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PLEDGE FOR EXCELLENCE
FOGSI 2014

FEDERATION OF OBSTETRIC & GYNAECOLOGICAL SOCIETIES OF INDIA
FOGSI

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Message from The President FOGSI 2014

Prof. Dr. Suchitra N. Pandit
President FOGSI 2014

It gives me great pleasure to write this message for this issue of Cybele which has a vast variety of topics related to woman's health right from preconception ,infertility to pregnancy and beyond !

My theme for this year is 'Empower Women - Empower India Pledge for Excellence ! So in keeping with this, I am very pleased that Dr. Roza Olyai, Vice President in my team has taken the initiative to bring forth this issue which makes very interesting reading

I must also congratulate Intas Pharmaceuticals Ltd., specially Mr. Manish Shah – General Manager, Sybella Division for his support in organising the Basic Infertility workshops & helping to spread knowledge across the country through this Cybele magazine for enhancing patient care

"A fit, healthy body-that is the best fashion statement"

- Jess C. Scott

Prof. Dr. Suchitra N. Pandit
President ,FOGSI & ICOG 2014
President, Mumbai Society of OBGYN 2013
Senior Consultant - Kokilaben Dhirubhai Ambani Hospital & Research Centre, Mumbai

Message from The Secretary General

Dr. Nozer Sheriar
Secretary General FOGSI

Dear Colleagues and Friends,

'Whether you think you can, or that you can't, you are usually right.'

- Henry Ford

Am very happy to note that the first issue of the Cybele Magazine is going to be released very soon. The contents of the magazine has been very well selected & written. The topics are very apt for the present scenario of our dealing with patients.

I would like to congratulate Dr. Roza Olyai Vice President FOGSI for this creative undertaking & am very happy to see that it will be carried out under the International Exchange Committee FOGSI with Dr. Fessy Louis as the Chairperson.

I wish Dr. Roza Olyai & Dr. Fessy Louis my very best and hope this will be an ongoing project for many years ahead & thank both of them on behalf of FOGSI for doing this very important work so sincerely.

Keep up the good work!

Dr. Nozer Sheriar
Secretary General FOGSI

Message from The Chairperson

Dr Fessy Louis T
Chairperson
International Academic
Exchange Committee FOGSI

It gives me immense pleasure in writing this message for the first issue of the Cybele Magazine.

Our country in the recent past has progressed in many fronts including health sector. But sadly our country's health indices, especially for women health, are still very bad. I am sure that Cybele magazine would capture all essential steps towards recognition, prevention and action for saving lives in high risk pregnancy cases and also would make a quick reading and effective recall of infertility and PCO. I am hopeful that Cybele would highlight the importance of quality clinical examination, timely and appropriate diagnosis and the utilization of modern technology in limiting the health problems in women of India.

Am very thankful to Dr. Roza Olyai Vice President FOGSI & Editor of Cybele for undertaking this important project with the International Academic Exchange Committee FOGSI.

With warm personal regards and happy reading to you all!

Dr Fessy Louis T

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Message from The Editor

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Member Board of Governing Council
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Dear Friends,

It gives me great pleasure to share with you the first issue of the ***Cybele*** magazine.

Am very happy to be a part of the team of Dr. Suchitra Pandit, President FOGSI (2014)& the responsibilities given to me by her.

One of my major project this year as Vice President FOGSI is organising ***"Basic infertility"*** CMEs in various FOGSI societies being coordinated by Dr. Sunita Tandulwadkar for which am very thankful to her.

Kudos also to, Dr. Fessy Louis Chairperson of the International Academic Exchange Committee through whose committee we are doing this activity. Am sure the committee will reach it's greater heights under his able leadership & I will be very happy to continue my support to all his activities.

The word ***Cybele*** depicts the "Goddess of Fertility & Womanhood" & hence in this issue of the ***Cybele*** magazine we have covered important topics related to the theme such as '*Evolution of progesterone in managing luteal support, GDM, Early pregnancy bleeding, PCOS update, Surrogacy in India today , Male profertility nutraceuticals & case studies on PROM'*.It's a mixture of interesting topics related to the common disorders & problems which are on the rise.

FOGSI is holding various CMEs & workshops this year to keep the Gynecologists abreast with a cascade of developments specially in basic infertility management. The scientific programme has been meticulously worked out. It is designed from basic to advances in the field of infertility considering the interest of each & every Gynecologist, Trainees & students to enable them to cater to the need of the public especially to the infertile couples in India.

We hope that at the end of workshops the delegates will go back with a take home message from the discussions on latest development in the field of infertility management.

Our aim is "Better Care of the Concerned Couples, knowledge about their investigations and further education of those who serve them"

Am very grateful to Intas Pharmaceuticals Ltd., specially Mr. Manish Shah – General Manager, Sybella Division for his interest in organising the Basic Infertility workshops & helping to spread the message across the country through this ***Cybele*** magazine for the betterment of our patients.

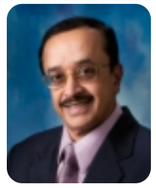
Your suggestions & feedback will be of great help, kindly share your

articles & achievements with us.

Wish you all a happy reading!

Dr. Roza Olyai
Vice President FOGSI 2014

Editorial Board



Dr. Sanjay Gupte,
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President FOGSI 2010
Member Central Supervisory Board of PCPNDT Act
Ex Hon Associate Professor B J Medical College, Pune
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Early Pregnancy Bleeding

Early pregnancy loss is one of the most common complications of pregnancy. Most of these pregnancy losses are not even diagnosed as they occur pre clinically. A patient coming with bleeding in early pregnancy provides a huge challenge to the obstetrician as so many uncertainties are involved in its prediction.

Let's consider a patient – a very common practice scenario – a patient who has done a pregnancy test at home when she has just missed her periods. The test is positive and she comes to the doctor at 5 weeks with minimal bleeding or spotting. At this stage it's very difficult to diagnose the status of the pregnancy. So all one can tell the patient is to wait for the final outcome – also called as the expectant management. But the patient is not happy and she wonders why no action is being taken. What the obstetrician needs to do at this time is to communicate and counsel her properly. The obstetrician needs to explain that at this stage, the pregnancy is too small to be seen, and any further investigations such as scanning are unlikely to yield any information. Also need to inform that many women experience 'spotting' during early pregnancy that resolves without the need of further intervention. Hence the patient needs to be advised to wait and to see how things progress during the next week before any further action can be considered.

However if the patient later has additional symptoms like cramping and pain; she may require additional investigations. Serum B hcg would be in order which may not be diagnostic at this stage; but will help in further prognostication. A sonography at this stage usually will not show any intra or extra uterine pregnancy hence will be labeled as pregnancy of unknown origin (PUL). The PUL on further progress can be seen as visualized intrauterine pregnancy but it's good to remember that 7-20% of PUL may get converted into ectopic pregnancies on further follow-up. Hence it's important to repeat Sr.B hcg levels after 48 hrs. If it shows doubling of the values then it will mean that the pregnancy is proceeding appropriately and it's probably an early intrauterine pregnancy.

On sonography there are some correlated landmarks which help in future assessment

Days	Expected MSD growth on USG
Per one day	>/= 0.6 mm
Over 5 days	>/= 3 mm
Over 7 days	>/= 4 mm

If they are not seen; it is an indication for failing pregnancy

Levels of B hcg also indicate different pregnancy parameters as below

Trans-vaginal findings	Weeks from LMP	B-HCG (mIU/ml)
Gestational sac (25mm)	4.5-5	1000
Yolk sac	5-5.5	1500-2500
Fetal pole	5-6	2000-5000
Fetal cardiac activity	5.5-6.5	4000-17000

On TAS cardiac activity is detectable only when B hcg is >/= 6500 m IU/ml

Generally a mean sac diameter of 20 mm with no fetal pole is taken as a sign of miscarriage, in today's terminology early fetal demise. There are other biomarkers available which assist the early pregnancy but still they are not used in routine practice.

Various biomarkers and their significance in early pregnancy

B hcg –

- In good growing viable pregnancy doubling titer of S. Bhcg is important
- If the ratio of Bhcg level at 48 hrs to Bhcg level at 0 hrs is two or more; then the pregnancy is growing well, on the other hand if the ratio is 0.87 or less; it's an indication of a failing pregnancy.

Progesterone –

Progesterone of <25 nmol/L is diagnostic of non-viability of pregnancy, especially in an anembryonic pregnancy on TVS.

17 OHP

The value of 17 OHP is seen to be lower in non-viable intra uterine pregnancies and ectopic pregnancies. The plasma concentration of 17 OHP rises from 2.6 ng/mL in the third week of pregnancy to 5.8 ng/mL at fifth week & then declines up to 13th week.

Inhibin A –

As the main synthesis of Inhibin A is from trophoblastic tissue, its levels are very low in biochemical pregnancies and missed abortions where trophoblastic tissue is absent. Inhibin A reaches a level of around 104.5 pg/mL on day 12 after ovulation, and then climbs from day 21 after ovulation to peak at 8 weeks of gestation.

Insulin Growth Factor Binding Protein -1 (IGFBP-1) –

IGFBP-1 inhibits binding of trophoblast to the decidual cells and in defective implantation; there occurs overproduction of IGFBP-1 by decidua. Thus increase values of IGFBP -1 are associated with failing pregnancies

The next question arises is what action to take if it appears to be early pregnancy failure. Should one wait for spontaneous abortion or go ahead with medical termination or surgical intervention. Generally medical treatment in this situation is preferred. There was an interesting trial conducted in 2007 **MIST trial** (miscarriage treatment trial)[1] investigated whether there was a clinically important difference existing in the incidence of infection between those women managed surgically, medically or expectantly. The result of the trial showed no difference in the rate of infection between the three groups; however, there were significantly more unplanned admissions and unplanned surgical curettage in those women who initially opted for expectant or medical management. Conversely a recent **Cochrane review**[2] of expectant care versus surgical care for miscarriage did show an increased risk of infection in those women undergoing surgical evacuation.

Misoprostol is commonly used to terminate failing pregnancies or so called missed abortions for termination. It is proposed that mifepristone may not be necessary for EPF because of the abnormal decidual lining in EPF[3,4]

There are many causes of early fetal wastage.

The earlier the pregnancy loss occurs, the greater the likelihood of genetic causation.

Chromosomal abnormalities- the most common trisomies in early pregnancy losses are 16,22,21,15,13,2 and 14 in descending order.

Aneuploidy – recurrent aneuploidy is a frequent cause of recurrent losses.

