loss of the clear space, placental lacunae, bladder wall interruption, and uterovesical hypervascularity (figure 4). These signs can be looked as early as early 11-14 weeks and also at a mid-trimester morphology scan. Being a progressive condition, PAS can also be picked up at serial follow-up scans, starting from 28 weeks of gestation.[1]

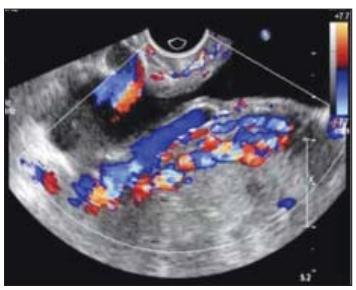

Figure 4: Color doppler USG showing uterovesical hypervascularity

This screening can accurately predict the degree and extent of the invasion, stratify the prognosis and plan the best surgical treatment.

FIGO Clinical Grading

The International Federation of Gynecology and Obstetrics (FIGO) introduced a clinical grading system for PAS which uses per operative findings for stratification of PAS disorders. Although it differentiates focal and complete placenta accreta from placenta percreta but it cannot differentiate placenta accreta from placenta increta.[3] Also, the clinical grading is performed at delivery so it cannot be used for prenatal counselling and planning case management.

Prenatal Diagnosis

For precise prenatal diagnosis, there was need of standardised USG system and predictive models which can help in meticulous case based management.

1. Standardised USG Terminologies

Accurate antenatal diagnosis, which is the basis of risk assessment and planning, depended on the USG findings which were very subjective with lot of inter-observer variability. There was no agreed terminology for these findings. **European working group on abnormal invasive placentation (EW-AIP)** identified and analyzed terms commonly used in the literature and proposed standardized unambiguous definitions of these AIP descriptors and accompanied them

Table 1: European working group on abnormal invasive placentation (EW-AIP) standard USG terminologies.

USG finding	EW-AIP suggested standardized definition
2D gray scale (6 descriptors) 1. Loss of 'clear zone' 2. Abnormal placental lacunae 3. Bladder wall interruption 4. Myometrial thinning 5. Placental bulge 6. Focal exophytic mass	1. Loss, or irregularity, of hypoechoic plane in myometrium underneath placental bed ('clear zone') 2. Presence of numerous lacunae including some that are large and irregular (Grade 3), often containing turbulent flow visible on grayscale imaging 3. Loss or interruption of bright bladder wall (hyperechoic band or 'line' between uterine serosa and bladder lumen) 4. Thinning of myometrium overlying placenta to <1mm or undetectable 5. Deviation of uterine serosa away from expected plane, caused by abnormal bulge of placental tissue into neighbouring organ, typically bladder; uterine serosa appears intact but outline shape is distorted 6. Placental tissue seen breaking through uterine serosa and extending beyond it; most often seen inside filled urinary bladder
2D color Doppler (4 descriptors) 1. Uterovesical hypervascularity 2. Subplacental hypervascularity 3. Bridging vessels 4. Placental lacunae feeder vessels	1. Striking amount of color Doppler signal seen between myometrium and posterior wall of bladder; this sign probably indicates numerous, closely packed, tortuous vessels in that region (demonstrating multidirectional flow and aliasing artifact) 2. Striking amount of color Doppler signal seen in placental bed; this sign probably indicates numerous, closely packed, tortuous vessels in that region (demonstrating multidirectional flow and aliasing artifact) 3. Vessels appearing to extend from placenta, across myometrium and beyond serosa into bladder or other organs; often running perpendicular to myometrium 4. Vessels with high-velocity blood flow leading from myometrium into placental lacunae, causing turbulence upon entry
3D ultrasound ± power Doppler (1 descriptor) 1. Intraplacental hypervascularity 2. Placental bulge (Focal exophytic mass) 3. Utero-vesical hypervascularity 4. Bridging vessels (figure 5)	Complex, irregular arrangement of numerous placental vessels, exhibiting tortuous courses and varying calibres (as in 2D)

Adapted from European Working Group on Abnormal Invasive Placentation (EW-AIP)[4]

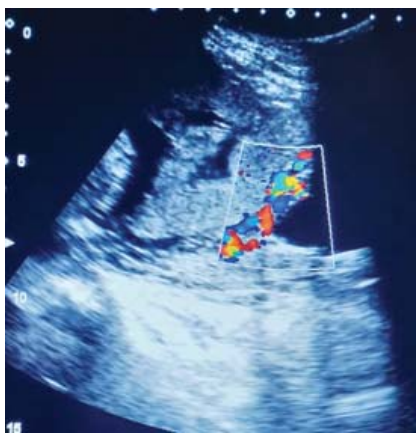

Figure 5: Color doppler showing bridging vessels

with characteristic ultrasound images. Following this EW-AIP meeting in November 2014 the various terminologies were unified into a set **of 11 descriptors, six for 2D grayscale ultrasound, four for 2D color Doppler and one for 3D power Doppler** (Table 1).[4]

2. **Predictive models for precise planning of management of PAS disorders**

The predictive models in the form of Scoring or Staging systems have been suggested which can help in standardizing evaluation of women at risk for PAS. This may help in individual risk stratification, planning of a multidisciplinary management approach and decision about delivery timing. Prediction models involving USG signs with or without pregnancy characteristics have been shown to predict PAS. Two such models suggested recently are **Placenta Accreta Index** and **Ultrasound staging system**.[5,6]

A. Placenta Accreta Index (PAI)

It was found that a score derived from the ultrasound parameters (smallest myometrial thickness, lacunar spaces, and presence of bridging vessels) alongwith the number of prior cesarean deliveries and placental location, was highly predictive of placental invasion among pregnancies at increased risk. The application of the PAI can be helpful in stratifying individual risk of invasion. It can help in counselling, preoperative planning and timely referral to a tertiary center. Also, instead of using each ultrasound variable individually, PAI is a scoring system for a standardized ultrasound evaluation of all patients at risk for morbidly adherent placenta that can be universally adopted. Assigning the PAI in clinical practice may be helpful in interpreting these various sonographic variables in light of the patient's history. (table 2)[5] Limitation of PAI: this model was developed for pregnancies in the third trimester with prior cesarean delivery and placenta previa. Other factors like maternal age, parity, and history of other uterine surgical procedures that have been associated with morbidly adherent placenta, such as dilation and curettage, myomectomy, and endometrial ablation were not included.

Table 2: Placenta Accreta Index Score and score related probability of invasion

Parameters	**Score**
>2 cesarean deliveries	3
Lacunae Grade 3 Grade 2	 3.5 1
Sagittal smallest myometrial thickness ≤1mm >1-≤3mm >3-≤5mm	 1 0.5 0.25
Anterior placenta previa	1
Bridging vessels	0.5
PAI SCORE RELATED PROBABILITY OF INVASION	
PAI Score	**Probability of invasion, %(95% CI)**
>0	5 (1-15)
>1	10 (4-22)
>2	19 (10-32)
>3	33 (22-47)
>4	51 (36-66)
>5	69 (50-83)
>6	83 (63-93)
>7	91 (73-97)
>8	96 (81-99)
Adapted from Rac et al(5)	

B. Ultrasound staging system

An ultrasound staging system of PAS disorders was proposed, based on the presence of ultrasound signs of PAS in women presenting with placenta previa. The last ultrasound examination prior to surgery was used to assess the presence and distribution of ultrasound signs of PAS and to build the staging system.[5] This is as follows.

PAS 0: Placenta previa with no ultrasound signs of invasion or placenta previa with placental lacunae but no evidence of abnormal uterus–bladder interface (i.e. no loss of the clear zone and/or bladder wall interruption);

PAS 1: Presence of at least two of placental lacunae, loss of the clear zone and bladder wall interruption;

PAS 2: PAS1 plus utero-vesical hypervascularity;

PAS 3: PAS1 or PAS2 plus evidence of increased vascularity in the inferior part of

the lower uterine segment extending into the parametrial region.

This prenatal ultrasound staging of PAS disorders was feasible and found that increased USG stage of PAS disorders was associated with significant increase in expected blood loss, units of blood products transfused during surgery, operation time, length of hospital stay and surgical complications. When considering the depth of invasion, **all women with PAS1 had placenta accreta or increta, while those with PAS 2 or PAS 3 had exclusively placenta percreta.** Though presenting with the same depth of placental invasion, women with PAS 3 were at significantly higher risk of hemorrhage and need for transfusion compared with those with PAS 2.

Moreover, this ultrasound staging system of PAS disorders showed good correlation with the clinical grading system suggested by FIGO.PAS0 and PSA1 correlated with FIGO grade 1-2 and 3 respectively, while PAS2 and PAS3 correlated with FIGO grade 4-5 and 6 respectively.

Magnetic Resonance Imaging (MRI)

MRI is the other major tool used for the antenatal diagnosis of PAS. Magnetic resonance imaging features associated with PAS include dark intra-placental bands on T2-weighted imaging, abnormal bulging of the placenta or uterus, disruption of the zone between the uterus and the placenta, and abnormal or disorganized placental blood vessels. The accuracy of MRI for the prediction of PAS is reasonably good, with sensitivities of 94.4% (95% CI, 86.0-97.9) and the specificity was 84.0% (95% CI, 76.0-89.8), which is comparable to USG. But MRI are even more prone to selection bias than USG because it is used generally for patients with an indeterminate USG or at very high risk of PAS. MRI is specifically useful for diagnosis of difficult cases, like posterior placenta previa, and to assess depth of invasion in suspected percreta. Compared to USG,MRI is more expensive, less widely available and needs expertise for interpretation. Thus, it is not the preferred recommended modality for the initial evaluation of possible PAS.

Role of Biomarkers

Some biomarkers have been found to be raised in condition of PAS. These are Maternal Serum Alfa fetal fetoprotein(MSAFP) PAPP-A(Pregnancy-Associated plasma protein A), pro-B type natriuretic peptide, Troponin, Free b-HCG(mRNA) and Human Placental Lactogen (cell-free mRNA) and total placental cell free mRNA. Though found to be raised in PAS but are nonspecific to be recommended for clinical use at present.

Conclusion

Identification of at risk women and timely antenatal diagnosis of PAS permits proper planning of management and a multidisciplinary facility thereby optimizing outcomes. During early first trimester scan, presence of CSP is a sensitive sonographic marker. USG with color Doppler examination can be done in the second or third trimester. Prenatal prediction of the extent of placental invasion and topography are the major determinants of maternal morbidity. Clinical grading can't be used for prenatal counselling and management. Use of subjective USG (Grayscale and Doppler) descriptors and prediction models can help in precise diagnosis and thus proper prenatal counselling and planned timely management.

References

1. Placenta Accreta Spectrum.Obstetric Care Consensus No. 7.American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;132:e259-75
2. Timor-Tritsch IE, D'Antonio F, Calí G, Palacios-Jaraquemada J, Meyer J, Monteagudo A. Early first-trimester transvaginal ultrasound is indicated in pregnancy after previous Cesarean delivery: should it be mandatory? Ultrasound Obstet Gynecol 2019; 54:156-63.
3. Jauniaux E, Chantraine F, Silver RM,Langhoff-Roos J; FIGO Placenta Accreta Diagnosis and Management Expert Consensus Panel. FIGO consensus guidelines on PAS disorders: Epidemiology. Int J Gynaecol Obstet 2018;140: 265–273.
4. Collins SL, Ashcroft A, Braun T, et al. Proposal for standardized ultrasound descriptors of abnormally invasive placenta (AIP). Ultrasound Obstet Gynecol. 2016;47(3):271-275. doi:10.1002/uog.14952
5. Rac MW, Dashe JS, Wells CE, Moschos E, McIntire DD, Twickler DM. Ultrasound predictors of placental invasion: the Placenta Accreta Index. Am J Obstet Gynecol. 2015;212(3):343.e1-343.e3437. doi:10.1016/j.ajog.2014.10.022
6. Cali G, Forlani F, Lees C, et al. Prenatal ultrasound staging system for PAS disorders. Ultrasound Obstet Gynecol. 2019;53(6):752-760. doi:10.1002/uog.20246

Antepartum Still Birth - Prediction & Prevention

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Stillbirth is one of the most common devastating complications of pregnancy. Currently, the most recognized definition of stillbirth is a fetal death that occurs at or greater than 20 weeks gestation or at a birth weight greater than or equal to 350 grams.[1] An estimated 98% of global stillbirths occur in low and middle-income countries.[2] Stillbirth affects at least 2.6 million families worldwide every year and it is a potential trigger for major economical and psychological consequences in women, families, healthcare providers, and communities.[3]

Globally, India has been ranked first in the absolute number of stillbirths. Wide range of variation in stillbirth rate (12.5 to 26.48) has been reported across the states of India. Recently, Government of India has set a target for bringing down the stillbirth rate to single digit by 2025[4].

