AOGD BULLETIN

Volume 18; Issue No.8; December 2018

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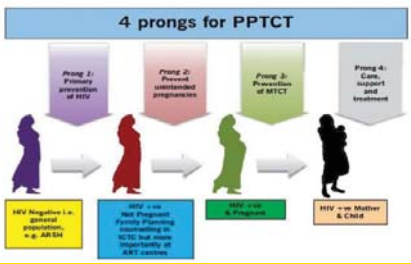
AOGD Theme 2018-19

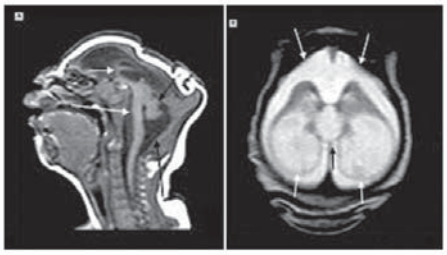
Empowering Providers: Enhancing Women's Health

***Issue:* Current Update**

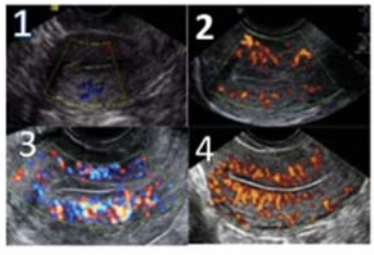
Perinatal Infections

Management of Infertility: Basic to advanced





Zone 1 - Myometrium surrounding the endometrium.
Zone 2 - Hyperechoic endometrial edge
Zone 3 - Internal endometrial hypoechoic zone
Zone 4 - Endometrial cavity



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President's Message

Dear members,

Greetings !

I take this opportunity to thank all AOGD members and delegates for their active participation in the 40th Annual Conference of AOGD. We are humbled by the heart felt appreciation and encouragement that we have received from members regarding the conduct and scientific content of the conference. There was good interaction and discussion in almost all seminars, panels and video sessions. Orations covered a wide range of subjects like Adbhut Matrutva, Evolution of screening tests for Cervical cancer, management of Genital TB and management of Previable Gestation. National and International faculty participating deserve our gratitude for making the scientific deliberations stimulating and enriching. We felt honored to felicitate senior AOGD members for their contribution to the profession.

The editorial team has brought forth this issue on "Perinatal infections" and "Infertility". Prevention of perinatal infections is a real challenge experienced by the obstetricians. Correct diagnosis, interpretation of lab results, appropriate counseling and management is the key to successful outcome.

Infertility is fast becoming an epidemic. It is a significant social and medical problem. Understanding the basic concepts of infertility and tailoring treatment according to the situation is important in management. Current issue will cover these aspects as well as provide an update on recent advances in the field.

Hope you will enjoy reading this bulletin.

Merry Chirstmas & a Very Happy New Year to all of you !

Dr Abha Singh
President AOGD (2018-19)

Secretary's Message

Greetings from the AOGD Secretariat LHMC,

It is the post conference time and we thank all of you for the overwhelming response to the 40TH Annual conference of AOGD at India Habitat centre on 24-25th November 2018.

We at Hardinge are humbled by the appreciation and laurels bestowed upon us for the success of the conference. The conference was very well attended and appreciated by one and all both faculty and the delegates. It was evident by the fact that halls were full till the last sessions. In fact the speakers commented that it was a pleasure speaking to full halls.

The programme was remarkably well applauded for the content, practical implications, skill enhancement and knowledge update.

The felicitation of our eminent and senior teachers and members of the association by the FOGSI president Dr Jaideep Malhotra and ICOG chairperson Dr Shantha Kumari was the high light of the conference The praise from our patrons, advisors and senior members of the association deserves special mention and we are extremely thankful to all for the words of encouragement and appreciation.

We had our eminent faculty from Delhi, NCR, National faculty and international speakers who gave their best. It was a privilege to interact with all of them. A special thanks to our chief guest and guest of honour and all dignitaries who graced the inaugural function.

All six preconference workshops spread over two days deserve special applause. We are extremely thankful to all convenors and co convenors for super content, a full attendance, and hands on skill enhancement well appreciated by all delegates.

We thank all our subcommittee chairpersons and thank them to be present at the valedictory function of the conference. It was a pleasure to felicitate them for all their hard work.