Chromosomal translocations- structural chromosomal rearrangements are one of the causes of recurrent abortions. About 4-5% of couples with repeated losses show balanced translocation. The frequency is higher if there is a family history of still born or abnormal live born. Examples of balanced translocations are Robertsonian translocation and Down's syndrome.

Thyroid abnormalities- Reduced conception rates and increased pregnancy losses are associated with overt hypo as well as hyperthyroidism. However a subclinical thyroid dysfunction is not an explanation for repeated losses.[6]

Diabetes Mellitus- poorly controlled Diabetes Mellitus increases the risk for fetal loss[7]

Intra uterine adhesions (Synechiae)- Synechiae could possibly interfere with implantation and hence early embryonic development. Around 15-30 % of individuals with uterine synechiae show repeated abortion.

Fibroids- location of fibroids is probably more important than the size. Sub mucus fibroids are most likely to cause abortion. Possible explanations are

Thin endometrial surface over fibroid	Poorly desidualised implantation site
Rapid growth of fibroid due to hormones	Compromising blood supply and increasing cytokine production

Cytokines- cytokines are believed to cause repetitive abortions through perturbations of T helper cells (TH1)

Thrombophilias- maternal hypercoagulable states are also associated with increased pregnancy losses. They are of two types acquired & inherited. Inherited hypercoagulable associations include factor V Leiden, Prothrombin, homozygocity for 677C-T polymorphism in MTHFR gene.

Other hypercoagulable conditions are deficiencies of antithrombin, protein C, Protein S and hyperhomocystenemia.

Generally for the first miscarriage these investigations are not carried out to find the cause but in repeat pregnancy loss situation they do have a major value. However advice regarding life style issues like smoking, obesity, drug use etc can go a long way in improving the prognosis during the next pregnancy.

Another problem the early pregnancy bleeding presents; is to answer if there is any positive treatment available. Especially if it is a viable pregnancy then usually the treating clinician is tempted to support the pregnancy with supplements of progesterone or injection of HCG. However though a lot is talked about regarding immune modulation, improving luteal phase and rescuing the corpus luteum; none of these theories have been proved with any convincing evidence and usually used empirically or for their placebo effect. If this PUL is further followed then two concepts have to be borne in mind. Discriminatory zone where Bhcg is more than 1500 but no intrauterine pregnancy is seen then this would usually point toward ectopic pregnancy. Secondly if homogeneous mass is found in the tube or near the ovary then likelihood of ectopic pregnancy is very high. Differentiation can be made between corpus luteum cyst and this mass by which is called as sliding organ sign where by putting a pressure on trans vaginal ultrasound probe the movement of the mass is observed. If it moves separately from the ovary then it's more likely to be ectopic mass.

The further management of ectopic pregnancy cannot be covered in a short space and needs an additional chapter.

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Inauguration of Basic Infertility CME done on 25th May 2014 at Bhubaneshwar. Topics covered were : Male infertility & semen preparations, Endocrinology of Ovulation-HPO Axis. The talks were followed by an interesting panel discussion on increasing success rate in IUI. Very grateful to Bhubaneshwar Society for organizing the same.

Gestational Diabetes Mellitus

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Chairman-Dr. V. Seshiah Diabetes Research Institute
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PRESIDENT FOGSI 2013

Gestational Diabetes Mellitus (GDM) is characterized by carbohydrate intolerance of varying severity with onset or first recognition during pregnancy.[1]The concern is GDM represents detection of chronic β cell dysfunction[2] and considered to be a stage in the evolution of Type 2 DM.[3]The implication is that women with a history of GDM are at increased risk of future diabetes, predominantly type 2 diabetes, as are their children[4]. The extent of this risk depends on the diagnostic criteria used to identify GDM. [4] Studies conducted in different populations and with different methodologies, consistently reported an increase in GDM in all race/ethnicity groups, suggesting that there is an increase in GDM prevalence.[5] A true increase in the prevalence of GDM aside from its adverse consequences for the infant in the newborn period might reflect or contribute to the ongoing pattern of increasing diabetes and obesity.[5] This implies that Universal screening and care of women with GDM is of paramount public health priority[6] in high risk population for GDM and diabetes like Asian Indians,[7] rather than risk factor screening[8]. Timely action taken now in screening all pregnant women for glucose intolerance, achieving euglycemia in them and ensuring adequate nutrition may prevent in all probability, the vicious cycle of transmitting glucose intolerance from one generation to another[9]

1. EPIDEMIOLOGY

The prevalence of GDM in India varied from 3.8 to 21% in different parts of the country, depending on the geographical locations and diagnostic methods used. GDM has been found to be more prevalent in urban areas than in rural areas. [10]For a given population and ethnicity, the prevalence of GDM corresponds to the prevalence of impaired glucose tolerance (IGT) (in nonpregnant adult) within that given population. [11]The global prevalence of hyperglycaemia in pregnancy in women (20–49 years) is 16.9%, or 21.4 million live births in 2013. The highest prevalence was found in the South-East Asia Region at 25.0% compared with 10.4% in the North America and Caribbean Region.More than 90% of cases of hyperglycaemia in pregnancy are estimated to occur in low- and middle-income countries[12]

1.1 SCREENING AND DIAGNOSIS

The term "Screening" and "diagnosis" are often used interchangeably.In contrast to a screening test, the diagnostic test will usually provide a definitive answer as to the presence or absence of diabetes

1.1a. American Diabetes Association Procedure:

Carpenter – Coustan's American Diabetes Association (ADA) procedure has become obsolete.

1.1b The International Association of the Diabetes and Pregnancy Study Groups:[13]

Based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, International Association of the Diabetes and Pregnancy Study Groups (IADPSG) suggested the guidelines. In this HAPO study, population from India, China, South Asian countries (except city of Bangkok, Hong Kong), Middle East and Sub Saharan countries were not included. Thus, essentially HAPO study was performed in Caucasian population.

The IADPSG recommends that diagnosis of GDM is made when any of the following plasma glucose values meet or exceed: Fasting: ≥ 5.1 mmol/L (92 mg/dL), 1-hour: ≥ 10.0 mmol/L (180 mg/dL), 2-hour: ≥ 8.5 mmol/L (153 mg/dL) [13] with 75 g OGTT. Though one glucose value is adequate to diagnose GDM, the decision can be made only after performing 2h OGTT.

The IADPSG also suggests: Fasting plasma glucose (FPG) > 7.0 mmol/L (126 mg/dL)/A1C > 6.5% in the early weeks of pregnancy is diagnostic of overt diabetes. Fasting > 5.1 mmol/L and < 7.0 mmol/L is diagnosed as GDM.[13]

1.1b.1 Disadvantages of the IADPSG suggestions are:

- Most of the time pregnant women do not come in the fasting state because of commutation and belief not to fast for long hours. The dropout rate is very high when a pregnant woman is asked to come again for the glucose tolerance test.[14]Attending the first prenatal visit in the fasting state is impractical in many settings. [13]A fasting blood test at the antenatal booking is often inconvenient even in UK[15]
- In all GDM, FPG values do not reflect the 2-hour post glucose with 75 g oral glucose [2-hour plasma glucose (PG)], which is the hallmark of GDM.[16] Ethnically Asian Indians have high insulin resistance and as a consequence, their 2-hour PG is higher compared to Caucasians.[17] The insulin resistance during pregnancy escalates further[18] and hence FPG is not an appropriate option to diagnose GDM in Asian Indian women. In this population by following FPG > 5.1 mmol/L as cut-off value, 76% of pregnant women would have missed the diagnosis of GDM made by WHO criterion[19].
- Asian and south asian ethnicity are both independently associated with increased insulin resistance in late pregnancy. A diagnostic FPG was present in only 24% of those with GDM in Bangkok and 26% in Hong Kong[20]
- Center to center differences occur in GDM frequency and relative diagnostic importance of fasting, 1-hour and 2-hour glucose levels. This may impact strategies used for the diagnosis of GDM.[20]
- A cost-utility analysis found that screening based on IADPSG criteria was not cost effective [21]
- Gestational Diabetes mellitus diagnosed by IADPSG criteria.

  Quality of evidence – Very low

  Strength of recommendation – Weak[22]
- There is no high quality evidence that women and their fetuses benefit from treatment if only the fasting value is abnormal. RCT shows benefit of treating GDM women identified primarily by post load values[22]
- The A1C is not possible to perform in the less resource countries, not only because it is expensive but also due to lack of technically qualified staff. The cost and standardization of A1C testing are issues for consideration.[23]

1.1c World Health Organization Procedure:

To standardize the diagnosis of GDM, the World Health Organization (WHO) recommends using a 2-hour 75 g oral glucose tolerance test (OGTT) with a threshold plasma glucose concentration of greater than 140 mg/dL at 2 hours, similar to that of IGT (> 140 mg/dL and < 199 mg/dL), outside pregnancy. [24]WHO Criterion of 2h>140 mg/dl is Evidence-based.

Short-term Outcome

Economical test:

- This procedure requires one blood sample drawn at 2 hours after 75 g oral glucose load for estimating plasma glucose. Even if the test is to be repeated in each trimester, the cost in performing the procedure will be 66% less than the cost of performing IADPSG recommended procedure. Thus, WHO procedure is feasible, sustainable, cost-effective and high impact best buy for less resource settings.

Evidence-based:

- A study performed by Crowther et al. found that treatment of GDM diagnosed by WHO criterion reduces serious perinatal morbidity and may also improve the women's health-related quality of life.[23]
- Diagnosis of GDM with OGTT 2-hour PG ≥ 7.8 mmol/L (140 mg/dL) and treatment in a combined diabetes antenatal clinic is worthwhile with a decreased macrosomia rate and fewer emergency cesarean sections. The treatment of GDM women as defined by WHO criterion was associated with reduced risk of pregnancy outcome.[25]
- Wahi et al. observed in their randomized controlled study, the advantage of adhering to a cut-off level of 2-hour PG ≥ 7.8 mmol/L in diagnosis and management of GDM for a significantly positive effect on pregnancy outcomes both in relation to mother as well the child.[26]
- Perucchini et al. also suggest one-step diagnostic procedure (2-hour PG ≥ 7.8 mmol/L) to diagnose GDM.[27]

Long-term Outcome:

A long-term outcome study conducted by Franks et al. documented that when maternal 2-hour PG was ≥ 7.8 mmol/L, the cumulative risk of offspring developing type 2 DM was 30% at the age 24 years.[28]

1.2 A Single Test Procedure to Diagnose GDM in the Community *(Diabetes in Pregnancy Study Group India)*[29]

Note: Diabetes in Pregnancy Study Group India (DIPSI diagnostic criteria 2-hour PG ≥ 140 mg/dL is similar to WHO criteria 2-hour PG ≥140 mg/dL to diagnose GDM)

"A Single-step procedure" was developed due to the practical difficulty in performing glucose tolerance test in the fasting state, due to the reasons alluded to vide supra (1.1b.1).In addition to this practical problem, OGTT is resource intensive and many health services, especially in low resource settings, are not able to routinely perform an OGTT in pregnant women. In these circumstances, many health services do not test at all for hyperglycemia in pregnancy. Therefore options which do not involve an OGTT are required.Further the request to attend the antenatal clinic in fasting for a blood test may not be realistic because of the long travel distance to the clinic in many parts of the world, and increased tendency to nausea in the fasting state. Consequently non-fasting testing may be the only practical option[30]. Hence, it is important to have a test that detects the glucose intolerance without the woman necessarily undergoing a test in the fasting state and it is preferable to perform the diagnostic test at the first visit itself.