Causes of Stillbirth

Stillbirth has diverse aetiology (Table 1) which includes maternal epidemiological risk factors, medical disorders, and obstetrical complications; placental diseases and fetal conditions. Late-onset prenatal care and prior home delivery are independent risk factors for subsequent adverse perinatal outcomes.[5] Cause of stillbirth may remain elusive in a significant number of cases despite extensive workup or due to failure of appropriate workup at the right time.

Maternal Factors: Stillbirths can also occur as an intrapartum complication and is of particular concern in neglected and mismanaged labor. Hence, institutional delivery is recommended for all.

Fetal: Monochorionic twins have higher incidence of stillbirth is due to the unique complications secondary to placental sharing. Monoamniotic twins have a higher risk of stillbirth due to the risk of

Table 1: Aetiology of Stillbirth

Maternal	Fetal	Placental
Risk Factors	Fetal Growth Restriction (FGR)	Placental insufficiency; FGR
Nulliparity	Multiple Gestation particularly Monochorionic twins including twin to twin transfusion syndrome	Placental abruption
Age		Cord prolapse
Obesity	Feto-Maternal Haemmorhage	Ruptured vasa praevia
Excessive weight gain in pregnancy	Fetal Anemia e.g. Rh isoimmunisation	Anatomical disorders
Cigarette smoking	Major Birth Defects	Placental chorio-angioma
Substance abuse	Genetic	Nuchal cord
Alcohol consumption	Autosomal Recessive Metabolic disorders e.g. galactosialidosis, sialic acid storage disease, neiman pick, GMI gangliosidosis type I, gaucher's disease	
Previous still birth	Hemoglobinopathies e.g. thalassemia	
Medical Diseases	Amino acid disorders e.g. glutaricaciduria type II	
Diabetes	Peroxisomal disorders e.g. zellweger syndrome	
Hypertension	Amniotic Fluid Abnormalities e.g. oligohydramnios, polyhydramnios	
Chronic renal disease		
Antiphospholipid syndrome		
Lupus erythematosus		
Maternal Infections		
Viral hepatitis E		
Malaria		
Syphilis		
Obstetric Complications		
Cholestasis of pregnancy		
Chorio-amnionitis		

cord entanglement. Fetal growth restriction (FGR) owing to placental insufficiency is identified in about 40–60% of stillbirths, also in otherwise unexplained stillbirths.[6] Many unexplained stillbirths are fetuses who fall in average for gestational age category when classified as per their weights but are actually growth restricted as there is significant lag in growth velocity. Post –term pregnancy is an independent risk factor for stillbirth. This may be due to progressive uteroplacental insufficiency when the pregnancy progresses past term.

Predictive Markers of Stillbirths

The Stillbirth Collaborative Research Network study found stillbirth risk factors known at the start of pregnancy accounted for only a small fraction of stillbirth risk.[7] Understanding the circumstances of the previous stillbirth is important for counseling about stillbirth recurrence risk and planning care for current pregnancy. The association of the risk factors and the estimated rate of stillbirth[8] is shown in table 2.

Table 2: Maternal factors and estimated Rate of Stillbirth

Conditions	Estimated Rate of Stillbirth (per 1000 births)	Odds Ratio
All pregnancies	6.4	1.0
Low risk pregnancies	4.0-5.5	0.86
Chronic hypertension	6-25	1.5-2.7
Pregnancy induced hypertension: MILD	9-51	1.2-4
Pregnancy induced hypertension: SEVERE	12-29	1.8-4.4
Diabetes: DIET ALONE	6.0-10	1.2-2.2
Diabetes: INSULIN+DIET	6.0-35	1.7-7
SLE	40-150	6-20
Renal disease	15-200	2.2-30
Thyroid disease	12-20	2.2-3.0
Thrombophilia	18-40	2.8-5.0
Cholestasis of pregnancy	12-30	1.8-4.4
Smoking of >10 cigarettes	10-15	1.7-3.0
Obesity: BMI 25-29.9	12-15	1.9-2.7
Obesity: BMI >30	13-18	2.1-2.8
Prior FGR (<10%)	12-30	2.0-4.6
Prior stillbirth	9-20	1.4-3.2
Multifetal gestation: TWIN	12	1.0-2.8
Multifetal gestation: TRIPLET	34	2.8-3.7
Maternal age: 35-39 YRS	11-14	1.8-2.2
Maternal age: >/=40 YRS	11-21	1.8-3.3

Biochemical Markers: The placenta is a powerful source of hormones and other placenta-derived proteins, which can be measured in the maternal circulation. Abnormal placental function measured either by aberration of the placental blood flow resistance or production of placenta-derived proteins, is associated with fetal growth restriction. Thus, this supports the role of placental hormones as a proxy for abnormal placental function and as a predictor of stillbirth. In the FASTER trial, elevated Alfa-feto-protiens, human chorionic gonadotropin (hCG), and inhibin A at or above 2.0 MoMs, each showed a significant association with fetal death at more than 24 weeks of gestation. However, the presence of two or more abnormal markers, although associated with fetal death at more than 24 weeks, was a poor predictor and does not support the use of these markers for screening for stillbirth in a general population.[9] The incorporation of these markers to more comprehensive algorithms may be the key to a better predictive performance regarding SGA and term stillbirth.

Monitoring Fetal Growth

Clinical monitoring: The measurement of fundal height in weeks is subjective. The plotting of symphysio-fundal height serially on growth charts (figure 1) has better accuracy for detecting FGR.[10] The sensitivity for the detection of SGA has increased from 29% to 48% with the use of growth charts.

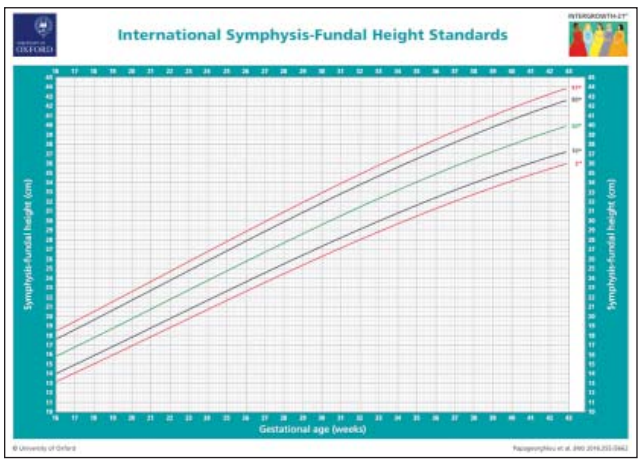

Figure 1: International Standards for Symphysio-Fundal Height

Ultrasound growth charts: Although in pregnancy ultrasound has several benefits, the current practice of ante-natal ultrasound in pregnancy (after 24 weeks gestation) has not demonstrated

benefit in reducing stillbirths.[11] The main limitation of an ultrasound-based program for the detection of SGA at term is effectively differentiating physiologically small babies from SGA babies compromised by placental dysfunction (reducing false-positives) and identifying the burden of disease in placental dysfunction where fetuses are still normal-sized (reducing false-negatives). Stillbirth is strongly associated with fetal growth restriction. The risk factors and potential causes of stillbirth and fetal growth restriction largely overlap. **The main purpose of the management of fetal growth restriction is the prevention of stillbirths**. The risk of stillbirth is relative to the degree of growth restriction, with the highest risk of stillbirth for those delivering the most growth-restricted fetuses. Fetuses weighing under the 10th centile are found approximately 2–3 times more frequently among stillbirths than live births.[12] The accuracy of the diagnosis of fetal growth restriction can be increased by serial ultrasound estimates of fetal weight. This is because serial estimates allow assessment of the rate of growth or the trend of declining growth.

Confounding the relationship between birthweight and stillbirth is the finding that intrauterine stillbirths progressively lose 20%–25% of body weight in utero through maceration in the time interval between demise and delivery due to shrinkage in fetal mass by dehydration.[13] Accounting for the post-demise fetal weight loss, the true prevalence of SGA births in stillbirth at term is near 20%–25%, meaning that the majority of adverse pregnancy outcomes occur in fetuses with average gestational weight but probably faltered growth velocity.[14]

Large for Gestational Age confers a significantly increased risk of stillbirth for pregnancies reaching 36 weeks' gestation, independent of maternal diabetes status. LGA fetus may benefit from antenatal testing starting at 36 weeks. In the setting of reassuring fetal testing, a reasonable delivery target would be 39 weeks in order to balance the risk of stillbirth with the risks associated with early term births.[15]

Umbilical and Uterine Artery Doppler: The fetal monitoring method that has been associated with a decrease in perinatal mortality is umbilical artery Doppler velocimetry in high-risk pregnancies including those with fetal growth restriction. There is a growing evidence for the use of uterine, umbilical, and middle cerebral artery Doppler indices - even in fetuses with abdominal circumference/EFW above the 10th centile as markers of FGR. FGR in current pregnancy is a very important risk factor for stillbirth. These Doppler parameters have utility in the detection of placental hypoperfusion (uterine Doppler) and fetal redistribution (umbilical and middle cerebral artery Doppler), as functional parameters with superior performance to isolated fetal biometric measurements.[16] There is emerging evidence of role of materno-fetal vessel dopplers in predicting adverse fetal outcomes particularly FGR both in AGA and SGA categories.

Antiphospholipid Antibodies (APS): APS in addition to thrombotic events, has been linked to stillbirths. An increased risk for pregnancy morbidity in women with APS is seen with a history of systemic lupus erythematosus (SLE), thrombosis, previous adverse pregnancy outcomes, and low complement levels in the first trimester. Patients with SLE have a 15% to 25% risk of stillbirth.[17]

Decreased Fetal Movements: Fetus at risk may stop movement to conserve energy in the presence of placental dysfunction. Decreased fetal movement at or near the end of the pregnancy places the pregnancy at substantial increased risk of poor pregnancy outcome. However, there is no evidence that fetal kick count monitoring is useful in all pregnancies or that it helps to prevent stillbirths. Despite this, fetal movement counting is recommended for all pregnancies.

Antepartum Fetal Testsing: Tests for fetal well-being: Although evidence to support the ability of the BPP and the MBPP to reduce stillbirth is lacking, the American College of Obstetrics and Gynecology supports starting testing no earlier than 32 weeks of gestation for high-risk pregnancies and sooner only if delivery is considered to impact perinatal benefit.[18] Vibroacoustic stimulation has also not been shown to reduce stillbirth rates.

Prediction Models: Multiparameter models and predictive algorithms using maternal risk factors, and biochemical and Doppler parameters have been developed, but need to be prospectively validated to demonstrate their effectiveness. Some authors have proposed a multiparameter validated algorithm with the objective of identifying fetuses

at high risk for fetal demise: the Individual Risk assessment (IRIS) prediction model. The combination of three antenatal factors (gestational age, parity, and cerebroplacental ratio) and three intrapartum factors (use of epidural, induction of labor, and use of oxytocin) can be used to assess the risk for intrapartum compromise requiring operative delivery. The IRIS algorithm demonstrated moderate to good discrimination and no sign of poor fit, and is available as a smartphone app to aid clinical decision making regarding the mode of delivery for SGA fetuses (https://mail13240.wixsite.com/website). Whether such management protocols or algorithms can improve pregnancy outcome can only be evaluated in adequately powered, blinded trials.[19]

Strategies for Prevention of Stillbirths

Stillbirth can be prevented by addressing and treating infections, malnutrition, non-communicable

diseases, lifestyle factors, preterm labor and post-term birth. Addressing birth control in adolescents, pregnancy spacing and poverty will also benefit. We must strive to provide access healthcare resources, which will help women to prepare for pregnancy. This includes providing effective antenatal care and support, folic acid supplementation, family planning services, intermittent treatment of sexually transmitted infections (syphilis), smoking cessation counseling, screening and management of maternal illnesses, and the detection and management of fetal growth restriction and other fetal disorders.