Congratulations to all the winners of the prizes at the conference. The list is there in the bulletin.

Here again the editorial team brings you a new issue of the bulletin with Perinatal infections and all about infertility as their core themes. It has all latest and carries an evidence based update. It is going to be an enjoyable reading issue to keep you updated with the latest.

The bulletin also carries pictorial glimpses of the conference and the preconference workshops.

As we move on with our journey of AOGD this year we hope to have a continued participation of all in the forthcoming events.

Happy reading

Dr Kiran Aggarwal
Secretary AOGD (2018-19)

Please note the change of the day

Monthly Clinical Meeting

Monthly Clinical Meet will be held at Sir Ganga Ram Hospital, New Delhi on **Thursday, 27th December, 2018 from 04:00pm to 05:00pm**.

Editorial Team's Message

Dr Ratna Biswas
Editor

Dr Pikee Saxena

Dr Sharda Patra

Dr Swati Agrawal

Co-Editors

Hello ! Friends,

Greetings of the winter season!!

We bring to you the December issue of AOGD bulletin with the themes "Perinatal Infections" and "Management of Infertility: Basic to Advanced"

The section on Perinatal Infection begins with "Standards of Care in Management of a HIV positive pregnant woman". HIV infection has shown a downward trend in prevalence which at present stands at 0.22 % in India. The goal of NACO is to eliminate HIV completely by 2030, that is no fresh cases of infection. Pivotal to this goal is the prevention of parent to child transmission program (PPTCT) which has the four prong approach: Primary prevention of HIV infection; Preventing unintended pregnancies in women with HIV; Preventing vertical transmission of HIV from women to their infants; Care, support and treatment of HIV positive pregnant woman and her child. This article gives a comprehensive review on the management of HIV in pregnancy.

The recent advances section focuses on "Congenital Zika Syndrome". With the outbreak of Zika Virus in Rajasthan, it has become mandatory to screen pregnant women living in Zika endemic areas for any evidence of infection in her and also to screen for possible Congenital Zika Syndrome in pregnant women who test positive for Zika infection.

Controversy section deals with the latest evidence on "Perinatal transmission of HPV infection" in women with HPV infection of genital tract.

Case Approach to Positive TORCH test will serve as a ready reference to how best to work up and manage a woman with positive TORCH test, a condition quite often encountered in our clinical practice.

The motivational article on "Stress Free Living and Mental Health in Pregnancy" emphasizes on reducing stress in pregnancy and enjoying motherhood so that the baby is brought up in a stress free, healthy environment.

The gynecology section on Management of Infertility begins with "Ovarian stimulation regimens in oncofertility" . Other than the routine protocols the "Random Start Protocol" and the "Protocols for Hormone Receptor Positive Cancers" are new concepts unique to this group. This article provides a detailed description of oocyte retrieval regimes for cancer patients before they embark on their onco-management.

Recent advances section on "Endometrial Receptivity Array" brings forth a concept of "Window of Receptivity" when the endometrium is receptive to implantation. Detection of this window is crucial for prevention of implantation failures.

Controversy on what is the current trend as regards to "IUI or IVF" has been dealt in detail by the authors of this article. Indications of IUI and IVF have been made clear in this chapter.

Case approach to "Male Infertility" focuses on the work up and management of male infertility. Management of non obstructive and obstructive azoospermia and medical management of oligospermia has been widely covered.

The maze of knowledge-crossword and the pictorial quiz will test your recapitulating capabilities, so go through the articles carefully to get the hidden answers.

Journal scan has done an interesting review on history of Zika Virus and the congenital zika syndrome which is similar to TORCH infections thereby increasing the spectrum of TORCH infections. Another interesting aspect which has been highlighted in Journal scan is the dual stimulation protocols in the same cycle, the pros and cons of which have been summarized.

We are immensely grateful to our contributors for the rich scientific content of their articles.

We look forward to any suggestions and comments from our readers

Happy Reading !!!