1.2a Procedure:

In the antenatal clinic, a pregnant woman after undergoing preliminary clinical examination, has to be given a 75 g oral glucose load*, irrespective of whether she is in the fasting or nonfasting state and without regard to the time of the last meal. A venous blood sample is collected at 2 hours for estimating plasma glucose by the GOD-POD method. GDM is diagnosed if 2-hour PG is ≥140 mg/dL(7.8 mmol/L).

*If 75 g glucose packet is not available, remove and discard 5 level teaspoons (not heaped) of glucose from a 100 g packet which is freely available. In hospitals where glucose is supplied in bulk, a cup or container of 75 g may be used. The glucose marketed is in anhydrous form.

Performing this test procedure in the nonfasting state is rational, as glucose concentrations are affected little by the time since the last meal in a normal glucose tolerant woman, whereas it will, in a woman with gestational diabetes. [31] After a meal, a normal glucose tolerant woman would be able to maintain euglycemia despite glucose challenge due to brisk and adequate insulin response, whereas, a woman with GDM who has impaired insulin secretion,[32] her glycemic level increases with a meal and with glucose challenge, the glycemic excursion exaggerates further.[33] This cascading effect is advantageous as this would not result in false-positive diagnosis of GDM.

1.2b. Point of Care

Considerations in testing for hyperglycaemia in pregnancy Feasibility: Laboratory glucose measurement is often not available and testing with a portable blood glucose meter is the only option[30]. The glucometer that is chosen should have been standardized for measuring plasma glucose. Yet another caution is to calibrate the glucometer everyday

1.2c Advantages of the DIPSI procedure are:

- Pregnant women need not be fasting[28]
- Causes least disturbance in a pregnant woman's routine activities
- Serves as both screening and diagnostic procedure.

This single-step procedure has been approved by Ministry of Health, Government of India[34] and also recommended by WHO.[22]

1.3 Gestational Weeks at which Screening is Recommended

By following the usual recommendation for screening between 24 weeks and 28 weeks of gestation, the chance of detecting unrecognized type 2 diabetes before pregnancy (pre-GDM) is likely to be missed.[35] If the 2-hour PG is > 200 mg/dL in the early weeks of pregnancy, she may be a pre-GDM and A_{1c} of ≥6.5 is confirmatory.[36] A pregnant woman found to have normal glucose tolerance (NGT), in the first trimester, should be tested for GDM again around 24th–28th week and finally around

32nd–34th week.[37]

1.4 MANAGEMENT OF GESTATIONAL DIABETES MELLITUS

1.4a Treatment

Target:

Maintaining a mean plasma glucose (MPG) level ~105–110 mg/ dL is desirable for a good fetal outcome.[38]This is possible if FPG and 2-hour postprandial peaks are ~90 mg/dL and ~120 mg/dL, respectively.

Medical Nutrition Therapy:

All women with GDM should receive nutritional counseling. The meal pattern should provide adequate calories and nutrients to meet the needs of pregnancy. The expected weight gain during pregnancy is 300–400 g per week and total weight gain is 10–12 kg by term.

Initiating Insulin Therapy:

Once diagnosis is made, medical nutritional therapy (MNT) is advised initially for 2 weeks. If MNT fails to achieve control, i.e. FPG ~90 mg/dL and/or post-meal glucose ~120 mg/dL, insulin may be initiated.

1.5 Monitoring Glycemic Control

The success of the treatment for a woman with GDM depends on the glycemic control maintained with meal plan or pharmacological intervention. Studies suggest 1, 1.5 and 2-hour post-meal for monitoring glycemic control.[39] 2-hour post-meal monitoring is preferred as the diagnosis of GDM is also based on 2-hour PG. It is easier to remember this timing, as the time for diagnosis and also for monitoring is the same, i.e. 2 hours. However, whichever time is targeted for monitoring glycemic control and adjusting insulin dose, blood tests must be performed at the same time at each visit. They should be advised to perform self-monitoring of blood glucose (SMBG) on a daily basis, failing which, at least weekly monitoring should be encouraged. If self-monitoring is not possible, laboratory venous plasma glucose has to be estimated for adjusting the dose of insulin.

Oral Antidiabetic Drugs:

Insulin secretagogue (glibenclamide) is being used in a few centers in India and abroad, but not yet approved by drug controller of India.

Metformin:

Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin.[40] Metformin has been found to be useful in women with polycystic ovarian disease (PCOD) who failed to conceive[41]

1.6 FOLLOW-UP OF GESTATIONAL DIABETES MELLITUS

Gestational diabetic women require follow-up. An OGTT with 75 g oral glucose, using WHO criteria for the nonpregnant population should be performed at 6–8 weeks postpartum. Diagnosis of diabetes is made if fasting >126mg/dl and or 2hrPG> 200mg/dl and Impaired glucose tolerance (IGT) if 2hrPG is >140 and<199mg/dl.If found normal, glucose tolerance test is repeated after 6 months and every year to determine whether the glucose tolerance has returned to normal or progressed. A considerable proportion of gestational diabetic women may continue to have glucose intolerance. It is important that women with GDM be counseled with regard to their increased risk of developing permanent diabetes.

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Events...

57thAICOG 2014 began with the dynamic team 2014 under leadership of Dr. Suchitra Pandit .
The theme of this year : Empower women ,Empower India Pledge for Excellence
Some memorable pictures during the events:





Evolution of Progesterone in Managing Luteal Support

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Abstract:

It has been well documented that stimulated ART cycles have supraphysiological levels of reproductive hormones, though, defective luteal phase; and the supplementation of the luteal phase with exogenous progesterone is necessary to optimize IVF cycle outcomes. Administration of intravaginal progesterone preparations is equally efficacious and better tolerated by patients compare to intramuscular preparations in ART cycles. HCG if used as a luteal support increases rate of ovarian hyperstimulation syndrome to many fold. There is no need to monitor serum progesterone level in luteal phase as blood level and endometrial level of progesterone may differ widely and does not affect implantation rate.

Here, we review the evidence for route, efficacy, dose and timing of different progesterone preparations. We also discuss the protocol of luteal phase support in different scenario of stimulated cycle with GnRH agonist, with antagonist, frozen embryo transfer cycle and cycle with donor oocyte recipient transfer. We also discuss other substances for co-treatment with progesterone to improve implantation.

Introduction:

The term used to describe the administration of medications aimed at supporting implantation process in luteal phase is Leuteal Phase Support (LPS). The prevalence of luteal phase insufficiency in natural cycles with infertility was demonstrated to be about 8.1% in normal ovulatory patients[1]. It has been established that the luteal phase of all stimulated IVF cycles is abnormal[2].

In search of aetiology of this luteal phase insufficiency, which is debatable for more than two decades, found many hypothesis.

1. **Prolonged GnRH modulators**: Use of GnRH agonist or antagonist in IVF cycles causes disruption of pulsatile released of GnRH from pituitary which is needed for adequate corpus luteum function, thus, leading to luteal phase dysfunction[3,4,5,6,7]
2. **Removal of Granulosa cells** in large quantity while egg retrieval: lead to depletion of cell pool needed to produce progesterone. This hypothesis has been disproved[8].
3. **hCG administration**: for final maturation of oocyte could potentially cause suppression of the LH production via a feedback mechanism[9], however it did not down-regulate the LH secretion in natural cycles[10].
4. **Supraphysiological Steroids level**: The most recent and accepted etiology for luteal phase defect in stimulated IVF cycle is the supraphysiological level of reproductive hormones. Consistent LH stimulus is required for the maintenance and the normal steroidogenic function of corpus luteum[11,12] and for the up-regulation of growth factors[13, 14] and cytokines[15,16] , which are important for implantation. Stimulated IVF cycles are different from natural cycles in supra-physiologicalEstrogen secreted by a high number of follicles directly inhibit the LH release via negative feedback actions at the hypothalamic-pituitary axis level[17] which causes luteolysis.

Role of Progesterone in luteal phase:

1. Progesterone induces a secretory transformation of the endometrium in the luteal phase[18] and by that it improves endometrial receptivity of adequate estrogen priming[19]. Thus, improves implantation rate.
2. Progesterone promotes local vasodilatation by inducting nitric oxide synthesis in decidua, which improves endometrial growth and secretory changes[20].
3. Progesterone has uterine-relaxing properties. High frequency of uterine contractions on the day of embryo transfer hindered transfer outcome, possible by expelling embryos out of the uterine cavity is negatively co-related to progesterone concentration was detected[21].

Optimum Route of progesterone administration

Progesterone is available in different formulations include oral, vaginal, rectal and intramuscular.

Oral: Micronized progesterone by oral route is not preferred as

1. It is subjected to first-pass hepatic metabolism having low bioavailability (only 10%)[22,23]
2. Erratic absorption
3. Serum levels of progesterone return to baseline in 6 hours
4. Having advantage of acceptability only

To overcome this problem, Dydrogesterone, a biologically active metabolite of progesterone having good oral bio availability, was introduced[24,25]. It was claimed to have similar pregnancy rates with micronized vaginal progesterone after IVF[26].

Contrary, many studies showed exogenous vaginal micronized progesterone is significantly more effective than oral dydrogesterone in creating an “in phase” secretory endometrium[27,28].