Perinatal audits may help to reduce the stillbirth rate. This is impacted by the accuracy and reliability of recording and retrieving stillbirth information from delivery or birth records.

Women and families with a stillbirth in current or previous pregnancy need emotional and psychological support

Approach for Women with No Prior Stillbirth

Intensive surveillance of development of pregnancy complications in the early part of gestation itself by employing inverted pyramid of pre-natal care.

- Routine ante-natal care like early booking and high risk triage
- Screening for diabetes, pre-eclampsia and aneuploidy
- Management of any ante-natal complications as warranted
- Institutional delivery
- Appropriate postnatal and neonatal care

Because nearly half of all stillbirths are associated with fetal growth restriction, serial monitoring of growth using growth charts should be performed. Primary triage in low risk pregnancies is clinical serial plotting of SFH, whereas in high risk pregnancies or if there is clinical suspicion of growth restriction, serial sonographic biometric assessment should be resorted to.

Existing evidence strongly supports infection control measures including syphilis screening and treatment and malaria prophylaxis in endemic areas, for preventing antepartum stillbirths. These interventions should be incorporated into antenatal care programs based on attributable risks and burden of disease.[20]

Approach for Women with Prior Stillbirths

Evaluation of the index pregnancy when the fetal demise had occurred is of paramount importance in guiding care for the next pregnancy.

Determining the cause and identifying the time of prior stillbirth are integral elements to plan the strategy of stillbirth prevention in next pregnancy. The most important opportunity to explore the cause of the index stillbirth is at the time of the event. At the time of stillbirth, tests should be conducted in accordance with the clinical picture. All parents should be offered an autopsy or equivalent, placental pathology, genetic testing from fetal source, and testing for feto-maternal hemorrhage. At the initial booking visit, if the previous stillbirth was not adequately investigated, it should be noted that no universal tests are recommended. Clinical history and workup at the time of stillbirth should be used to guide testing on a case-by-case basis.[21] Verbal autopsy is a beneficial tool to evaluate SB in limited resource settings. But many a times, the death was assigned to 'unexplained' category due to non-investigation or under-investigation, in such cases treatment for placental causes may improve outcomes.

An outline of approach for care for these women is as follows:

Preconception or Initial Prenatal Visit

- Detailed medical history (diabetes, hypertension, autoimmune conditions, infections), examination and prenatal optimization of medical condition if any
- Obstetric history: Evaluation/workup/review of previous stillbirth- Universal preconception and antenatal tests are not recommended, but specific tests based on the clinical scenario might help guide management in the subsequent pregnancy.
- Antiphospholipid antibodies / Thrombophilia workup depending on previous pregnancy circumstances
- Determination of recurrence risk: Stratified on basis of cause of previous still birth and other known maternal risk factors
- Modifiable risk factors for stillbirths like alcohol, smoking, substance abuse, obesity, undernutrition should be appropriately addressed.
- Genetic counseling if family genetic condition exists or evidence/suspicion of genetic disorder in index fetus

Families have increased psychosocial needs in pregnancies after stillbirth. Respectful and supportive care is essential, including bereavement care after a stillbirth.

During Pregnancy: Management plan depends on cause of previous stillbirth.

- Early booking from first trimester onwards
  - o Dating ultrasonography by crown-rump length
  - o First-trimester aneuploidy and PE screen: Pregnancy associated Plasma protein-A (PAPP-A), hCG, and nuchal translucency, Placental growth factor (PlGF), Uterine Artery Pulsality Index, Mean arterial pressure, etc
  - o Diabetes screen
  - o Appropriate prenatal testing if indicated (genetic cause)
- Close surveillance in current pregnancy is warranted with intensified maternal and fetal monitoring at least two weeks prior to the gestational age of previous demise. Some women may require admission electively or opt for it and such cases need to be individualized.
  - o Serial sonograms with biometry plotting on growth charts to rule out fetal growth restriction, starting at 28 weeks and to be considered earlier (24-26 weeks) in women where loss was at earlier gestation
  - o Antepartum fetal surveillance starting at 32 weeks or 1–2 weeks earlier prior to gestational age of previous stillbirth as clinically appropriate. Antepartum fetal testing, such as twice weekly nonstress tests and amniotic fluid index or biophysical profiles, may be initiated at 32 weeks or 1–2 weeks before the gestational age of the previous stillbirth as clinically appropriate. Caution must be used when interpreting the antepartum fetal surveillance of a fetus at less than 32 weeks of gestation. At 28 weeks of gestation, only approximately 60% of normal fetuses will have reactive nonstress testing.[18] This is not a result of uteroplacental insufficiency but reflects the immature fetal autonomic nervous system.
- Individual care plans are required for women during a pregnancy following stillbirth.
- When the cause of the previous stillbirth is known, appropriate treatment of the underlying cause may reduce the risk of recurrence.
- Unexplained or unexplored stillbirths, as well as those related to fetal growth restriction and early or severe pre-eclampsia, may be attributed to placental insufficiency. In these cases, the use of low-dose aspirin (LDA) may be beneficial.[21]
- In women with antiphospholipid antibody syndrome or known thrombophilias, low-molecular-weight heparin therapy is initiated but there is no role in cases of previous stillbirths where these diseases are not present.
- Cases where the index stillbirth is known to be obviously of a nonplacental, nonrecurrent cause, such as cord accident or infections (TORCH, malaria, hepatitis E), may not require additional treatment or increased frequency of monitoring and ultrasound, though women need reassurance in current pregnancy and care may be tailored accordingly.
- Evidence does not support the use of third-party leukocyte immunization, intravenous IgG and progestogen therapies for prevention of recurrent stillbirth.[3]
- Delivery plan to be formulated in advance-of the third trimester: Decisions around timing of birth should incorporate the circumstances

surrounding the previous stillbirth, the clinical picture of the current pregnancy and the wishes of the couple. In select cases, there may be a role of early term (37–39weeks) birth. There is no evidence for delivery before 37 weeks based on the risk factors of stillbirth alone.[21]

- Intrapartum care- High quality obstetric and midwifery care should be universally available. Childbirth must be provided with skilled attendants who can perform assisted vaginal deliveries and cesarean sections for fetal and maternal indications. Of all stillbirths, half occur during birth. Seventy-five percent of these are preventable with access to quality care. The ability to provide induction of labor for premature rupture of membranes and post-term pregnancy needs to be addressed. Continuous cardiotocography, when compared to no or intermittent cardiotocography, was associated with higher cesarean rates but less neonatal seizures and improvement in stillbirth.[22]

Conclusion

The challenges to be overcome in preventing stillbirths are:

Incomplete workup of index case: Few reasons are the unwillingness of parents for fetal autopsy due to ethical and religious reasons, non-availability of resources, poor follow-up of patients for further screening for medical causes and psychological trauma due to stillbirth experience.

The dilemma of unexplained stillbirth seems far from resolution.

Furthermore it is probable that there is heterogeneity of many of the antecedent causes

However, for improvement in prediction and prevention of stillbirth, modifiable risk factors should be targeted. To date there are no effective methods of stillbirth prevention. Effective risk assessment algorithms using combinations of maternal, ultrasonic, and biochemical measures need to be developed similar to aneuploidy or preclampsia screening.

References

1. Maslovich MM, Burke LM. Intrauterine Fetal Demise. NCBI Shelf. A service of the National Library of Medicine, National Institutes of Health. 2020 Jan. Last Update: May 23, 2020.
2. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I et al. Lancet's Stillbirths Series steering committee. Stillbirths: Where? When? Why? How to make the data count? Lancet. 2011 Apr 23;377(9775):1448-63. [PubMed: 21496911]
3. Wojcieszek AM, Shepherd E, Middleton P, Lassi ZS, Wilson T, Murphy MM et al. Care prior to and during subsequent pregnancies following stillbirth for improving outcomes. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD012203. DOI: 10.1002/14651858.CD012203.pub2
4. Newtonraj A, Kaur M, Gupta M, Kumar R. Level, causes, and risk factors of stillbirth: a population-based case control study from Chandigarh, India. BMC Pregnancy and Childbirth 2017: 17, 371 DOI 10.1186/s12884-017-1557-4
5. Bililign YN, Tenaw Z, Solomon K, Mulatu T. Inadequate Prenatal Visit and Home Delivery as Determinants of Perinatal Outcomes: Does Parity Matter? J Pregnancy. 2019; 1-9. Doi:10,1155/2019/9024258
6. Flenady V, Koopmans L, Middleton P, Frøen JF, Smith GC, Gibbons K et al: Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. Lancet 2011, 377, 1331–1340.
7. Stillbirth Collaborative Research Network Writing Group. Causes of death among stillbirths. JAMA. 2011 Dec 14;306(22):2459-68. [PMC free article: PMC4562291] [PubMed: 22166605
8. Cunningham SG,Leveno KJ, Bloom SL, Dashe JS, Hoffman VL, Casey BM et al. Estimated maternal risk factors and risk of stillbirths. Williams Obstet 25;35:644-50.
9. Dugoff L, Hobbins JC, Malone FD, Porter TF, Luthy D, Comstock CH, et al. First-trimester maternal serum PAPP-A and free-beta subunit human chorionic gonadotropin concentrations and nuchal translucency are associated with obstetric complications: a population-based screening study (the FASTER Trial). Am J Obstet Gynecol 2004;191:1446–51
10. Papageorghiou AT, Ohuma EO, Gravett MG, Hirst J, daSilveira MF, Lambert A et al.Inetrnational standards for symphysio-fundal height based on serial measurements from fetal growth longitudinal study of the INTERGROWTH-21st project:prospective cohort study in eight countries. BMJ 2016;355:i5662.
11. Bricker L, Medley N, Pratt JJ. Routine ultrasound in late pregnancy (after 24 weeks' gestation). Cochrane Database Syst Rev. 2015 Jun 29;(6):CD001451. [PMC free article: PMC7086401] [PubMed: 26121659]
12. Getahun D, Ananth CV, Kinzler WL. Risk factors for antepartum and intrapartum stillbirth: a population-based study. Am. J. Obstet. Gynecol. 2007 Jun;196(6):499-507. [PubMed: 17
13. Man J, Hutchinson JC, Ashworth M, Heazell AE, Levine S, Sebire NJ. Effects of intrauterine retention and postmortem interval on body weight following intrauterine death: implications for assessment of fetal growth restriction at autopsy. Ultrasound Obstet Gynecol. 2016;48(5):574–8.
14. Coutinho CM, Melchiorre K, Thilaganathan B. Stillbirth at term: Does size really matter? Intern J of Obstet and Gynecol. https://doi.org/10.1002/ijgo.13229

15. Ebony B, Carter EB, Stockburger J, Tuuli MG, Macones GA, Odibo AO, Trudell AS. Large for gestational age and stillbirth: Is there a role for antenatal testing? Ultra in Obstet and Gynecol.2018 Doi: 10.1002/uog.20162
16. Khalil A, Morales-rosello J, Townsend R, Morlando M, Papageorghiou A, Bhide A et al:Value of third-trimester cerebroplacental ratio and uterine artery Doppler indices as predictors of stillbirth and perinatal loss.Ultrasound Obstet Gynecol 2016;47:74-80.
17. Fredi M, Andreoli L, Aggogeri E, Bettiga E, Lazzaroni MG, Le Guern V. Risk Factors for Adverse Maternal and Fetal Outcomes in Women With Confirmed aPL Positivity: Results From a Multicenter Study of 283 Pregnancies. Front Immunol. 2018;9:864. [PMC free article: PMC5949611] [PubMed: 29867924]
18. Reddy UM. Prediction and Prevention of Recurrent Stillbirth. Obstet gynecol. 2007; 110, 1151-1164
19. Kalafat E, Morales-Rosello J, Scarinci E, Thilaganathan B, Khalil A. Risk of operative delivery for intrapartum fetal compromise in small-for-gestational-age fetuses at term: external validation of the IRIS algorithm. J Matern Neonatal Med [Internet]. 2019;0(0):1–10. Available from: https://doi.org/10.1080/14767058.2018.1560412
20. Menezes EV, Yakoob MY, Soomro T, Haws RA, Darmstadt GL, Bhutta ZA. Reducing stillbirths: prevention and management of medical disorders and infections during pregnancy. *BMC Pregnancy and Childbirth* 2009, 9(Suppl 1):S4- 2009. doi: 10.1186/1471-2393-9-S1-S4
21. Ladhani NNN, Fockler ME, Stephens L, Barrett JFR, Heazell AEP. No. 369-Management of Pregnancy Subsequent to Stillbirth. J Obstet Gynaecol Can 2018;40(12):1669–1683. Doi: 10.1016/j.jogc.2018.07.002
22. Devane D, Lalor JG, Daly S, McGuire W, Smith V. Cardiotocography versus intermittent auscultation of fetal heart on admission to labour ward for assessment of fetal wellbeing. Cochrane Database Syst Rev. 2012 Feb 15;(2):CD005122. [PubMed: 22336808]

AOGD Events Held

On 17th February 2020, Web CME on **"Optimizing Menopausal Health"** was held under the aegis of IMS Delhi Chapter & QI Committee of AOGD.