Editorial Team

STANDARDS OF CARE

Management of a HIV Positive Pregnant Woman

Muntaha Khan
Associate Professor, Lady Hardinge Medical College & SSK Hospital, New Delhi


Dr Muntaha Khan

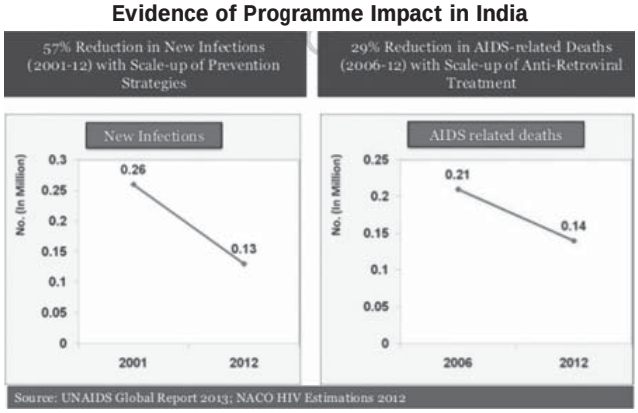
HIV (AIDS) can be transmitted from an HIV positive women to her child during pregnancy and labor in the percentage of about 15-45% and ART can reduce the risk to below 5%. Mother to child transmission (MTCT), which is also referred to as vertical transmission account for the vast majority of new infections in the children.

The NACO (National AIDS Control Organization) technical estimate report (2015) estimated that out of 29 million annual pregnancies in India 35,255 occurs in HIV positive pregnant women. In the absence of any intervention, an estimated cohort of 10,361 infected babies will be born annually. The PPTCT program aims to prevent the perinatal transmission of HIV from an HIV infected pregnant mother to her newborn baby.

Effective prevention of mother to child transmission (PMTCT) programs require women and their infants to have access to interventions including antenatal services and HIV testing during pregnancy; use of ART by pregnant women living with HIV; safe childbirth practices and appropriate infant feeding; uptake of infant HIV testing and other postnatal healthcare services.

India has an estimated 2.1 million persons living with HIV in 2011.The HIV prevalence among adult population in India has consistently declined over the last one decade as shown in the graph

Evidence of Programme Impact in India



There is a significant result of HIV counseling and testing, Prevention of Parent- to- Child Transmission (PPTCT) program increased from 0.8 million to 8.83 million and reach of the services has expanded to rural area to a large extent under NACP. India has opted new recommendations (2013) by WHO under plan B+ which are –

1) Providing lifelong ART to all the pregnant women and breast feeding women living with HIV regardless of CD4cell count or clinical stage or trimester of pregnancy.
2) Offer multiple ART drug therapy (AZT+LMT+EFV) instead of single agent chemotherapy of Nevirapine.

The different steps of PPTCT care are-

Care during the Antenatal period –
Initial assessment
Criteria for ART initiation
Care for mental health

Care during Intra partum period-
Women already receiving ART
ART for women presenting in active labor
False labor
Safer delivery technique
Cesarean section precautions

Care during Postnatal period-
ARV prophylaxis in infant
Infant feeding practice
Care and follow up of HIV exposed infants

Clinical and laboratory monitoring of ART regimen-
Essential gynecological care of HIV infected pregnant women-
Cervical cancer screening
Family planning and birth spacing

Special considerations-
Pregnant women with active TB
Pregnant women with HIV 2
Pregnant women with Hepatitis B or Hepatitis C virus co infection

Care During Antenatal Period-

Initial assessment-

- Offer HIV counseling and testing to all pregnant women (universal screening)

  Four scenarios where pregnant women may attend the counseling and testing services include –
  - Women attending antenatal clinics
  - Pregnant spouse of HIV positive men, or those with high risk behavior
  - Pregnant women screened at the sub Centre level by ANM/Nurse (whole blood finger prick test) and confirmation at ICTC.
  - Women presenting directly –in-labor (un booked cases, require a HIV screening test before delivery
- Offer antenatal routine screening tests hemoglobin to be checked at booking, and at 28 -32 weeks, urine albumin/sugar in every visits, VDRL/RPR, hepatitis B, blood grouping &typing and the benefits of testing for HIV, screening for STIS if any symptom.