Intamuscular: it was... The most common form of progesterone that has been used for luteal phase support in IVF has been progesterone oil administered as intramuscular injections (IMP)[29,30]. IMP gives rise to higher plasma concentrations, with levels being maintained for a longer duration[31]. While reasonably effective, IMP are painful for the patients, inconvenient to administer, needs another person to help with administration, associated with severe side effects, such as infections, abscesses, allergic rashes to even pulmonary complications[32,33,34,35]. On the bases of presented evidence, IMP is not recommended as a “first choice” luteal phase support method in stimulated IVF cycles.

Vaginal:

Following intravaginal administration of progesterone, high uterine progesterone concentrations with low peripheral serum values are observed, due to both counter current exchange in progesterone transport between anatomically close blood vessels and the uterine first-pass effect, where liver metabolization is absent[36,37]. Vaginal progesterone gained popularity rapidly being equally effective, most convenient to administer, well tolerated by patients as well as cost effective.

There is growing evidence that vaginal progesterone is at least as effective as intramuscular progesterone for luteal support in induced cycles provided in proper dose and had comparable implantation and clinical pregnancy rates[38].

Efficacy and Acceptance of various vaginal progesterone preparations

There are three standardized vaginal progesterone formulations commercially available for the use. Micronized progesterone capsules, Crinone 8% vaginal gel and natural progesterone in capsules (Endometrin 100 mg).

Out of all three, Crinone bioadhesive gel has property of sustained released delivery over time allowing for once-daily administration. It has excellent coefficient of absorption into endometrial tissues and capable of inducing appropriate secretory endometrial changes necessary for luteal phase support[39,40,41,42]. Both micronized progesterone and crinone have been compared and found equal effective in appropriate doses (discussed below) with IMP. Endometrin at twice a day and 3 times a day doses is noninferior in efficacy than Crinone once-daily dose in women <35 years. However, data are insufficient for its definite role in women over age 35[43]. But patients expressed superior tolerability and acceptability of crinone gel[38,44,45].

A recent meta-analysis, concluded that all vaginal progesterone preparations in adequate doses were equally efficacious for luteal support in IVF/ ICSI cycles with respect to clinical pregnancy rates[46].

Optimum Dose of progesterone administration

The body of scientific evidence confirms equal efficacy of IMP and intravaginal progesterone preparations in therapeutic doses for luteal phase support[46].

A single daily dose (90 mg) of Crinone vaginal gel was approved by FDA for progesterone supplementation in ART, while twice-daily dose was recommended for replacement in postmenopausal or agonadal women[47,48].

The safely effective dose of micronized progesterone in oil capsules is 600 mg daily (200 mg 3 times a day). It has been well demonstrated in histopathological as well as clinical studies that progesterone capsules in doses less than 300 mg/day are inferior in efficacy to IMP.

The optimum dose of Endometrin is 100 mg twice or thrice a day for women <35 years of age. Data are lacking for women ageing > 35 years.

In a dose of 50-100 mg daily intramuscular injections are equally efficacious.

Optimal Timing of Progesterone initiation

While progesterone supplementation in the luteal phase is important, it is similarly important not to advance endometrial maturation out of phase with embryo development. If starting progesterone too early in the cycle has negative effect on the outcome, starting too late could be equally detrimental. Various studies conclude that is an acceptable window of time 24-48 hours after oocyte retrieval for initiation of vaginal progesterone supplementation with optimal cycle results[42,43,49,50,51,52,53]. Further studies are needed to establish the best timing of onset of LPS. Referring to published data, it is recommended to start progesterone at least as early as the oocyte retrieval up to day of embryo transfer (day-3).

Protocols of Progesterone administration

1. **Stimulated ART cycle:** By now, we know that there is definite luteal phase defect in all stimulated ART cycles, but does hormonal milieu differ in conventional Long GnRH agonist protocol vs. GnRH Antagonist protocol?

Long GnRH agonist protocol: With the prolonged pituitary desensitization following a long gonadotrophin-releasing hormone-agonist (GnRHa) down-regulation might result in circulating LH concentrations too low to support the corpora lutea, causing a luteal-phase defect[6,7].

More than 50 years ago, exogenous hCG (5000–10,000 IU) was successfully introduced as a substitute for the endogenous LH surge to induce final oocyte maturation. However, due to the significantly longer half-life of hCG, the ovulatory dose will support the corpora lutea for 7–10 days and prolong the luteotrophic effect. The development of multiple corpora lutea raiseserum concentrations of oestradiol and progesterone throughout the luteal phase[63]and increase the risk of ovarian hyperstimulation syndrome (OHSS)[54].

Thus, conventional method of progesterone supplements (intravaginal gel/ micronized tablets or intramuscular injections) is effective enough to produce desirable changes endometrial environment.

GnRH antagonist protocol: With the introduction of GnRH antagonists in IVF protocols (in 1997) it was anticipated that luteal-phase supplementation would be unnecessary due to the rapid recovery of the pituitary (within 2 days) after GnRH-antagonist discontinuation[55].On the contrary, luteolysis was also induced prematurely after GnRH-antagonist co-treatment, resulting in a significant reduction in the luteal-phase length and a compromised reproductive outcome[56, 57]. Thus, despite the rapid recovery of the pituitary in GnRH-antagonist protocols, luteal-phase supplementation was necessary[58,59].

As hCG increases the risk of OHSS many fold, GnRH antagonist protocol with a bolus of GnRH agonist trigger for ovulation reduces the risk of OHSS even in high risk patients for OHSS.

The advantage of GnRHa triggering

1. A significant reduction in or even total elimination of OHSS as compared with hCG triggering[60,61,62].
2. The retrieval of more metaphase II (MII) oocytes has been reported after GnRHa triggering compared with hCG triggering[63,64,65]. This finding could be the result of the endogenous FSH surge elicited along with the LH surge after GnRHa triggering[66].

The GnRHa-induced LH surge has a shorter duration of action thus, reduced total amount of gonadotrophins being released from the pituitary when GnRHa is used to trigger[54]. Importantly, the endogenous mid-luteal LH concentration was reduced by 75%, this causes a defective luteal phase[67,68], necessitating a modification of the standard luteal-phase support commonly used in GnRH agonist long protocol to secure the reproductive outcome[69]. In one study by Humaidan reported one bolus of hCG (1500 IU) administered either at the time of triggering (dual trigger) or after oocyte retrieval rescues the luteal phase after GnRHa triggering, resulting in a reproductive outcome comparable with that of hCG triggering. At the same time, the risk of OHSS seems to be decreased, even in the OHSS high-risk patient[70].

2. **Frozen Embryo transfer cycle/ Donor oocyte Recipient cycle:**

These cycles are different from stimulated IVF cycles in that there is no endogenous progesterone production, and thus, there is a need for luteal phase "creation" or replacement.

Intramuscular progesterone in doses 50-100 mg daily has been the most common practice. Yet, no definite data available regarding the role of vaginal progesterone preparation compare to intramuscular progesterone in frozen embryo or donor oocyte recipient cycle. FDA has approved Crinone gel once- daily application supplement and twice-daily for replacement therapy. Both routes are equally effective and similar in pregnancy rate[33,43,48].

Optimal Timing of withdrawing progesterone in case of pregnancy

There is limited data and little consensus on the necessary duration for progesterone supplementation in early pregnancy. Andersen et al suggested the progesterone support can safely withdraw after the first positive beta-hCG result[71]. Proctor et alconcluded the first trimester progesterone in IVF may support early pregnancy through 7 weeks by delaying a miscarriage, but it does not improve live birth rates. While Aboulghar et al concluded that there was no advantage to continuing progesterone support beyond the time of first ultrasound viability study[72].

Monitoring of Serum progesterone level, what evidence says?

Since the first group of study by Smitz et al showed lower serum progesterone levels but adequate endometrial maturation and similar pregnancy rates with vaginal progesterone preparations compared to intramuscular preparation, there has been little reason to be concerned with serum progesterone level monitoring. Other studies by Bulletti and Ciccinelli also confirmed that there was no correlation between the desired endometrial maturation effect and serum progesterone levels, and thus, there is no reason to subject patients to unnecessary blood test and potential anxiety involved with serum level monitoring[39,40] when they are on progesterone therapy.

Conclusion:

1. Supraphysiological hormonal profiles are the cause of luteal phase defect observed in stimulated IVF cycles.
2. Luteal phase support with vaginal or intramuscular progesterone after ART results in increased pregnancy rates and is necessary for optimum results. The vaginal route is preferred over the IMP as an equally effective, easier, less painful, and less time-consuming and is associated with less discomfort. Oral progesterone seems not to be efficient for supporting the luteal phase of stimulated IVF cycles.
3. Once daily Crinone gel, or twice or three times daily Endometrin, or Micronized progesterone 200 mg 3 times a day are optimal doses of vaginal progesterone.
4. The use of hCG in luteal phase support is associated with a marked increase in the risk of OHSS
5. Although there have been attempts to introduce GnRH agonist as a novel approach to LPS, it is too early to adopt. Ascorbic acid, aspirin, naloxone, prednisolone, all of them have been suggested to be beneficial previously, have not been proven usefulness in LPS as co-treatment of progesterone.
6. There exists a window of time when vaginal progesterone should be initiated for optimal pregnancy rate. It is best started within 24-48 hours after oocyte retrieval and continued for at least 15 days, until the day of positive hCG test. There is insufficient data to date to establish the right time for discontinuing support.
7. There is no need for serum progesterone level monitoring with vaginal supplementation as there is little correlation between serum levels and local endometrial effects or pregnancy outcome.
8. The addition of Estrogen to progesterone for LPS does not increase the probability of pregnancy in IVF.
9. More large, prospective, randomized studies are needed to assess the ideal dose, the optimal route, the duration of progesterone administration in stimulated IVF cycles and in frozen embryo transfer or donor oocyte recipient cycles.

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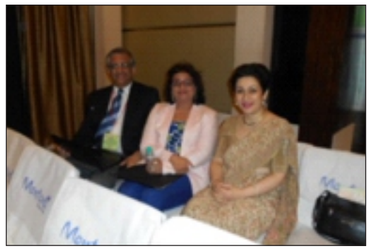
4th National Conference on Gynae-Endocrinology was held on 26th April, 2014 at New Delhi
Some glimpses of the event: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Women Presenting with Premature Rupture of Membrane in Pregnancy

Abstract

Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor. In most cases, this occurs near term, but when membrane rupture occurs before 37 weeks' gestation, it is known as preterm PROM. It increases the risk of prematurity and leads to a number of other perinatal and neonatal complications, including a 1 to 2 percent risk of fetal death. Obstetrician should be versed in the management of PROM because rapid diagnosis and appropriate management can result in improved outcomes.