On 25th November 2020, E-CME on **"Urogynaecology Master Class"** was held under the aegis of Urogynaecology committee of AOGD.

On 26th November, **"FOGSI-JOGI-E-PICSEP 2020 Webinar"** was held under the aegis of AOGD.

On 27th November, "**AOGD Monthly Meeting"** was organized by MAMC & LNJP Hospital, New Delhi.

On 28th November, "**Virtual CME on Diabetes in Pregnancy: Providing Optimum Care" was held under** the aegis of Quality Improvement and Safe Motherhood Committee of AOGD & Delhi Diabetic Forum to celebrate World Diabetes Day.

On 29th November, **"Sankalp travelling workshop for FP, Updates in contraception: Part-1"** was conducted by Department of Obstetrics & Gynaecology UCMS & GTB Hospital, Delhi.

On 10th December 2020, **"FAQ on Ovarian Cyst"** was conducted under the aegis of AOGD.

Forthcoming Events

On 18th December 2020, "**AOGD Monthly Meeting"** will be organized by Sir Ganga Ram Hospital, New Delhi.

On 20th December 2020, **"Panel on IUGR"** will be conducted under the aegis of AOGD

Rational Use of Antenatal Corticosteroids

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The survival of preterm neonates has improved a lot in last thirty years and the better respiratory management of these neonates is one of the extremely important reasons for that. Along with better ventilation strategies, early and more widespread use of CPAP & surfactant, antenatal corticosteroids (ACS) have made the respiratory care much better in current neonatal units. It all started in 1969 when Liggins observed that lambs who received ACS and then delivered prematurely had relatively partially expanded lungs.[1] This led to a human RCT involving 282 mothers who were at risk for preterm delivery, to assess the effect of ACS on neonatal morbidity which showed reduction in respiratory distress syndrome (RDS). This finding was reconfirmed in multiple subsequent trials followed by first Cochrane review in 1996 which has been recently updated. The recent Cochrane review (2017) consolidating results of multiple RCTs confirmed the results that ACS not only reduces the risk of RDS but also has significant impact in preventing other morbidities such as necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), need for mechanical ventilation as well as mortality.[2] For these reasons ACS for pregnancies at risk of preterm delivery between 24 and 34 weeks is a standard of care as recommended by WHO and obstetric societies worldwide.

However, there are still many questions regarding the use of ACS which are unanswered and needs further research. This article aims to address various controversial aspects of steroid use during antenatal period so as to use ACS rationally in our day to day practice.

1. **Choice of ACS**

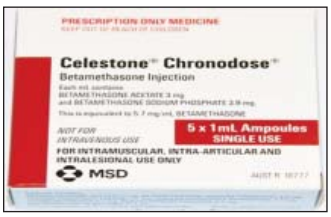
   Betamethasone and dexamethasone have both been acceptable options differing by only 1 methyl group and are noted to cross placenta without getting metabolized by placental enzyme. They both have high affinity towards the glucocorticoid receptor with minimal mineralocorticoid activity. Standard treatment dose consists of two 12-mg doses of betamethasone given intramuscularly 24 hours apart or four 6-mg doses of dexamethasone administered intramuscularly every 12 hours. Best effect is expected 24 hours after the last dose.

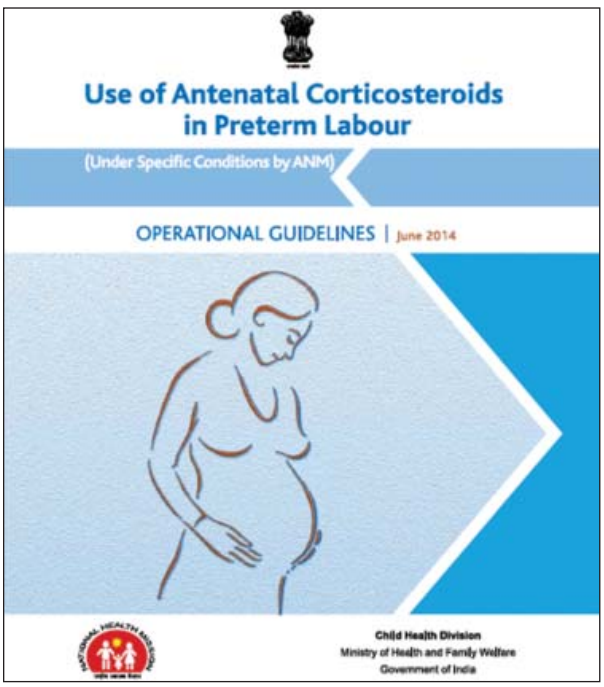
   Despite having similar biological activity, there are no clear evidence confirming superior clinical efficacy of one steroid over another and also there are only few direct comparisons between them. In 2013 Cochrane review which included 12 RCTs to assess the superiority of 1 corticosteroid over the other found that dexamethasone was associated with a reduced risk of IVH compared with betamethasone (RR, 0.44; 95% CI, 0.21–0.92). In addition, in one trial significantly shorter stay in NICU was noted in those exposed to dexamethasone. In contrast Lee and colleagues found decreased likelihood of impaired neurodevelopmental status and reduced risk of hearing impairment among those who were exposed to betamethasone as compared with dexamethasone in antenatal period. Results of STEROID trial which randomized 1500 women at risk of preterm birth comparing the two steroids with primary outcome of death or any neurosensory disability in children at two years of age is awaited. Due to present insufficient evidence supporting the recommendation of one corticosteroid regimen over the other, choice of ACS use is based on provider preference, ease of administration, cost, and availability.

   The route of ACS has been preferably intravenous (IV) only and the trial of oral dexamethasone as compared to IV dexamethasone has shown to be associated with increased risk of sepsis (15.9 vs 1.6%, P=0.009) and IVH (15.9 vs 3.3%, P=0.03).[3]

   There is a very India specific issue related to ACS which needs to be discussed before making a final decision regarding the choice of ACS. Most of trials globally have been done on Celestone

(MSD) which is a combination of betamethasone acetate and betamethasone sodium phosphate. Unfortunately in India the only betamethasone preparation available (Betnesol; GSK) contains only betamethasone sodium phosphate and hence the use of this preparation is not expected to show similar results to that of celestone. There are no trials with this preparation to support its use. Keeping this fact in mind along with the cost and easy availability of dexamethasone, Govt of India, Ministry of health and welfare have issued guidelines on the use of dexamethasone for all expected preterm deliveries between 24-34 weeks of gestation.





2. **Use of ACS in previables**

With advancement of neonatal care and documented increased survival rates of approximately 25-35% for infants born at 22 weeks' gestation, limits of viability is ever changing and tends to be pushed further lower.[4] Observational data from NICHD Neonatal Research Network demonstrated a significant reduction in death or neurodevelopmental impairment at 18 to 22 months for neonates who had been exposed to ACS and born at 23 weeks' gestation (83.4% with steroids vs 90.5% without steroids; adjusted odd ratio [AOR], 0.58; 95% CI, 0.42–0.80).[5] There was no significant difference in these outcomes but was associated with significant less death or NEC (73.5% with steroids vs 84.5% without steroids; AOR, 0.54; 95% CI, 0.30–0.97) at 22 weeks of gestation. This led to consideration of steroids for pregnant women starting at 23+0 weeks of gestation" at risk of preterm delivery within seven days by ACOG in its most recent Committee Opinion update. This is amenable to change in future with further improvement in neonatal care.

3. **ACS in late preterm**

Despite the fact that late preterms comprise 70% of total preterm birth, use of ACS in this group is still controversial. In the original NIH recommendation (1995), there was no consideration of extended use of steroids beyond 34 weeks because of lack of studies showing benefit and misbelief that late preterms have almost similar outcomes as that of term.[6]

Antenatal Late Preterm Steroids (ALPS) trial, double-blinded, placebo-controlled, randomized, controlled trial assessed 2831 women with a singleton gestation, who were at high risk for preterm birth between 34 0/7 and 36 6/7 weeks' gestation between 2010 and 2015.[7]randomized trial involving women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation who were at high risk for delivery during the late preterm period (up to 36 weeks 6 days In this trial need for respiratory support within the first 72 hours of life (14.4% vs 11.6%; RR, 0.80; 95% CI, 0.66–0.97) along with significant decreases in the rates of severe respiratory morbidity, bronchopulmonary dysplasia, transient tachypnea of the newborn, the need for resuscitation at birth, and the need for postnatal surfactant was demonstrated (Table 1). Neonates treated with betamethasone did have an increased risk of hypoglycemia (24% vs 14.9%; RR, 1.61; 95% CI, 1.38–1.88). Also patients treated with ACS as compared to placebo had increased risk of clinical chorioamnionitis, endometritis, or cesarean delivery.

Table 1: Results of ALPS trial

Outcome	Placebo (n=1400) n (%)	Betamethasone (n=1427) n (%)	RR(95%CI)	P val	NNT/NNH
Primary outcome	202(14.4)	165(11.6)	0.80(0.66-0.97)	0.023	35.7
Severe respiratory morbidity	169(12.1)	115(8.1)	0.67(0.53-0.84)	<0.001	25
RDS	89(6.4)	79(5.5)	0.87(0.65-1.17)	0.356	
TTN	138(9.9)	95(6.7)	0.67(0.53-0.87)	0.002	31.25
Surfactant use	43(3.1)	26(1.8)	0.59(0.37-0.96)	0.031	76.9
Chorioamnionitis	32(2.3)	20(1.4)	0.61(0.35-1.07)	0.080	
Proven neonatal sepsis	11(0.8)	9(0.6)	0.80(0.33-1.93)	0.623	
Neonatal hypoglycemia(<40mg/dl)	210(15.0)	343(24.0)	1.60(1.37-1.87)	<0.001	11.1
Gestation at delivery	36.1±8.2	36.1±7.5		0.517	
Time from initial dose to delivery (hours; median(Q3,Q1)	30.6(14.6-111)	33(15.2-111.6)		0.565	

NNT=number needed to treat; NNH= number needed to harm; RDS= respiratory distress syndrome; TTN= transient tachypnea of neonate

In ALPS study benefit was shown despite the fact that only 60% of enrolled women received the full course of two doses of betamethasone before delivery and tocolysis was not routinely administered. Notably ACS have not adequately been studied for all women with threatened late preterm birth as women with pre-gestational diabetes, multiple gestations, or who had received previous ACS were excluded from the study. It is important to draw pertinent conclusions from ALPS; numbers needed to treat for primary outcome (respiratory morbidity) is 35.7 while numbers needed to harm for hypoglycemia is 11.1. It means in simple terms that if ANS is given to 35.7 late preterm neonates, one preterm would be saved from respiratory distress but 3.2 neonates would have hypoglycemia. The risk of hypoglycemia becomes much more relevant as most of these neonates are cared with mother in most situations without routine blood sugar monitoring.