Premature rupture of the membranes is defined as spontaneous membrane rupture that occurs before the onset of labor. When spontaneous membrane rupture occurs before 37 weeks' gestation, it is referred to as preterm PROM. Preterm PROM complicates approximately 3 percent of pregnancies and leads to one third of preterm births. As such it is currently more clinically relevant to differentiate preterm PROM into "previable PROM," which occurs before the limit of viability (less than 24 weeks), "preterm PROM remote from term" (from viability to about 34 weeks' gestation), and "preterm PROM near term" (approximately 34–36 weeks' gestation).

In most cases the cause of premature rupture of membranes is not known. Choriodecidual infection or inflammation may cause preterm PROM (1) A decrease in the collagen content of the membranes has been suggested to predispose patients to preterm PROM (2) There are risk factors however that increase the risk of developing the condition. These risk factors include: lower socioeconomic status, cigarette smoking, sexually transmitted diseases, genital tract infections, poor maternal nutrition, multiple gestation, polyhydramnios, PROM in a previous pregnancy and cervical cerclage or amniocentesis (3). Each of these may be associated with preterm PROM through membrane stretch or degradation, local inflammation, or a weakening of maternal resistance to ascending bacterial colonization.

In certain circumstances, immediate delivery of the fetus with PPROM irrespective of gestational age is indicated. These circumstances include chorioamnionitis, advanced labor, fetal distress, and placental abruption with nonreassuring fetal surveillance. If fetal lung maturity has been documented by either amniocentesis or collection of vaginal fluid, delivery should be facilitated. In a noncephalic fetus with advanced cervical dilatation, the risk of cord prolapse may also outweigh the benefits of expectant management and delivery should be considered.

Premature rupture of membranes (PPROM) is associated with significant risk to the mother and her unborn child. Prematurity is the most significant factor in the increased perinatal morbidity and mortality associated with PROM. An analysis of studies (4) evaluating patients with preterm PROM between 16 and 26 weeks' gestation determined that 57 percent of patients delivered within one week, and 22 percent had a latent period of four weeks. Complications of PROM for the fetus and newborn consist of prematurity, fetal distress, cord compression, necrotizing enterocolitis, neurologic impairment, intra ventricular hemorrhage, respiratory distress syndrome altered pulmonary development leading to pulmonary hypoplasia and pulmonary hypertentsion.

Sterile speculum examination is by far the most accurate for diagnosis of ROM. It also estimate cervical dilation, collects amniotic fluid for tests, and obtains samples for cervical cultures.

A series of tests have been used to confirm membrane rupture; the most widely used has been the Nitrazinetest, which detects pH change which has a sensitivity of 90% and a false positive rate of 17 % (5). Blood contamination of the Nitrazine paper and ferning of cervical mucus may produce false-positive results. More recently, fetal fibronectin and raised insulin-like growth factor binding protein-1 have been evaluated in cervical secretions with reported sensitivities of94% and 75% and specificities of 97%, respectively (6,7).

A new product, Amni Sure, is being marketed with claims of positive and negative agreement that exceed 95%. The use of this product in certain instances when a speculum examination cannot be performed may be of some use as an initial evaluation. Digital vaginal examination is best avoided unless there is a strong suspicion that the woman maybe in labour. This is because micro-organisms may be transported from the vagina into the cervix, leading to intrauterine infection, prostaglandin release and preterm labour.

All women with PPROM should be monitored for signs of clinical chorioamnionitis. The criteria for the diagnosis of clinical chorioamnionitis include maternal pyrexia, tachycardia, leucocytosis, uterine tenderness, offensive vaginal discharge and fetal tachycardia.

There is a variation in the literature regarding the accuracy of the laboratory tests of leucocytosis and raised C-reactive protein in the prediction of chorioamnionitis. The presence of leucocytosis may be useful clinically in cases where there is doubt about the diagnosis of chorioamnionitis. High vaginal cultures should be obtained, that may indicate group B streptococcus, which provides the opportunity for intrapartum antibiotic therapy.

Ultrasonographic documentation of gestational age, fetal weight, fetal presentation, and amniotic fluid index should be established. Abnormal biophysical profile scores and increased systolic/diastolic ratios in the umbilical artery have been shown to be markers of intrauterine infection.

Between 24-34 weeks

When the mother and fetus are in stable condition, a policy of expectant management usually is adopted to try to gain additional time for the fetus in utero. Management requires balancing risk of infection when delivery is delayed with risks due to fetal immaturity when delivery is immediate. It is important that the patient be well informed regarding the potential for subsequent maternal, fetal, and neonatal complications regardless of the management approach.

Antibiotic therapy for PPROM is now routinely used and it is associated with prolonged time to delivery and reduced neonatal morbidity. The goal of antibiotic therapy is to reduce the frequency of maternal and fetal infection and delay the onset of preterm labor. There was inadequate data to determine whether any antibiotic regimen (drug, dose, duration) was better than another, but macrolide antibiotics (eg, erythromycin) appeared to be safer than beta-lactam antibiotics (eg, amoxicillin-clavulanate), as the latter were associated with an increased risk of necrotizing enterocolitis.

Therapy longer than 7 days should be avoided; it has not been shown to be more effective and may promote the emergence of resistance organisms.(8,9)

The use of corticosteroids to accelerate lung maturity should be considered in all patients with PPROM with a risk of infant prematurity from 24-34 weeks' gestation.

Antenatal corticosteroids reduce the risk of RDS, intraventricular hemorrhage, and perinatal death and have been shown to have long- term neurological benefits when given in a timely fashion before preterm birth(10). The current NIH consensus conference recommendations regarding corticosteroid ad- ministration in the setting of preterm PROM are that a single course of betamethasone (12 mg intramuscularly [IM], two doses every 24 hours) or dexamethasone (6 mg IM, four doses every 12 hours) be given during conser- vative management of preterm PROM before 30–32 weeks' gestation because of the potential for reduction of intraventricular hemorrhage (11). However, regularly scheduled repeat courses or more than 2 courses are not recommended.

Limited data are available to help determine whether tocolytic therapy is indicated after preterm PROM. A recent retrospective case–control study showed that tocolysis after PPROM did not increase the interval between membrane rupture and delivery or reduce neonatal morbidity (12). Prophylactictocolysis in women with PPROM without uterine activity is not recommended. Women with PPROM and uterine activity who require intrauterine transfer or antenatal corticosteroids should be considered for tocolysis.

Transvaginal amnioinfusion in labour as well as transabdominal amnioinfusion is not recommended as a method of preventing pulmonary hypoplasia in very preterm PPROM. Transvaginal amnioinfusion during labourl involving 66 women with PROM between 26 and 35 weeks of showed no significant difference for caesarean section, low Apgar scoresand neonatal death (13).

More than 34 weeks

The management of pregnancies complicated by PPROM between 34 and 37 weeks of gestation continues to be a contentious issue. Studies have shown that labor induction clearly is beneficial at or after 34 weeks' gestation.

Where expectant management is considered beyond 34 weeks of gestation, women should becounseled about the increased risk of chorioamnionitis and its consequences versus the decreased risk of serious respiratory problems in the neonate, admission for neonatal intensive care and caesarean section. Although corticosteroids are not indicated after 34 weeks' gestation, physicians should prescribe appropriate antibiotics for group B streptococcus prophylaxis and should consider maternal transport to a facility skilled in caring for premature neonates, if possible.

Before 24 weeks

Premature preterm rupture of membranes (PPROM) prior to fetal viability is a rare problem that occurs in less than 0.4% of all pregnancies. The major maternal risk is chorioamnionitis 35%; abruption 19%; and sepsis 1%. The major morbidity in the fetus is lethal pulmonary hypoplasia , RDS (66%), sepsis (19%), grade III-IV IVH (5%), and contractures (3%) also occur with high frequency, resulting in intact survival rates of more than 67%. Fetal death is common and occurs in more than 30%.Expectant management may be appropriate in select patients who are well informed and educated about the risks and the dismal prognosis for the neonate. The patient needs to be educated and informed of warning signs of intra-amniotic infection, and they must take their temperature 3 times a day at home that indicate the need for immediate evaluation. Frequent examinations are necessary to ensure maternal safety. Group B streptococcal prophylaxis and Corticosteroids is not recommended. There are incomplete data on use antibioticsin prolonging latency. Until viability, maternal safety should be the primary concern. After viability is reached, inpatient management needs to be considered.

Conclusion

In conclusion, management of PROM requires an accurate diagnosis and evaluation of the cost, risks and benefits of continuing pregnancy or expeditious delivery. To determine the potential benefits of conservative management of preterm PROM at any gestation, an understanding of gestational age–dependent neonatal morbidity and mortality is important. In these cases expectant active management with corticosteroids and antibiotics may be suitable for carefully selected patients. In such a condition the final treatment option may be the patient's decision, which should be confirmed by a consent form. Close and careful follow-up may prolong the latency period to bring a desperate fetus from the lower limits of viability to "life-zone". Alternatively, when preterm PROM occurs near term, the patient is generally best served by expeditious delivery, particularly if fetal pulmonary maturity is evident. It is important that the patient be well informed regarding the potential for subsequent maternal, fetal, and neonatal complications regardless of the management approach.

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Pro fertility Neutraceuticals in the Male

Introduction

Approximately 10-15% of all couples seek fertility assessment. With a greater participation of women in workforce and the associated delay in the ages of marriage and first child bearing, infertility services are being increasingly utilized. With the advent of assisted reproductive techniques, and the tremendous success it has enjoyed, the evaluation of the male and an attempt at curative treatment is often overlooked. Male factor is involved in about half of the infertility cases. Therefore, identifying the pathology and treating the male may allow couples to improve their fertility potential and conceive through natural intercourse.

Treatment options in Oligoasthenoteratozoospermia (OATS):

1) Medical therapy Specific or Empirical
2) Surgical therapy
3) Assisted reproductive techniques (ART): Intrauterine insemination (IUI) or Intra cytoplasmic sperm injection (ICSI).

Specific medical management of OATS is based on identifying reversible causes of infertility and treating them with appropriate medications to achieve a pregnancy. Despite the advancements in diagnostic methodology, no identifiable cause can be found in 25% of infertile males. This is referred to as Idiopathic Oligoasthenoteratozoospermia. These patients are treated with nonspecific empirical medications based on theoretical concepts, in an attempt to improve semen parameters and fertility potential.