A recent meta-analysis of three trials, including ALPS, had similar conclusions to the ALPS trial. (Table 2).[8]

Table 2: Results of outcome of RCTs included in meta-analysis by Saccone et al for effect of ACS for fetal maturity at term or near term gestation

STUDY	Hypoglycemia %
Balci, et al (2010)	Not reported
Porto et al (2011)	11 vs 7 (NS)
Ramadan et al (2016)	20.3 vs 10.9 (p<0.04)

World Health Organization's (WHO) guidelines on interventions to improve preterm birth outcomes last updated in 2015 and RCOG Green-top Guideline on ACS published in 2010 both before the ALPS study does not recommend the use of ACS in late preterms. But current ACOG guidelines say "a single course of betamethasone is recommended for pregnant women between 34+0 weeks and 36+6 weeks of gestation at risk of preterm birth within 7 days, and who have not received a previous course of ACS."[9] It's also worth mentioning here that these recommendations are still with betamethasone acetate and betamethasome sodium phosphate combination and not with betamethasone sodium phosphate and definitely not with dexamethasone as there are no trials with dexamethasone in late preterms.

4. **ACS in Early term**

Infants born at 37 0/7 weeks to 37 6/7 weeks are at 1.7 times increased risk for respiratory complications than those born between 38 0/7 and 38 6/7 weeks' gestation; and these neonates are at 2.4 times increased risk than those born between 39 0/7 and 39 6/7 weeks' gestation. These risks are even higher for infants born via planned cesarean section, prior to the onset of labor.[10]

The Antenatal Steroids for Term Caesarean Section (**ASTECS)** randomized trial tested whether ACS reduce respiratory distress in neonates born by elective cesarean section at term and found significantly decreased

rates of RDS requiring admission to the NICU (RR, 0.46; 95% CI, 0.23–0.93) in the treatment group.[11] Similarly, Cochrane review, updated in 2018---comparing ACS (either betamethasone or dexamethasone) to placebo or control prior to planned cesarean delivery at term (3956 women and four trials) concluded that ACS decrease the risk of RDS by approximately 50% and TTN by approximately 60% and NICU admission rates for respiratory complications by 55%.[12]However, the quality of evidence for all of these outcomes was rated as low.

Only long term outcome reported by ASTECS2 at 8-15 years found overall no adverse consequences from a single ACS course at term.[13] Though, lower proportion of children in the ACS group were perceived to be in the top quartile of achievement (p=0.03) by their teachers, no significant differences were found in any other outcomes between the groups, including objective assessments of achievement and test scores. Larger randomized trials with longer follow up are needed to resolve the conflict in recommendation in this group by varying national obstetrical societies.

5. **Rescue dosing versus repeated dosing**

There are some studies which shows that beneficial effect of antenatal steroids diminishes beyond seven days of administration.[14] It is seen that less than 10% of women that present in preterm labor deliver within seven days.[15] 24-35 This led to weekly administration of steroids till delivery to ensure steroid coverage within one week of delivery. A meta-analysis in 2015 of ten randomized controlled trials involving 4700 women and 5700 babies compared those that received a single course of ACS to those with multiple courses.[16] The results showed a decreased risk of RDS and severe lung disease with concomitant increased risk of reduced birth weight. It is thus a difficult clinical challenge for providers to balance the risk of imminent preterm birth and avoiding additional doses of ACS. Rescue course regimen of steroid was evaluated in a multi centric RCT in 2009 where women<33+0 weeks who had received a course of ACS at least 14 days previously and were judged to have a recurring threat of preterm labor within the next seven days were either administered one additional course or placebo.[17] A decreased risk of RDS, ventilator support and surfactant use with repeat ACS with no documented difference in birth weight, intrauterine growth restriction or head circumference in either group was found by author in the group of women who received an additional dose of steroids. Long term outcome from multiple Courses of ACS trial (at 5 years) and the Australasian Collaborative Trial of Repeat Doses of Corticosteroids for the Prevention of Neonatal Respiratory Disease (at 6-8 years-old) were reassuring without any increased risk of neurodevelopmental disability, cardiometabolic problems, or other serious outcome in those that received more than one course of ACS.[18,19] Also, body size and composition were similar in groups receiving multiple ACS courses compared to single courses. Currently ACOG recommends considerations of a single repeat course of ACS in women <34 0/7 weeks' gestation [<33 6/7 wks] who is at imminent risk of delivery within the next 7 days and in whom prior course of ACS was administered >14 days ago [as earlier as 7 days--WHO]. However maternal chorioamnionitis remains a contraindication of second course of antenatal steroids. RCOG guidelines are very conservative regarding the second course of antenatal steroids and recommend it only for mothers who have received first course before 26 weeks of gestation.

6. **Steroids in multiple gestation**

Preterm delivery is six times more likely to occur in women with multiple gestation as compared to them with singleton gestation.[20] Moreover, neonates from multiple pregnancies are also at an increased risk cerebral morbidity, including IVH and periventricular leukomalacia.[21]Only a small number of multiple gestations were included in the antenatal corticosteroid trials in recently updated systematic review.[2] This lack of robust data precluded a definite conclusion about the effectiveness of the therapy or the optimum dose. RDS in multiple gestations exposed to antenatal steroids has relative risk of 0.90, 95% CI 0.67-1.22; 4 trials, 320 infants. Current recommendation of a course of ACS to women with multiple gestations at risk of preterm delivery within seven days at less than 34+0 weeks' gestation by ACOG is based

on undeniable benefits of steroids in singleton pregnancy.[22] Theoretically higher doses of ACS may be required in multiple gestation but in a randomized trial similar levels of betamethasone was found in maternal and cord blood in singleton and multiple gestations.[23] Outcome data from a French cohort for ACS for twins between 24 and 31 weeks of gestation were comparable in those who received repeated courses versus a single course.[24] and further document the influence of the ACS-to-delivery interval. Design: EPIPAGE-2 is a nationwide observational multicentre prospective cohort study of neonates born between 22 and 34 completed weeks of gestation. Setting: All French maternity units, except in a single administrative region, between March and December 2011. Population: A total of 750 twin neonates born between 24 and 31 weeks of gestation. Methods: Exposure to ACSs was examined in four groups: single complete course, with an ACS administration-to-delivery interval of ≤7 days; single complete course, with an ACS-to-delivery interval of >7 days; repeated courses; or no ACS treatment. Main outcome measures: Neonatal outcomes analysed were severe bronchopulmonary dysplasia, periventricular leukomalacia or intraventricular haemorrhage grade III/IV, in-hospital mortality, and a composite indicator of severe outcomes. Results: Compared with no ACSs, in multivariable analysis, a single course of ACSs with an administration-to-delivery interval of ≤7 days was significantly associated with a reduced rate of periventricular leukomalacia or intraventricular haemorrhage grade III/IV (aOR 0.2; CI 95% 0.1–0.5 As per ACOG guidelines single rescue course of steroid is considered for multiple gestation.

7. **ACS in PPROM**

Reduction in the risk of RDS, IVH, NEC, and neonatal death without any increase in risk of maternal and neonatal infection has been demonstrated with the administration of a single course of ACS to women with a history of preterm rupture of membrane at gestation <34 weeks of gestation.[2] Also, single rescue course of steroids in PPROM has been found to be associated with short term benefits with no adverse long term effects in children followed at 6-8 years of age.[19]But in maternal chorioamnionitis ACOG recommends against use of second course of antenatal steroids.

8. **ACS in Low and middle income countries (LMIC)**

Though evidence for benefits of antenatal steroids are undeniable, there are several limitations in generalizing the results of recent evidence from Cochrane review to lower and middle income countries. All 30 trials included in this evidence were done in high resource setting, in high-income (20 trials) and upper middle-income (nine trials) countries, except one trial that was conducted in Tunisia (a lower middle-income country). In 2015, findings of antenatal corticosteroid trial (ACT) which was a community-based, cluster-randomised trial was published.[25] This multicentric trial conducted in six LMIC -Argentina, Guatemala, India, Kenya, Pakistan and Zambia capturing nearly 100000 live births was aimed to evaluate effectiveness and feasibility of multiple interventions designed to increase the use of ACS at all level of health care. While use of ACS was shown to be increased by fourfold there were few concerning findings which need reconfirmation before generalizing his practice in LMIC. (Table 3) These alarming findings included lack of benefit in the less-than-fifth-percentile newborns, evidence of increased perinatal mortality in larger newborns and the increase in suspected maternal infection.

Table 3: Results of antenatal corticosteroid trial

21 studies (7000+ Infants) – ACS led to Neonatal death<34weeks	21 studies (7000+ Infants) – ACS led to Neonatal deaths>36weeks	Maternal infection (Puerperal sepsis-3 studies)
30% lower	3.25 times high(CI-0.99-10.66)	1.35 times high (CI:0.93-1.95)

WHO recommends ACS for women at risk of preterm birth from 24 weeks to 34 weeks gestation in settings where certain criteria are met with:

- Gestational age assessment can be accurately undertaken
- Preterm birth is considered imminent
- There is no clinical evidence of maternal infection
- Adequate childbirth care is available (including the capacity to recognize and safely manage preterm labor and birth)

- The preterm newborn can receive adequate care if needed (including resuscitation, thermal care, feeding support, infection treatment and safe oxygen use)

9. **Safety concerns with ANS: short term/ long-term: impaired growth, hypoglycemia, hypertension, Poor glucose tolerance)**

   Long term studies by *Dalziel SR, 2005 in* 24-33 weeks gestation over 30 years have shown no side effects except mild insulin resistance. But similar long-term harmful effects of usage of ANS in late preterm and term pregnancies is not known. ASTEC trial in term pregnancies has shown some serious concerns related to developmental outcome. ASTECS trial compared administration of betamethasone 48 hours before planned cesarean delivery at ≥37 weeks to usual care. When follow-up was performed at 8 to 15 years of age, schools were more likely to perceive steroid-exposed children to be in the lowest achievement group compared with the control group. However, objective testing of academic ability was not performed as part of the trial and results from national standardized assessments did not show statistical differences between the scores for each group.

   There is a biological mechanism suggested for harmful effects of ANS in late preterm and term pregnancies. A surge in endogenous cortisol occurs near term when the fetus is in a critical period of brain development in preparation for parturition and transition to life ex utero. High levels of 11β-hydroxysteroiddehydrogenase-2 in the fetal brain help to protect it from the effects of the physiological rise in endogenous cortisol, but do not protect it from maternally administered betamethasone or dexamethasone due to the resistance of these drugs to metabolism by 11β-HSD-2. Thus, these steroids may cause unphysiological activation of glucocorticoid receptors in the fetal brain near term leading to potential of brain damage.

Key Messages

1. Single course of dexamethasone (6 mg 12 hrly four doses) is recommended by GOI MoFW for all threatened preterm births between 24-34 weeks of gestation (24 weeks to 33 weeks 6 days at start of therapy). ACOG recommend betamethasone acetate and betamethasone sodium phosphate combination (12mg 24 hrly two doses) or dexamethasone between 24-33 weeks of gestation. Use of ANS in 29-34 weeks has reduced the incidence of RDS and mortality while use in 24-28 weeks has not reduced the incidence of RDS but has reduced severity, mortality and risk of intraventricular hemorrhage.
2. Second course of ANS (only one more) is recommended by ACOG after 7-14 days of first course with gestation till 33 weeks except in maternal chorioamnionitis. RCOG recommends second course only if first course given at gestation less than 26 weeks.
3. Use of ANS in late preterm has respiratory benefits but has increased risk of hypoglycemia.
4. Use of steroids in term pregnancies has reduced transient tachypnea of newborn but long term follow up studies raise concerns.