This article will review the specific and nonspecific medical treatment of OATS.

But first, it is essential to know who the candidates are for a trial of medical therapy? And who should be counseled for ART.

Factors that influence choice of therapy in OATS:

1) Age of the couple and duration of infertility. A young couple with a short trying time should be given the option of medical therapy in order to buy time to achieve a natural pregnancy. On the other hand, an older couple with a much longer trying time should be counseled to move towards ART.

2) Severity of OATS and realistic chances of improvement expected a patient with severe OATS (less than 5 million/ml with very poor progressive motility) with no obvious reversible factors is more likely to benefit from ART.

3) Past illness causing irreversible damage? For example, a patient who had post-mumps orchitis and testicular atrophy, or who was operated for undescended testes. In such patients, it is unlikely that medical therapy will help.

4) Reversible, correctable gonadotoxic factors? If there is occupational exposure to gonadotoxins (heat, chemical fumes), heavy smoking, recent febrile illness, accessory gland infections, etc., then such patients can be given supportive medical therapy to buy time for improvement of semen parameters once the gonadotoxic factors are eliminated/modified.

5) Treatment history is imperative. It's important to know what drugs a patient has already tried in the past (whether they were effective or not) so there is no repetition. If various drugs have already proved ineffective there is no point in giving further medical therapy.

6) Socioeconomic status of the couple should also be considered when deciding medication since many empirical drugs are rather expensive.

7) Psycho-social pressures on the couple play an important role in decision making. In a couple who is socially hard-pressed for a baby, less time should be spent on medical therapy.

Specific medical therapy

With history, physical examination and specific investigations, it is possible to diagnose and treat certain specific medical conditions that will contribute to OATS.

a) Chronic scrotal fungal dermatitis: This can affect fertility by thickening the scrotal skin and thus increasing the local temperature. This is treated with topical antifungal plus steroid creams.

b) Genital tract infection: The World health organization (WHO) defines leucocytospermia as seminal white blood cells (WBC) levels more than or equal to 1 X 10^6 /ml (WHO 1999) with the prevalence among male infertility patients being about 10-20%.The clinician must ensure that the laboratory should clearly differentiate between leucocytes and immature germ cells using cytologic staining or immunohistochemical techniques. All men with elevated seminal WBC levels (>1 × 10^6/mL) should be evaluated for a genital tract infection or inflammation, and a semen culture should be performed. Common organisms responsible are *Streptococcus fecalis* and *Escherichia coli, Chlamydia trachomatis* and *Ureaplasma urealyticum. Because of the difficulty of culturing chlamidia or ureaplasma we often give* Doxycycline 200 mg/day *on an empirical basis for 15 days and then start a*ntibiotics as per culture reports. Commonly used are: Fluoroquinolones 0.5 to 1 g/day, Cotrimoxazole (Sulfamethoxazole 800 mg, Trimethoprim 160 mg) or Erythromycin 1.5 to 2 g/day. These drugs are administered for 2 to 3 weeks. However, culture-negative patients with proven leukocytospermia should be treated with anti-inflammatory therapy and frequent ejaculation because empiric antibiotic therapy generally provides no benefit and may be harmful.

c) Immunologic infertility: Oral prednisolone is commonly used to suppress antibody production, but no double-blind, randomized trial has confirmed their efficacy. ICSI is considered to be the treatment of choice for patients with severe sperm autoimmunity. Recently, higher fertilization rates during in vitro fertilization (IVF) were reported in patients with antisperm antibodies and immun-osuppressive therapy compared to IVF alone. Thus, treatment of antisperm antibodies using corticosteroids should not be prescribed routinely, but it can be considered in patients with antisperm antibodies and earlier failed fertilization during IVF or ICSI. High doses of prednisolone should be avoided even on short term due to the rare but catastrophic risk of avascular necrosis of femoral head.

d) Chronic epididymo-orchitis : Many subfertile men have clinical evidence of chronic filarial epididymo-orchitis residence in an endemic area, enlarged adherent epididymis, thickened cord, lax hydrocoele, h/o hydrocele surgery, h/o testicular swelling with fever, and occasionally ultrasound evidence of the "filarial dance". Such men sometimes show good improvement in semen parameters after a course of anti-filarial therapy (DEC 100mg thrice-a-day for 20 days in combination with doxycycline 100mg twice-a-day for 10 days) followed by low dose steroids as given above.

Specific surgical therapy:

Varicocele ligation can play a useful role in selected cases but a discussion on this controversial topic is outside the scope of this article.

Nonspecific or empirical therapy:

In patients with idiopathic OATS, a variety of empirical medical therapies have been recommended. Although there are numerous reports that support a multitude of compounds, the

vast majority are nonrandomized studies and unfortunately no medical therapy has demonstrated consistent efficacy in multiple, rigorous, well-controlled, randomized, placebo controlled trials.

Non-specific treatments include

A. Hormonal agents: Androgens, Anti-estrogens, Aromatase inhibitors, Gonadotropins.
B. Antioxidants: Glutathione, Lycopene, Vitamin -E,
C. Sperm vitalisers : L -carnitine, Co-enzyme Q 10
D. Nutritional supplements : Folic acid, Zinc, Multivitamins, Trace elements
E. Miscellaneous: Indomethacin, Kallikrien, Low dose corticosteroids.
F. Elimination of gonadotoxic factors

HORMONAL AGENTS:

ANDROGENS:

- **Rationale**

- Direct therapy: Exogenous androgens, administered at a dose that will not influence the pituitary-gonadal axis, may have a direct stimulatory effect on spermatogenesis or influence sperm transport and maturation through an effect on the Epididymis, Vas deferens and Seminal vesicles.

- Rebound therapy: High doses of exogenous androgens will suppress the H-P-T axis and result in azoospermia. Subsequently, after cessation of androgens, the gonadotropin levels will rise again, during which period there may be a rebound increase in sperm counts above baseline.

- **Drugs used and dosage**

- Direct therapy: Mesterolone 25mg thrice daily; Testosterone undecanoate 40mg two to four capsules daily.

- Rebound therapy: has been given up because of uncertain results and risk of permanent azoospermia

ANTIESTROGENS :

- **Rationale:** Antiestrogens inhibit the negative feedback effect of estrogen by blocking estrogen receptors in the hypothalamus, which in turn increases endogenous gonadotropin secretion. In turn, FSH and LH stimulate Sertoli and Leydig cells with a possible improvement in spermatogenesis.
- **Drugs used and dose:**

i. Clomiphene citrate : 25mg daily, or on alternate days
ii. Tamoxifen citrate : 10 to 20 mg daily

- **AROMATASE INHIBITORS :**

Rationale: Estrogen has a potent negative feedback effect on gonadotropin secretion. Obese men have excessive aromatization, in their fat cells, of Testosterone to Estrogen resulting in excess estrogen and an altered Testosterone to Estrogen ratios (T/E). Aromatase inhibitors correct this by inhibiting the peripheral conversion of Testosterone and may thereby enhance spermatogenesis.

- **Drugs used and dose :**

i. Letrozole 2.5mg daily orally

GONADOTROPINS :

- **Rationale:** Some patients with idiopathic infertility may have a subclinical endocrinopathy which results in abnormalities in the bio-activity, half-life or pulsatility of gonadotropin secretion. Such men may benefit from exogenous gonadotropins despite normal levels on immunoassay.
- **Drugs used**: Human chorionic gonadotropin (HCG) (1500 IU i.m 3 times per week), Human menopausal gonadotropin (HMG) (37.5-75 IU i.m 3 times per week) ,

ANTIOXIDANTS:

- **Rationale:** Elevated seminal Reactive Oxygen Species (ROS) levels have been recognized as an independent marker of male factor infertility, irrespective of whether patients have normal or abnormal semen parameters. Spermatozoa are particularly susceptible to oxidative stress-induced damage. Antioxidants in seminal plasma are the most important form of protection available to spermatozoa against ROS. Many studies have supported the use of exogenous antioxidants in the treatment of idiopathic infertility.
- **Drugs used and dose:** Glutathione 250mg daily (50-600mg/day), Lycopene 4-8 g daily, Vitamin E 400 to 800 mg daily.

SPERM VITALISERS:

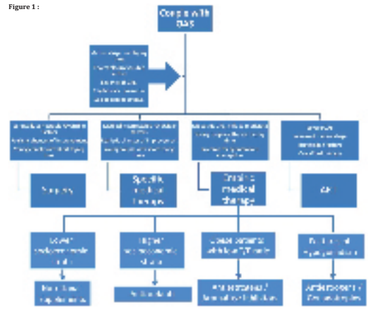
- **Rationale:** Act through varying mechanisms with a common end-point of energizing the sperm and making them more capable of fertilization. They may have a role in sperm maturation during the transit through the epididymis. Some of them have an antioxidant action in addition.
- **Drugs used and dose:** L-Carnitine and Acetyl Carnitine 1 g, thrice-a-day;

: Coenzyme Q10 100-300 mg per day.

NUTRITIONAL SUPPLEMENTS :

- **Rationale:** In our country, majority of the people from the lower socioeconomic strata are nutritionally depleted and therefore may not have the necessary levels

Figure 1 :



of vitamins and trace elements to facilitate spermatogenesis.

- **Drugs used :** multivitamin combinations with zinc, selenium, folic acid, and B12

MISCELLANEOUS :

- **Rationale:** Some of these therapies have aimed at improving sperm quality by boosting the Kallikrein-Kinin system (Kallikriens) or by interfering with the production of prostaglandins (Phosphodiesterase inhibitors, Nonsteroidal anti-inflammatory agents)
- **Drugs used:** Kallikriens 600 IU daily; Indomethacin.

ELIMINATION OF GONADOTOXIC FACTORS

Elimination of chronic exposure to heat at the workplace (furnace, kitchen, etc) or in leisure activities (sauna, steam bath), cessation of heavy smoking, avoidance of exposure to pesticides (DDT spray) or chemical fumes (aromatic amines), reduction of excessive stress, regularization of diet and lifestyle can also help some men significantly.

Conclusions:

As physicians taking care of couples with OATS, it is our duty to give the patients a very clear road map of their course of therapy. Therapy must be individualized and it is mandatory that a treatment timeline and endpoints be established prior to initiation of medical therapy. When empiric pharmacologic therapy is going to be used, treatment should last at least 3 months to incorporate a full 74-day spermatogenic cycle, and should be followed by a semen analysis. If there is significant improvement then the medications should be continued and further improvement monitored monthly. If there is no improvement then the medication should be changed. Patients must be counseled regarding the inconsistent response to medical therapy and to have realistic expectations from the same. Most importantly, we must not be guilty of wasting precious time and money over medical therapy when the circumstances call for assisted reproductive therapy. Figure 1 summarizes a practical approach to the management of OATS.