Bibliography

1. Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol. 1969;45:515–23.
2. Roberts D, Brown J, Medley N, Dalziel SR. ACS for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;CD004454.
3. Egerman RS, Mercer BM, Doss JL, Sibai BM. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. Am J Obstet Gynecol. 1998;179:1120–3.
4. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics. 2013;132:62–71.
5. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, et al. Association of ACS with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. Obstet Gynecol Surv. 2012;67:215–7.
6. Wright LL. Effect of corticosteroids for fetal maturation on perinatal outcomes: Introduction. Am J Obstet Gynecol. 1995;173:253.
7. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374:1311–20.
8. Saccone G, Berghella V. ACS for maturity of term or near term fetuses: Systematic review and meta-analysis of randomized controlled trials. BMJ. 2016;355:1–10.
9. Antenatal corticosteroids therapy for fetal maturation. Committee opinionNo.713. American College of Obstetricians & Gynecologists. Obstet Gynecol 2017; 130:e 102-9.

10. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Semin Perinatol. 2006;30:34–43.
11. Stutchfield P, Whitaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: Pragmatic randomised trial. Br Med J. 2005;331:662–4.
12. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JPA, Mcgoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. Cochrane Database Syst Rev. 2018:CD006614.
13. Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJM. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed. 2013;98:195–200.
14. McLaughlin KJ, Crowther CA, Walker N, Harding JE. Effects of a single course of corticosteroids given more than 7 days before birth: A systematic review. Aust New Zeal J Obstet Gynaecol. 2003;43:101–6.
15. Fuchs IB, Henrich W, Osthues K, Dudenhausen JW. Sonographic cervical length in singleton pregnancies with intact membranes presenting with threatened preterm labor. Ultrasound Obstet Gynecol. 2004;24:554–7.
16. Crowther CA, Mckinlay CJD, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev. 2015;CD003935.
17. Garite TJ, Kurtzman J, Maurel K, Clark R. Impact of a "rescue course" of ACS: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol. 2009;200:248.e1-9.
18. Asztalos E V., Murphy KE, Willan AR, Matthews SG, Ohlsson A, Saigal S, et al. Multiple courses of ACS for preterm Birth study outcomes in children at 5 years of age (MACS-5). JAMA Pediatr. 2013;167:1102–10.
19. Crowther CA, Anderson PJ, Mckinlay CJD. Mid-Childhood Outcomes of Repeat ACS: A Randomized Controlled Trial. 2016;138:e20160947.
20. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final data for 2016. Vol. 67, National Vital Statistics Reports. 2018.
21. Rettwitz-Volk W, Tran TM, Veldman A. Cerebral morbidity in preterm twins. J Matern Neonatal Med. 2003;13:218–23.
22. Borders AEB, Gyamfi-bannerman C. Antenatal Corticosteroid Therapy for Fetal Maturation. Pediatrics. 2017;140:102–9.
23. Gyamfi C, Mele L, Wapner RJ, Spong CY, Peaceman A, Sorokin Y, et al. The effect of plurality and obesity on betamethasone concentrations in women at risk for preterm delivery. Am J Obstet Gynecol. 2010;203:219.e1–219.e5.
24. Palas D, Ehlinger V, Alberge C, Truffert P, Kayem G, Goffinet F, et al. Efficacy of ACS in preterm twins: the EPIPAGE-2 cohort study. BJOG An Int J Obstet Gynaecol. 2018;125:1164–70.
25. Althabe F, Belizán JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, et al. A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: The ACT cluster-randomised trial. Lancet. 2015;385:629–39.

Answer: December 2020 Issue

Crossword

Across

3. Eleven
4. Pappa
5. Six
7. Thirty Two
8. CPR
9. Magnet

Down

1. Dexamethasone
2. DIPSI
6. Torch
10. NMDA

Pictorial Quiz Answers

Ans. 1: Three distinct lines are seen at the level of the fetal nose:

a. The top line represents the skin.
b. The bottom one, which is thicker and more echogenic than the overlying skin, represents the nasal bone.
c. A third line in front of the bone and at a higher level than the skin represents the tip of the nose.

Ans. 2: The nasal bone is considered to the present if it is more echogenic than the overlying skin and absent if it is either not visible or its echogenicity is the same or less than that of the skin.

Antenatal Magnesium Sulphate for Fetal Neuroprotection: The controversies

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Introduction

Improving neurological outcomes in preterm births remains the most important objective of neonatologists and obstetricians alike. It also continues to be the unresolved issue in the care of preterm neonates. The causes of injury to preterm brain are numerous and include cerebral white matter injury, periventricular leukomalacia and intraparenchymal hemorrhage. Data from the National Institute of Child Health and Human Development (NICHD), Neonatal Research Network and EPICure studies[1] show the prevalence of moderate to severe disability to be ranging between 20-30% in preterm infants born at 26 weeks gestational age, with disability increasing further with decreasing gestational age. Abnormal neurological outcomes were seen in 25% of extremely low birth weight infants followed up till 2 years in Indian settings[2]. Multiple neuroprotective interventions have been attempted to reduce the morbidity in preterm neonates. Antenatal administration of Magnesium Sulfate (MgSO4) in mothers with threatened preterm labour to reduce neurological morbidity has been widely studied. In this article, we attempt to briefly review the role of antenatal MgSO4 in fetal neuroprotection and controversies related to its long term effects.

Mechanism of Action

Biological Perspectives

Magnesium is fourth most prevalent ion in the human body. Skeletal system accounts for 60% of total body magnesium, while the rest 40% is stored between the muscles and soft tissues. It plays a major role in multiple physiological processes including oxidative phosphorylation, glycolysis, cell membrane integrity and aggregation of DNA, protein synthesis, nerve conduction and neuromuscular excitability. It also functions as a cofactor in various enzymatic processes. Its calcium channel blocking effect, along with the modulation of the Na-K ATPase activity plays an important role in cardiac function, nerve impulse conduction and muscle activity.

Mechanisms Involved in Neuroprotection

The anti-inflammatory and anti-excitotoxic properties of MgSO4 through various mechanisms confer it with neuroprotective effects. Multiple studies in animal models emulating various forms of brain injury explored the effects of magnesium sulfate. Magnesium sulfate has been found to have dose dependent neuroprotective effect on postnatal rats who were administered N-methyl d-aspartate (NMDA), known to cause excitotoxicity-induced neuronal death[3]. Similar neuroprotective effects have also been seen following intracerebral injection of ibotenate[4]. The anti-excitotoxic effect of MgSO4 is thought to be due to the non-competitive inhibition of NMDA receptor. It reduces excitotoxic injury due to glutamate release by decreasing the influx of calcium. Decreased calcium influx further reduces induced apoptosis of neurons. Magnesium sulfate in addition also causes reduction in expression of glutamate in ischemic regions of brain.

Anti-inflammatory effect of MgSO4 has been also demonstrated in eclampsia rat models, where it attenuated seizure severity, neuronal hippocampal loss, cerebrospinal fluid levels of neuro-inflammatory markers like ferritin, S-100 and cerebral edema. Magnesium sulfate has been also found to ameliorate microglial and astrocyte activation and promote neuronal survival in CA3 region in eclampsia rat models[5]. Pretreatment of rats in hypoxia-ischemia model with MgSO4 have also resulted in reduced neuronal apoptosis and loss in the hippocampal regions of the brain[6].

Role of Magnesium Sulfate in Obstetrics

Magnesium sulfate has been for long, used in prevention or treatment of seizures in women with pre-eclampsia/eclampsia. Systematic review on role of MgSO4 in preclapmisa/eclampsia reported that administration of MgSO4 compared with placebo resulted in reduced risk of eclampsia (RR 0.41; 95% CI, 0.29– 0.58) and placental abruption (RR 0.64; 95% CI, 0.50–0.83)[7]. Role of MgSO4 as tocolysis is less clear and evidence is not suggestive that it is effective in delaying preterm birth.

Early Clinical Observational Studies on Fetal Neuroprotection

Following data on neuroprotective effects of MgSO4 in animal model, multiple observational studies assessing its role in neuroprotection of preterm infants were published. Nelson and Grether observed that very low birth (VLBW) infants born to mothers exposed antenatally to MgSO4 had lower incidence of cerebral palsy with an odds ratio of 0.14 (95% CI 0.05-0.51)[8]. Although results across observational studies were not consistent, meta-analysis of observational studies showed that antenatal MgSO4 in mothers with preterm birth reduced the risk for mortality (RR 0.73; 95% CI 0.61–0.89) and cerebral palsy (OR, 0.64; 95% CI 0.47–0.89)[9]. Suggested benefits in reduction of mortality and cerebral palsy, albeit retrospective, has led to multiple large scale randomized trials assessing the benefit of antenatal administration of magnesium sulfate.

Randomized Trials Assessing Neuroprotective Effects of Magnesium Sulfate

Five large RCTs were conducted between 1990 and 2010, while two RCTs are still continuing longer follow up. The MAGnet trial, ACTOMgSO4 trial, BEAM trial and PREMAG trial[10-13] were done to assess the role of antenatal MgSO4 for neuroprotection in preterm infants while the Magpie trial was done to assess the role of MgSO4 for neuroprotection in neonates born to mothers with pre-eclampsia/eclampsia[14]. Apart from the MAGnet trial, all other RCTs were multicentric. These RCTs and their outcomes are summarized in ***table 1 and 2.***

Table 1: Characteristics of major RCTs

Study	Period	Inclusion criteria	Groups	Number of participants
MitMittendorf et al[10]	MagNET 1995-97	GA > 24wk and < 34 weeks with or without PPROM Cervical dilation < 4cm	MgSO4 – 4 g bolus followed by infusion of 2-3 g/hr. Other tocolytics –ritodrine, indomethacin, nifedipine	MgSO4 – 55 Other tocolytics – 51
Mittendorf et al[10]	MAGnet 1995-97	GA > 24wk and < 34 weeks with or without PPROM Cervical dilation > 4cm	MgSO4 – 4 g bolus and no maintenance. Placebo – Saline	MgSO4 – 30 Placebo – 29
Marret et al[13]	PREMAG 1997-2003	Women in preterm delivery with GA < 33 wk and delivery expected with 24 hr	MgSO4 – 4 g bolus IV and no maintenance. Placebo – Saline	MgSO4 – 362 Placebo – 336
Crowther et al[11]	ACTO MgSO4 1996-2000	Women in preterm delivery with GA < 30 wk and delivery expected with 24 hr	MgSO4 – 4 g bolus IV and maintenance with 1 g/h IV until delivery or upto 24 h. Placebo – Saline	MgSO4 – 629 Placebo – 626
Rouse et al[12]	BEAM 1997-2004	Women of GA 24-31 wk with PPROM or in active preterm labour with cervical dilation of 4 – 8 cm with intact membranes or indicated preterm delivery anticipated in 2 – 24 h	MgSO4 loading 6 g over 30 mins IV followed by maintenance of 2 g/h for 12 h. Placebo not reported	MgSO4 – 1188 Placebo – 1256
Altman et al[14]	Magpie Trial 1998-2001	Women of GA < 37 wk with pre-eclampsia who had not given birth or were < 24 h postpartum and at risk of eclampsia	MgSO4 loading dose 4 g IV followed by maintenance of 1 g/h for upto 24 h Placebo - Saline	MgSO4 – 5055 Placebo – 5055

GA: gestational age; PPROM: preterm premature rupture of membranes.

Table 2: Results of major RCTs[10-14]

Outcomes	PREMAG	BEAM	Magpie	MAGnet	ACTOMgSO4
Pediatric mortality	0.87 (0.61–1.07)	1.18 (0.89–1.55)	1.27 (0.96–1.68)	9.41 (1.23–71.9)	0.81 (0.61–1.07)
Intraventricular hemorrhage	0.83 (0.62–1.09)	0.91 (0.78–1.08)	-	1.11 (0.53–2.34)	1.11 (0.92–1.34)
Periventricular leukomalacia	0.92 (0.55–1.53)	0.82 (0.47–1.45)	-	2.83 (0.12–68.37)	1.04 (0.58–1.88)
Cerebral palsy at 2 yrs	0.70 (0.41–1.19)	0.59 (0.40–0.85)	0.40 (0.08–2.05)	0.94 (0.20–4.53)	0.85 (0.55–1.31)
Death or cerebral palsy	0.80 (0.58–1.10)	0.90 (0.73–1.10)	1.09 (0.92–1.29)	4.83 (0.60–38.90)	0.82 (0.66–1.02)

Values reported as Relative risk (Confidence interval)

Meta-analyses Assessing Neuroprotective Effects of Magnesium Sulfate

Till date, five meta-analyses have been published and these have included data from major RCTs evaluating neuroprotective effect of antenatal MgSO4 in preterm infants[15-19]. Pediatric mortality, cerebral palsy (CP) and composite of two were assessed in all studies. The outcomes of meta-analyses were consistent with reduction in risk of CP at 18-24 months in children with in -utero exposure to MgSO4. The relative risk (RR) varied from 0.61 to 0.7 and the number needed to treat (NNT) to prevent one case of CP was 56 to 74 for infants born before 34 weeks gestation and 29 for infants born before 28 weeks gestation. No significant difference was seen in mortality or composite of CP and mortality in the standard meta-analyses. An individual patient data meta-analysis was performed by the AMICABLE (Antenatal Magnesium sulfate Individual participant data international Collaboration: Assessing the benefits for babies using the Best Level of Evidence) group[20]. Individual patient data meta-analyses are considered to be superior to standard meta-analyses because of the better availability of patient data and hence can overcome the limitations posed by standard meta-analyses. The combined outcome of death and CP at 2 years was seen to be significantly lower with a RR of 0.86 (95% CI of 0.75-0.99). No major side effects were seen in the mothers receiving MgSO4 and minor side effects included flushing, sweating, nausea or vomiting and injection site pain. These reports are consistent with robust compelling evidence supporting the role of antenatal MgSO4 as a neuroprotective agent.

Long Term Follow Up Data of PREMAG and ACTOMgSO4 Cohorts

Long term follow up data on neurodevelopmental outcomes of PREMAG and ACTOMgSO4 preterm cohorts have been published recently[21,22]. Children in the ACTOMgSO4 and PREMAG cohort were assessed at the age of 6-11 yrs and at 7-14 yrs of age respectively. Lost to follow up rate was 27% in the PREMAG cohort and 23% in the ACTOMgSO4 cohort. Follow up data from both these cohorts showed no significant difference in the motor, cognitive and behavioral aspects in children with in utero exposure to magnesium sulfate. The limited power of the studies might be attributed to the number of participants lost to follow up from the original cohorts.

Recommendations According to Various International Societies

Benefits of antenatal MgSO4 administration has been accepted by various international societies. Guidelines, however are not uniform regarding the dose of MgSO4, duration of therapy and gestational age below which it should be administered. ACOG[23] recommends antenatal MgSO4 to be administered for fetal neuroprotection below gestational age of 32 weeks, although the dose and duration of therapy has not been mentioned. Similarly, NICE guidelines[24] recommend offering antenatal MgSO4 between gestational age of 24-29^{+6} weeks and considering the same for gestational age of 30-33^{+6} weeks at a dose of 4 g IV loading followed by an infusion of 1 g/hour till birth or 24 hours whichever is earlier. WHO recommends administration of antenatal MgSO4 to mother below 32 weeks gestation with risk of preterm birth in the next

24 hours[25]. Therefore, most guidelines in general recommend administration of antenatal MgSO4 in threatened preterm delivery, although uniformity is lacking and further clarity in desirable.

Contraindications and Toxicity

The only absolute contraindication for administration of MgSO4 is a patient with myasthenia gravis. Relative contraindications include patients with chronic kidney disease, heart block or myocardial damage. Injection site discomfort, pain, flushing and sweating can be seen with administration of magnesium sulfate. Monitoring of serum magnesium levels and patients general condition is necessary. Clinical indications of safe dosage regimen include presence of deep tendon reflexes (knee jerk) and absence of respiratory depression (>16 breaths/minute). Caution must be exercised while being used concomitantly with neuromuscular blocking agents, cardiac glycosides and central nervous system depressants.

Conclusion

Magnesium sulfate is a safe intervention with role in fetal neuroprotection in threatened preterm delivery. Although long term benefits in motor, cognitive and behavioral aspects are lacking at school age, its benefit in reducing CP at 2 years age, the possible benefit in composite outcome of death and CP and the cost effectiveness have been established[26]. Further studies are required to address issues regarding duration of therapy, the best dosing regimen and long term effects of antenatal MgSO4 at school age.

Key points

- Magnesium sulfate has anti-inflammatory, anti-apoptotic and anti-glutaminergic properties through which it is thought to exert its neuroprotective effect.
- Multiple RCTs have been conducted to study the effect of antenatal magnesium sulfate in fetal neuroprotection, largest among which are the PREMAG trial, BEAM trial, ACTOMgSO4 trial and MAGnet trial.
- Meta-analyses have shown the efficacy of antenatal magnesium sulfate in reducing incidence of cerebral palsy at 2 years with a NNT of 56-74 for infants born before 34 weeks and 29 for infants born before 28 weeks.
- International organisations like WHO, ACOG and NICE have adopted the administration of magnesium sulfate in preterm birth for fetal neuroprotection.
- The recommended loading dose of MgSO4 is 4 gm intravenous followed by a maintenance of 1 gm/hr for 12-24 hours.

References

1. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ*. 2012;345:e7976.
2. Mukhopadhyay K, Mahajan R, Malhi P, Kumar A. Neurodevelopmental Outcome of Extremely Low Birth Weight Children at Corrected Age of Two Years. *Indian Pediatr*. 2016;53:391-3.
3. McDonald JW, Silverstein FS, Johnston MV. Magnesium reduces N-methyl-D-aspartate (NMDA)-mediated brain injury in perinatal rats. NeurosciLett 1990; 109: 234–8.
4. Marret S, Gressens P, Gadisseux JF, Evrard P. Prevention by magnesium of excitotoxic neuronal death in the developing brain: an animal model for clinical intervention studies. Dev Med Child Neurol 1995; 37: 473–84
5. Li X, Han X, Yang J et al. Magnesium Sulfate Provides Neuroprotection in Eclampsia-Like Seizure Model by Ameliorating Neuroinflammation and Brain Edema. *MolNeurobiol*. 2017;54:7938-48.
6. Koning, G, Lyngfelt, E, Svedin, P, Leverin, A.L, Jinnai, M, Gressens, P et al. Magnesium sulphate induces preconditioning in preterm rodent models of cerebral hypoxia ischemia. International Journal of Developmental Neuroscience (2008), 70: 56-66.
7. Duley L, Gülmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev*. 2010;2010 (11):CD000025.
8. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* (1995) 95:263–69.
9. Wolf HT, Hegaard HK, Greisen G, Huusom L, HedegaardM. Treatment with magnesium sulphate in preterm birth: a systematic review and meta-analysis of observational studies. J ObstetGynaecol 2012; 32: 135–40.
10. Mittendorf R, Covert R, Boman J, Khoshnood B, Lee KS, Siegler M. Is tocolytic magnesium sulphate associated with increased total paediatric mortality? Lancet 1997; 350: 1517–18.
11. Crowther CA, Hiller JE, Doyle LW, Haslam RR, Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. JAMA 2003; 290: 2669–76.

12. Rouse DJ, Hirtz DG, Thom E et al. A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med 2008; 359: 895–905.
13. Marret S, Marpeau L, Zupan-Simunek V et al. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. BJOG 2007; 114: 310–18.
14. Altman D, Carroli G, Duley L et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet 2002; 359: 1877–90.
15. Doyle LW, Crowther CA, Middleton P, Marret S. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* (2007):CD004661.
16. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* (2009):CD004661.
17. Conde-Agudelo A, Romero R. Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis. *Am J ObstetGynecol*(2009) 200:595–609.
18. Costantine MM, Weiner SJ; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Effects of antenatal exposure to magnesium sulfate on neuroprotection and mortality in preterm infants: a meta-analysis. *ObstetGynecol* (2009) 114:354–64
19. Zeng X, Xue Y, Tian Q, Sun R, An R. Effects and safety of magnesium sulfate on neuroprotection: a meta-analysis based on PRISMA guidelines. *Medicine (Baltimore)* (2016) 95:e2451.
20. Crowther CA, Middleton PF, Voysey M, Askie L, Duley L, Pryde PG, et al. Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: an individual participant data meta-analysis. *PLoS Med* (2017) 14.
21. Chollat C, Enser M, Houivet E, Provost D, Bénichou J, Marpeau L, et al. School- age outcomes following a randomized controlled trial of magnesium sulfate for neuroprotection of preterm infants. *J Pediatr*(2014) 165:398–400.
22. Doyle LW, Anderson PJ, Haslam R, Lee KJ, Crowther C; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgSO4) Study Group. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. *JAMA* (2014) 312:1105–13.
23. American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee Opinion No. 455: Magnesium sulfate before anticipated preterm birth for neuroprotection. *Obstet Gynecol*. 2010;115:669-671.
24. https://www.nice.org.uk/guidance/ng25 accessed on 15 August 2020.
25. WHO recommendation on the use of magnesium sulfate for fetal protection from neurological complications (November 2015). The WHO Reproductive Health Library; Geneva: World Health Organization. https://extranet.who.int/rhl/topics/newborn-health/who-recommendation-use-magnesium-sulfate-fetal-protection-neurological-complications accessed on 15 August 2020.
26. Shih STF, Tonmukayakul U, Imms C et al. Economic evaluation and cost of interventions for cerebral palsy: a systematic review. Dev Med Child Neurol 2018; 60: 543–58.

Proceedings of AOGD Monthly Clinical Meeting held at Maulana Azad Medical College & Lok Nayak Hospital Hospital, New Delhi on 27th November, 2020

A Rare Case of COVID 19 with Hypopituitarism

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Patient is Mrs K w/o Mr Y 25 yr, resident of Delhi, G3P1L1A1 with 35 weeks, Gestational hypertension and moderate anaemia, with complaints of cough and breathlessness referred in view of COVID + ve. Patient delivered vaginally and had traumatic post partum haemorrhage with blood loss of 1.5 litre. Patient was given general anaesthesia for stitching but she could not be extubated and transferred to ICU. Her vitals were stable and extubated on 5th post natal day and put on O2 at 8 litres/min through non rebreathing mask. Patient started having polyuria and hyponatremia. On postnatal day 6th patient had seizures for which she was started on anticonvulsant. She also complained of polydipsia and polyuria with 8 litres of input and 9 litres of output and there was failure of lactation. On postnatal day 7th, patient had developed aggressive behaviour and agitation. She was started on Tab Haloperidol. Medicine opinion was taken and and was advised to get all hormone levels after keeping the possibility of Sheehan's Syndrome or COVID 19 associated hypopituitarism. Her seum FSH,LH,Prolactin, was low and TSH was mildly raised.Her MRI showed normal pituitary gland and hypothalamus. Patient was symptomatic for 21 days and she failed to lactate her baby. She could be discharged after one month. Her investigations were repeated on day 21 which showed the low levels of FSH, LH, Prolactin which got normalized on Day 40. Normal MRI and involvement of anterior and posterior pituitary excluded the diagnosis of Sheehan's syndrome and patient was diagnosed as a case of COVID 19 associated hypopituitarism.

Desaturation in 2020: Is it always COVID ???

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Cognitive error is universal in medicine can lead to errors. It is hard not to focus on the diagnosis of covid-19 while evaluating a patient in 2020, specially the one with desaturation. In the 2 cases, final diagnosis was helped by a negative RTPCR report and clinical response of patients.