PCOS diagnosis : an update

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PCOS diagnosis ,as we all know is all about consensus till now. It looks apt to quote Michael Crichton here, who said ,

'Consensus is the business of politics' and, 'If it's consensus, it isn't science. If it's science, it isn't consensus'.

Introduction:

PCOS is the commonest endocrinopathy affecting women of reproductive age group .It's quoted prevalance is in the range of 5-10%,but,the said prevalance does vary as per geographical area. In Indian context, a study of young women of age 18-25 years found the prevalance rate of 3.7% by NIH and 11.9% by Rotterdam's criteria.

Correct diagnosis of PCOS is of utmost importance as it is known to adversly affects reproductive as well as general health of the females.

Stein IF and Levental ML originally described it in 1935 in seven women as a syndrome consisting of a combination of hirsutism, obesity, amenorrhea, and enlarged bilateral polycystic ovaries,

The amount of research,curiosity and controversy in this syndrome since then is enormous, and possibily unparalleled. Presently available diagnostic criterias for PCOS are as heterogeneous as the disorder itself.

The diagnosis of PCOS is becoming increasingly common, due not just to increasing prevalence, but also to imperfect diagnostic criterias along with inclination of the clinician to reach to a diagnosis. This needs to be avoided at all costs considering the life long implications which the diagnosis of PCOS carries with it including diabetes, hypertension. dyslipidemia, subfertility, endometrial malignancy and cardiovascular risk to the women as well as her relatives.

In this update,we would discuss the available criterias, their pros and cons, recent evidence advocating changes in them and the possible newer diagnostic modalities of the future.

Available diagnostic criterias:

Ironically, PCOS still remains a diagnosis of exclusion. There are 3 major criterias present till date to define PCOS. Importantly, all, barring none, were primarily based on expert opinion rather than on evidence.

The first concerted effort to define PCOS (**NIH criteria**) in 1990,defined PCOS was as the combined presence of hyperandrogenism and oligo-anovulation in the absence of all other causes for anovulatory infertility,

NIH criteria considered PCOS as primarily a defect of androgen homeostasis with resultant effect on ovary and menstrual cyclicity.

In a consensus meet in 2003 at Rotterdam, the ESHRE and ASRM modified the consensus criteria to include sonographic evidence of polycystic ovaries as a third diagnostic marker. The 2003 criteria required at least two of the following three conditions to be present for the diagnosis of PCOS: *(a)* oligo- or anovulation, *(b)* clinical or biochemical signs of hyperandrogenism, and *(c)* polycystic ovaries.

The diagnosis of PCO morphology (PCOM) by Rotterdam's criteria was based on counting 12 or more follicles measuring 2 to 9 mm in diameter and/or have an increased volume of 10 ml or greater.

This criteria has been criticized by researchers on various fronts:

1) It gives rise to phenotypes that may not actually represent PCOS,namely,the mild form, characterized by absence of hyperandrogenism.
2) The threshold of 12 follicles between 2-9 mm to diagnose PCOS has been challenged recently as it is present as an isolated finding in many non - PCOS women.
3) The subjective bias in measuring follicle number or ovarian volume.
4) Resultant over diagnosis of PCOS.

The Androgen Excess and PCOS Society came up with updated criteria in 2009, as they considered hyperandrogenism to be a quit essential feature in the diagnosis. As per the criteria, PCOS was diagnosed in presence of both *(a)* hyperandrogenism (hirsutism or biochemical hyperandrogenemia) and *(b)* ovarian dysfunction (oligo- or anovulation or polycystic ovaries).

AES-PCOS criteria removed the polycystic ovaries on ultrasound as an independent marker. Instead, it was clubbed with ovulatory disorder to constitute what was quoted as ovarian dysfunction.

Which criteria of the three presently used constitutes the best definition of PCOS is still a matter of debate.

As can be noticed above, ovulatory dysfunction, PCO morphology on scan and hyperandrogenism are presently the most utilized modalities for arriving at PCOS diagnosis. But, each one of these still have limitations.

PCO morphology:

The introduction, followed by the advances in ultrasound technology might be the most important factor contributing to an artificial increase in prevalence of PCO. This, perhaps was possible due to more accurate detection of small antral follicles by the newer machines with higher resolution, which otherwise would have gone unnoticed.

There are various end points which have been studied for their diagnostic accuracy like follicle number per ovary (FNPO), ovarian volume (OV), follicle number per single cross-section (FNPS), follicle distribution pattern, stromal area and ovarian area among others. FNPO has been shown to be the best of all the above.

Studies have shown that up to one fourth of women of reproductive age group can have polycystic ovaries on ultrasound.

While only 5-10% of these might fulfill the criteria of polycystic ovarian syndrome.

More so, the Rotterdam's criteria of the threshold of>/= 12 follicles throughout the entire ovary was based on a single study of 214 women claiming to have 99% specificity and 75% sensitivity in distinguishing between polycystic and normal ovaries.

These values have not been reproduced in the studies that followed and appears to be an unusually low threshold for the PCOS diagnosis.

Recently, evidence has surfaced questioning these cut-off values as upto 58% of the control subjects in one of the studies had> 12 follicles per ovary.

A threshold of 26 follicles throughout the entire ovary was shown to have a better diagnostic potential to distinguish between women with PCOS and controls compared to follicle counts made in a single plane or ovarian volume

Cybele
Goddess of Fertility & Womanhood

A recent task force report by AES-PCOS society recommends >/= 25 follicles for PCO diagnosis while using newer technology that affords maximal resolution of ovarian follicles (i.e. transducer frequency ≥ 8 MHz).Incidentally,the first author of the this report was co-author of the paper in 2003 based on which PCOM criteria of Rotterdam's came in vogue.

Even the antral follicle counts varied in the same woman from 7 to 22 during the early follicular phase of the menstrual cycle (day 2, 3, or 4) in women less than 30 years of age.

Subjective differences in interpretation of ultrasonographic images of polycystic ovaries is another major drawback of the present criterias. In a study where ultrasound images of polycystic and normal ovaries were duplicated and randomized for evaluation by four observers, an inter-observer agreement of 51% and intra-observer agreement at only 69% of the time was demonstrated.

This raises serious questions over reliability of single scan for PCO morphology in the diagnosis.

To reduce the risk of recounting or overlooking follicles in real-time examination, Lujan and colleagues recommended offline assessments of images taken after compartmentalizing the ovary into grid sections and performing focused follicle counts on individual segments of the ovary to generate estimations of FNPO. This reduced inter and intraobserver variations significantly.

Ovulatory or menstrual dysfunction:

What constitutes oligomenorrhea is still unclear.

One of the suggested definition of oligomenorrhea or infrequent menses in an adult women is the presence of less than 9 menstrual periods per year, or 3 cycles greater than 38 days during the past year.

Mere presence of regular menstrual cycles in women with hyperandrogenism does not ensure ovulatory status, since upto 40% of these women have oligo-anovulation when laboratory tests are performed.

Hyperandrogenism:

The NIH and Rotterdam classifications does consider hirsutism, acne and alopecia as signs of clinical hyperandrogenism, whereas the AES classification only considers the presence of hirsutism as a genuine marker of HA.

The reliability of acne in the diagnosis of hyperandrogenism is questionable. Almost all teenagers and 54% of women over25 years of age show a degree of physiological acne.

In one of the study of PCOS women, 58% of the control women had acne.

Hirsutism diagnosis is complicated by the fact that the standard scoring system designed by Ferriman and Gallwey does not give any additional weightage depending on site of hair growth.

The position for androgenetic alopaecia is much less clear and relates more closely to iron deficiency than androgen excess.

Pertaining to biochemical hyperandrogenism, all the three available diagnostic criterias are consistent that measurement of androgens are necessary.

There is an absolute lack of clarity on type of androgen to be measured, frequency of measurement, and the type of analytical technique to be employed.

What is still unclear is the reliability of these assays.

The contentious issues being:

1) Variability of concentration of testosterone with age and time of day.
2) With only 1–3% of testosterone being unbound to plasma proteins, it raises questions about whether total or free testosterone is the most clinically useful measure.
3) Non availability of age and gender-corrected normal ranges, using a standardized assay.
4) Absence of a universally recognized testosterone calibrating standard.
5) Significant cross reactivity of testosterone with dehydroepiandrosterone-sulphate (DHEAS).

The measurement of free testosterone by direct radioimmunoassay (RIA) may be inaccurate.

For these reasons, it might be advisable to rely on free androgen index (FAI) that correlates well with the levels of free testosterone measured by equilibrium dialysis, and has been shown to have excellent sensitivity and specificity in women with PCOS.

The recent studies, though do not support FAI measurement to be that reliable citing its over dependence on SHBG levels leading to changes in FAI levels independent of androgen production, thus introducing a nonspecific metabolic bias.

Role of AMH:

Due to the said limitations of the 3 diagnostic criterias, focus has shifted to assessment of role of AMH for diagnosing PCOS.

Serum AMH concentrations have a potential to differentiate between normal ovaries, PCOM and PCOS

The AMH cut off value of 3.8 ng/mL in one study showed that AMH alone had 80 % sensitivity and 80.2 % specificity for AES criteria, 81.6 % sensitivity and 85.1 % specificity for Rotterdam's criteria and 80.7 % sensitivity and 74.7 % specificity for NIH criteria.

Similarly, on replacing PCO morphology by AMH for the diagnosis of PCOS,100 % specificity and 96 % sensitivity

Was obtained for Rotterdam's criteria and 96 %sensitivity and 93 % specificity for the AES criteria.

Thus AMH, as a single screening tool, has relatively low sensitivity and specificity, but, combining it with hyperandrogenism or oligomenorrhea increases the diagnostic accuracy appreciably.

In a recent meta-analysis,a cutoff value of AMH of 4.7 ng/mL was found to have nearly 80% sensitivity and specificity for PCOS diagnosis making it a useful first-line investigation.

This could have significant effect on the prevalance of PCOS as shown in one article where by replacing the criterion for polycystic ovaries by antral follicle count of > 19 or AMH > 35 pmol/l, the prevalence of PCOS by Rotterdam's criteria was reduced from 16.6% to 6.3 and 8.5%, respectively.