Case 1

Referred as a COVID suspect, G3P2L2 at 40 + weeks with severe pre-eclampsia with SOB & desaturation in second stage of labour, had a NEWS 2 score of 10

(RR-3 + Spo2-3 + Supp Oxygen-2 + Temp-0 + SBP-0 + PR-2, Alert +0)

Supportive management was given and delivery was conducted. Patient was admitted in ICU on oxygen by NRBM. Rapid antigen test was negative but CXR showed multiple ground glass opacities, basal and peripheral in location s/o typical COVID pattern. RTPCR for SARS CO V 2 was negative. She improved on diuretics, rate control with beta blocker, antibiotics, anticoagulants and steroids. A repeat CXR after 48 hours was normal. Final diagnosis was severe pre-eclampsia, type 1 respiratory failure with pulmonary edema. Patient was transferred back to non - COVID facility in stable condition on post-natal day 3.

Case 2

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Reena Rani, Deepti Goswami

A COVID suspect, Primigravida at 29+ weeks with hypothyroidism, high grade fever, severe headache, vomiting and malaise was referred from non- COVID facility. At 2 hours of admission she developed dizziness, hallucinations and altered sensorium

along with desaturation, SPO2 was 91% on room air (started on NRBM at 8l/min). With a NEWS 2 score of 9 (2+0+3+0+0+ 1+3+0= 9) she was shifted to ICU. She had neck rigidity. Differential diagnosis was a COVID suspect with neurological symptoms with ?Encephalo-meningitis ?Cerebral malaria ?Hepatic encephalopathy. She was empirically started on IV Ceftriaxone, Inj Artesunate, Rifaxamine and lactulose for encephalopathy protection. Her RTPCR (22.8.20) was negative for SARS CO V 2, CXR was normal, NCCT head was also reported normal.

Patient was stabilised and was shifted back to non-COVID facility for further management. Follow up CSF and MRI were s/o Tubercular meningitis. Final diagnosis was a Primigravida at 29+5 weeks with tubercular meningitis

Discussion: How we approach medical decision making during the COVID-19 pandemic? Eventually not diagnosed with COVID-19 but with Pulmonary edema and Tubercular meningitis which should have been considered as the primary alternative diagnosis. Desaturation in 2020 does not imply only COVID, there are other pulmonary and non-pulmonary causes too.

Non-specific overlapping symptoms and signs with ambiguous laboratory investigations make diagnosis difficult. Chest radiographs though may show typical bilateral air-space ground glass opacities are non-specific, chest computerized tomography findings are also non-specific though sensitivity is reportedly 97% and has limited availability and high cost.

It is important that we avoid the biases that affect our medical decision making in the situation of a pandemic and follow the evidence based clinical approach to avoid multiple drug therapy, repeated transfer entailing risk of further infection, deterioration and transit complications and provided better and safer medical care.

A Case of Obstetric Emergency in Covid Times

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27 years old G3P1L1A1 with 30 weeks of gestation with DADC twins with severe anemia with pancytopenia with preeclampsia with covid 19 was admitted in LNJP Hospital on 28/8/20 after being referred from district hospital in Delhi. . Injection Mgso4 was given for neuro protection and Injection dexamethasone was given for lung maturity in the same district hospital .Patient was diagnosed with severe anemia (Hb-5.1) pancytopenia (TLC-2900 ,platelets -10000) and severe preeclampsia (BP-160/90 , urine albumin-2+) with partial HELLP syndrome .Patient was worked up and stabilized on antihypertensives.She was asymtomatic for covid infection .On 3rd day of admission patient had complain of headache,vomiting and had all features of HELLP SYNDROME . Induction of labour was done in view of uncontrolled BP and HELLP syndrome followed by preterm vaginal breech delivery . .Inj MgSO4 and Injection nitroglycerine drip was started during intrapartum period and titrated.. Prophylactic balloon tamponade was put and removed after 24 hours .No PPH. Total 5 units of packed RBC and 14 units of platelets in the antepartum and intra partum period was transfused .She went into hypertensive crisis just after delivery and was managed by NTG drip and antihypertensives. Both mother and twin babies were discharged after 18 and 45 days of admission respectively with a negative covid report. COVID 19 is an emerging epidemic showing significant impact on mother and fetus . Systematic reviews and meta-analyses conclude that pregnant women experiencing coronavirus infection are at increased risk of miscarriage, preeclampsia, cesarean birth and perinatal death.Laboratory parameters of pre-eclampsia and covid infection mimic each other and are confusing . Pregnant women with severe COVID-19 can develop a PE-like syndrome that might be distinguished from actual PE by sFlt-1/PlGF, LDH and Uterine artery pulsatility Index(UtAPI) assessment. UtAPI and sFlt-1/PlGF ratio have a high negative predictive value to predict the short-term absence of PE, but are not diagnostic criteria of Pre-eclampsia .More studies are required to confirm or refute this association. Early diagnosis and timely intervention of rare entities in pregnancy like pancytopenia and HELLP syndrome can arrest further complications and bring favourable maternal and fetal outcome.

Journal Scan

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Ultrasound Obstet Gynecol 2020 May;55(5):676-682.

Natural History of Pregnancy-related Enhanced Myometrial Vascularity following Miscarriage

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Abstract

Objectives: Our primary aim was to report the incidence of enhanced myometrial vascularity (EMV) in consecutive women attending our early pregnancy assessment unit, following first-trimester miscarriage. We aimed further to evaluate the clinical presentation and complications associated with expectant and surgical management of EMV in these women.

Methods: This was a prospective cohort study conducted in a London teaching hospital between June 2015 and June 2018, including consecutive patients with an observation of EMV on transvaginal ultrasonography following first-trimester miscarriage. The diagnosis was made following the subjective identification of EMV using color Doppler ultrasonography and a peak systolic velocity (PSV) ≥ 20 cm/s within the collection of vessels. Women were followed up with repeat scans every 14 days. Management was expectant unless intervention was indicated because of excessive or prolonged bleeding, persistent presence of retained tissue in the endometrial cavity or patient choice. The final clinical outcome was recorded. Time to resolution of EMV was defined as the interval from detection of EMV until resolution.

Results: During the study period, there were 2627 first-trimester fetal losses in the department and, of these, 40 patients were diagnosed with EMV, hence the incidence of EMV following miscarriage was 1.52%. All cases were associated with ultrasound evidence of retained products of conception (RPOC) at presentation (mean dimensions, 22 × 20 × 20 mm). Thirty-one patients opted initially for expectant management, of which 18 had successful resolution without intervention, five were lost to follow-up and eight subsequently had surgical evacuation due to patient choice. No expectantly managed case required emergency intervention. Nine patients chose surgical evacuation as primary treatment. No significant correlation was seen between PSV within the EMV at presentation and blood loss at surgery. Median PSV was 47 (range, 20-148) cm/s. The estimated blood loss in all cases managed surgically ranged from 20-300 mL. Presence of RPOC was confirmed in all specimens that were sent for analysis following surgery. For cases successfully managed expectantly, the mean time to resolution was 48 (range, 21-84) days. In the nine cases managed surgically from the beginning, the mean time to resolution of EMV was 10.6 (range, 3-29) days.

Conclusions: This study suggests that EMV is an uncommon finding following miscarriage and is associated with the presence of RPOC. Expectant management was a safe option in our cohort, with minimal bleeding, although it was associated with protracted time to resolution. In patients who opted for surgery, the maximum blood loss was 300 mL and no patient required blood transfusion or embolization.

Cross Word Puzzle

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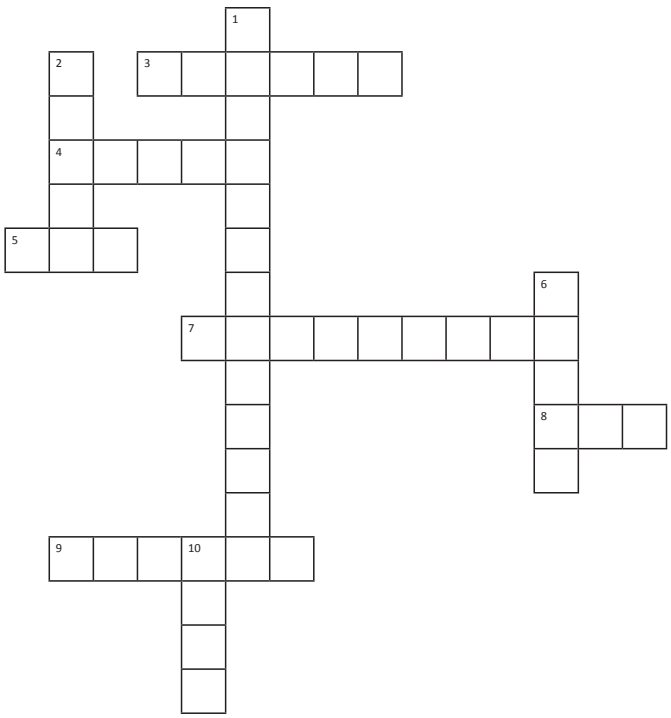
CROSSWORD

Test your knowledge of Reproductive Anatomy and Physiology



Across

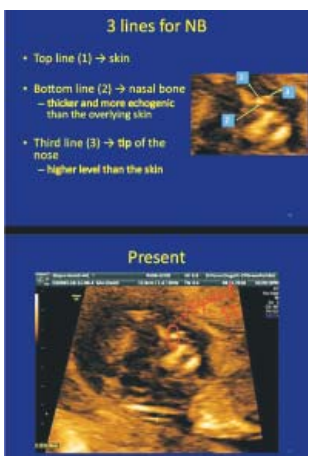
3. In women with Anterior placenta praevia and one cesarean section, the risk of Placenta accrete syndrome is ------ % (6)
4. In pre-eclampsia screening in first trimester, measurement of Placental growth factor could be substituted with ----- (5)
5. European working group on abnormal invasive placentation (EW-AIP) defines how many descriptors on 2-D ultrasound grey-scal
7. The gestational age in weeks before and after which "Early' and "Late" fetal growth restriction is diagnosed is (9)
8. In late FGR the Doppler parameter to watch out for is... (3)
9. Trial done to assess the role of antenatal MgSO4 for neuroprotection in preterm infants. (6)

Down

1. Antenatal steroid most preferred for fetal lung maturity (13)
2. This study group supports universal screening for diabetes amongst pregnant women. (5)
6. A non-recurrent, infectious cause of Still birth, that does not require special monitoring in the next pregnancy (5)
10. The anti-excitotoxic effect of MgSO4 is thought to be due to the non-competitive inhibition of ------ receptor (4)

PICTORIAL QUIZ

Sharmistha Garg



Ques 1. What is "equal to '' sign in the assessment of the fetal nasal bone?
Ques 2. What is the criteria of for absent nasal bone?

Answer to November Crossword and Pictorial Quiz given on Page No. 47

AOGD Sub Committee Nomination (2021-23)

Nominations are invited for the post of chairperson of the following sub-committees for the year 2021-23

1. Urogynecology committee
2. Endoscopy Committee
3. Adolescent Committee
4. Safe Motherhood Committee
5. Fetal Medicine and Genetics committee
6. Oncology Committee
7. Reproductive Endocrinology Committee
8. Endometriosis committee
9. QI Obst & Gynae Practice committee

Eligibility Criteria

1. Person should be a member of AOGD and have at least 10 years standing in the profession with at least 5 years duration of holding senior position in the respective institutions.
2. Chairperson of a subcommittee has to be a member of any subcommittee earlier for at least 1 year.
3. No repeat nomination will be considered after one term of two years.
4. In case of two people applying for the same post, the decision of the executive committee will be final.
5. In case of any deviation, the decision would be taken by executive committee.
6. Two posts cannot be held by any member at one particular time.

Please send the nominations by email on secretaryaogdsgrh2020@gmail.com

Or

By post, the nominations on plain paper should reach: Gynae Office, Institute of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Sarhadi Gandhi Marg, Old Rajinder Nagar, New Delhi-110060 by 31st January, 2021 along with bio-data stating the eligibility.

Dr Monika Gupta
Safdarjung Hospital

Received FOGSI DC DUTTA Award
for Best Textbook Publication