At the moment, AMH looks very promising and exudes potential to become a routine and reliable test in the PCOS diagnosis.

To conclude, it appears that time has arrived to increase the cut off for antral follicle from the present number of 12.Also,incorporation of AMH looks inevitable for accurate diagnosis in the near future. These modifications along with the existent markers of oligo-anovulation and hyperandrogenism can substantially reduce over diagnosis and unnecessary interventions in non PCOS females.

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Surogacy in India: Have We Come of Age

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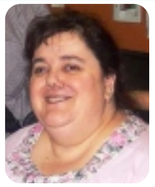

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Modern medicine has advanced by leaps and bounds bringing in its realm advances in fertility treatment making possible procedures such as surrogacy. The roots of surrogacy however, can be traced back to Hindu mythology. When Devaki, wife of Vasudeva found herself pregnant for a seventh time, the unborn child (who was at grave risk from Devaki's brother Kansa) was miraculously transferred into the womb of Rohini, the first wife of Vasudeva. Rohini in due course gave birth to Balarama, Lord Krishna's older brother. This is believed to be the first recorded example of surrogacy. The first successful baby birth from gestational surrogacy in India is believed to be a singleton born in Chennai on 23 June 1994. There is little doubt that celebrities who have built their family using surrogacy have contributed to its growing acceptance in modern India. Since 2002, compensated (more commonly known as commercial) surrogacy in India has gained popularity nationally and throughout the global community as a fertility treatment in situations where a child cannot be carried to term safely by a parent.

When discussing surrogacy in the Indian context, it should be noted that we are talking about Gestational "surrogacy", means an arrangement in which a woman agrees to a pregnancy, achieved through assisted reproductive technology, in which neither of the gametes belong to her or her husband, with the intention to carry it and hand over the child to the person or persons for whom she is acting as a surrogate" (p4).Traditional Surrogacy where the surrogate mother is also the oocyte donor are prohibited in India as per National Guidelines.

Surrogacy is a medical procedure entwined with important legal, social and ethical issues and in cases where the commissioning parents are International and additional element of International Law comes into play.

Legal Construct: There is no specific legislation/ law which governs surrogacy in India. At the same time there is no law which prohibits it. However it would be wrong to suggest that there is a lack of legal construct. Questions surrounding surrogacy, parentage, the rights of parents, surrogates and the child have been tested in both District courts (Saket Court New Delhi being an example) and the Honourable Supreme Court of India. The current legal construct consists of: The ICMR Guidelines, Report 228 of the Law Commission of India, The Honourable Supreme Court of India's Judgment in the Baby Manji Yamada case and decrees in various civil courts in India, the ART (Regulation) Bill 2010 and the Ministry of Home Affairs (MHA) Guidelines. (MHA Guidelines are specific for international commissioning parents).

Complementing theguidelines are the following Acts that all practitioners must follow. These include, but are not limited to:

- Artificial Conception Amendment Act, 2000, Gazette 28-9-2000 (including donor anonymity), the PCPNDT Act, the current privacy laws with regards to medical and personal information, the MTP Act, 1971.

For day to day practice, in the present time, the Surrogacy Contract between the parties (as recognized by the Honourable Supreme Court in baby Yamada's case) and the ICMR/ MHA guidelines are the main guiding force for surrogacy arrangements in India.

BIRTH CERTIFICATES: It is worth also touching on the issue of birth certificates in surrogacy cases as this is often something that is misunderstood. There is consistency with Registrar's across India and current ART Guidelines (2010) that both intended parents name will be on the birth certificate and not the surrogate mother's name.

ROLE OF ART BANKS: As per the National Guidelines No: 3.10.4 Advertisements regarding surrogacy should not be made by the ART clinic this responsibility should rest with the couple, or a semen bank/ ART Bank.

The ART Bank operates as an independent entity to recruit and screen surrogate mothers as per form M2 in the National Guidelines and to look after their welfare. Along with background checks, a psychological assessment of the prospective surrogate mother by a qualified post-graduate psychologist is mandatory. It is desirable to maintain contracts in the local language understood by the surrogate mother.

Either an ART clinic or a law firm or any other suitable independent organization may set up a semen bank. If set up by an ART clinic it must operate as a separate identity.(Guideline 3.9.1.1). The surrogate mother would also be entitled to a monetary compensation from the couple for agreeing to act as a surrogate; the exact value of this compensation should be decided by discussion between the couple and the proposed surrogate mother. (Guideline 3.5.4)

MEDICAL ASPECTS: The following are the key to a successful treatment program

1. Proper screening and counselling of both the Intended parents and the prospective surrogate mother are the two basic pillars of the treatment process.
2. Medical care for the surrogate mother should be of the highest quality with no compromise on any aspect
3. Life Insurance policy should be clarified.
4. Schedule of pregnancy to be discussed with the surrogate mother and her husband, risks and challenges though uncommon should be discussed
5. Intended parents should understand what types of updates are given during the treatment and the pregnancy and what format of communication is followed and any special requirements should be clarified.
6. Nominees are required to sign contracts, Local guardian in India should be appointed.
7. Perfect documentation, with all discussions summarised – no verbal promises.
8. Finances in various scenarios to be discussed before the start of the program.
9. Realistic expectations: for successful outcome, surrogate mother interaction, medical treatment and processes
10. An expert Lawyer involved in the process from the beginning
11. Foreign Intended parents to consult their Embassy in New Delhi and the Indian MHA before start of the process as babies are born stateless and need to be given the citizenship and passport of the country of the Commissioning/ Intended parents.
12. It is always desirable to refer to the ICMR website for newer updates.

ETHICAL AND SOCIAL ASPECTS: In India, there remains questions as to whether Indian women can and should make choices regarding becoming surrogates, is surrogacy a form of exploitation or empowerment of women? This question is answered by the Honourable Supreme Court of India which stated that, "A woman right to make choices regarding her body and also the right of procreation under the right to life is guaranteed by Article 21 of the Constitution of India"

There is more discussion to be had on the social implications of surrogacy, certainly a consented agreement to have a child outside the traditional bounds of wedlock is not the norm. There is also further debate as to what happens when women are perceived to be "taken away from their families"? Pictures presented to both Indian and Western audiences often portray women being "kept" in dormitories' away from families and social supports, isolated and ashamed, with everything being done in secrecy and isolation.

However, recent events such as the INSTAR Walk 'Surrogacy builds Families', in which over 200 surrogate mothers and their families marched to bring awareness of both their informed decisions and their families' support have shown that the picture in the metros is different and more open and supportive of surrogacy.

These inconsistencies are part of the complexities that surround surrogacy. We would argue that this debate should be an Indian debate, rather one that is dictated or funded by the West.

Practice knowledge in working with International patients: Many Indian Practitioners are very experienced with medical tourism and working with International patients, but there are some significant differences when it comes to working with families seeking surrogacy treatment. The most obvious of these is the longer term relationship (12 – 18 months) with patients who are situated in another country; dealing with the psychological challenges of patients with significant grief and loss issues after years of failed treatments in their own home countries ; working with patients who may have limited understanding of their own infertility as well as supporting patients who often have never travelled out of their own countries, dealing with cultural shock and anxiety of this while undergoing treatment. An empathic approach and excellent open communication lines are key for a successful process.

New developments

The "Parentage / Surrogacy Project" of the Hague Conference: The Hague Conference on Private International Law is currently seeking responses to two online questionnaires. They aim at "A possible new global treaty on international surrogacy agreements/ legal parentage". They further state that "With so many children born by way of surrogacy arrangements, the time has now come for the establish-ment and implementation of international standards by way of a multi-lateral convention". Indian clinics and Societies have been approached by the Hague to participate, the focus lies on trying to find a consensus on important issues such as legal parentage of the child born by surrogacy across borders in the modern era.

DRAFT BILL FOR ART (2013): ICMR is working towards developing National guidelines for ART and a new Draft Bill (2013) with the aim that it will guide practice across India in Third Party Reproduction. While some have expressed frustration over the length of time for this bill to be passed, the authors are proud of the work being done in India taking a leading role in the global community. India is of the few countries in the world to have consistent guidelines for both ART and Third Party Reproduction across the country.

The latest draft Art Guideline (2013) was shared publically for the first time at the INSTAR Workshop held on the 20th of April, 2014.

Broadly speaking, the guidelines confirmed that surrogacy contracts will be legally binding; that surrogate mothers retain no parental rights and that birth certificates will be in the name of the intended parents, being consistent with what we have previously discussed.

The following points were further elaborated:

1. Confirmation of the registration process for all services providing ART
2. Confirmation that surrogacy should only be offered to patients in which it would by "physically or medically impossible/ undesirable to carry a child to term
3. Confirming the current requirements for foreign patients, which include
   a. The foreign man and women should be married and the marriage should be sustained for more than two years (this is not applicable to India citizens)
   b. A letter from the Embassy of the foreign country in India or the Foreign Ministry of the country should be enclosed with the visa application stating clearly that;
      i. the country recognizes surrogacy and
      ii. the child/ children to be born to the commissioning couple through the Indian surrogate mother will be permitted entry into their country as a biological child/ children of the couple commissioning surrogate.
4. The couple will furnish an undertaking that they would take care of the Child/ children born through surrogacy
5. The treatment should be done only at one of the registration Assisted Reproductive Technology clinics recognized by ICMR.
6. The couple should produce a duly notarized agreement between the applicant couple and the prospective Indian surrogate mother

Foreign couple can be permitted to visit India on a reconnaissance trip on Tourist Visa, but no samples may be given to any clinic during such preliminary visit. All treatment must be done after the couples have received their medical visa.

The authors would encourage readers to refer to the footnote with regards to the process of sending and receiving embryos, but within the context of surrogacy, it should be noted that parents must travel to India prior to any transfer occurring.

Treatment can only ever occur with one surrogate at any time and transferring embryos to both the women and surrogate is prohibited.

The newest draft of the guidelines make it clear that an Indian citizens (women) , residing in India must be between the ages of 21 – 35 to be considered a surrogate and that no women should act as a surrogate for more than three live births, including her own children, with no less than a two year gap between pregnancies.

This is a work in progress and people should refer to the website for the latest information.

CONCLUSION: Thousands of happy families built by surrogacy in India not only in the country but across the globe are a testament that Surrogacy in India has come of age. The crucial aspects include adherence to the National Guidelines and recognising that the woman – the surrogate mother is the centre of the program and her welfare and well being are paramount to the process along with the welfare of the child/ children born through this process.