- Iron and folic acid supplementation as per recommendations in normal pregnant woman, anemia management
- TT schedule as normal pregnancy
- Pre and post HIV test counseling
- Counseling on nutrition, rest, warning signs, birth planning, institutional deliveries
- Tracking of HIV positive pregnant women to ensure that they are reaching services and have been registered
- Refer her at ART Centre for CD4 test, TB screening and clinical staging (TB is approximately 10 times higher in HIV infected pregnant women, cause of death in 25% HIV infected pregnant women
- The combined screening test for trisomy 21 is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing.
- Invasive prenatal diagnostic testing should not be performed until after the HIV status of the mother is known, and should ideally be deferred until HIV viral load has been adequately suppressed to <50 HIV RNA copies/mL.
- If not on cART and the invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women should commence cART to include raltegravir and be given a single dose of nevirapine 2–4 hours prior to the procedure. (BHIVA guidelines2018)
- External cephalic version (ECV) can be performed in women with HIV.

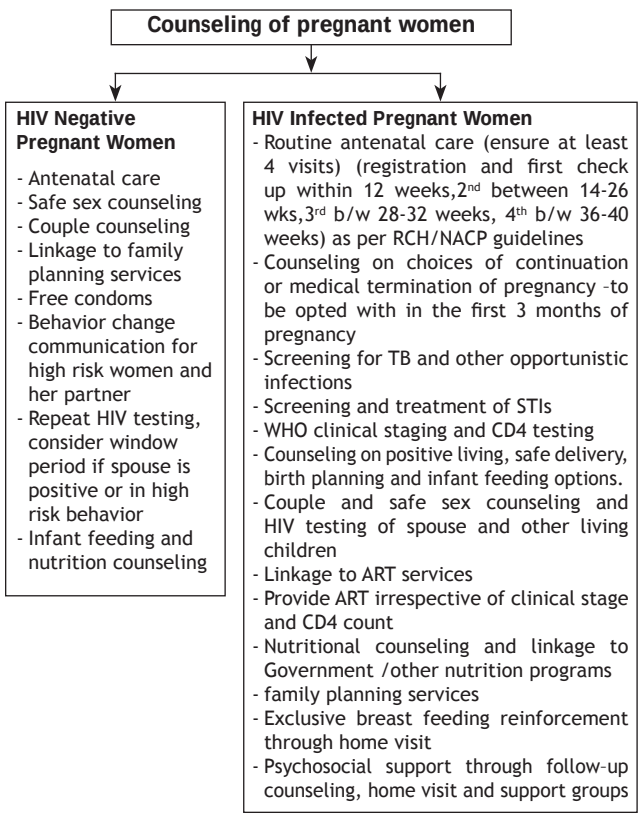
Criteria for ART Initiation-

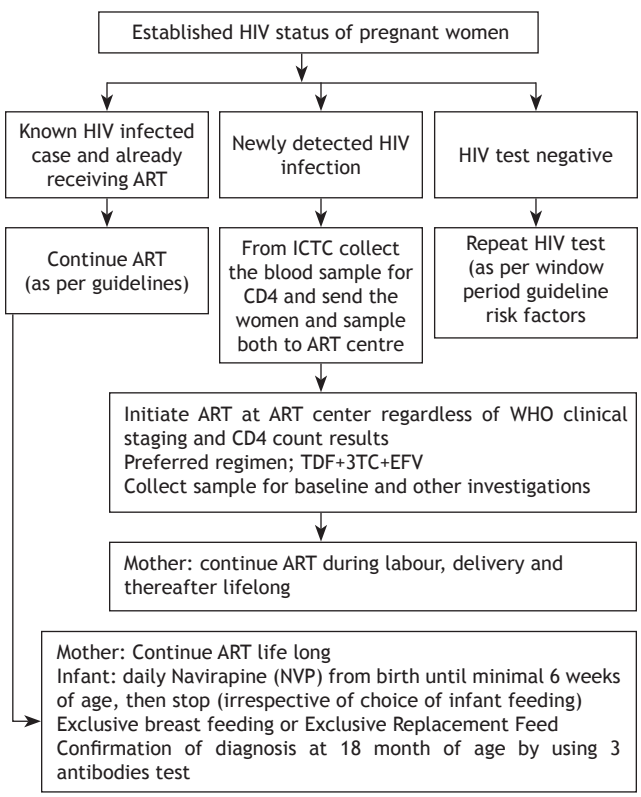
- All HIV infected women should be started on lifelong Multi Drug Anti-retroviral Regimen irrespective of WHO clinical stage or CD4 cell count or trimester of pregnancy.
- CO TRIMEXAZOLE therapy should be started if CD4 count is ≤ 250 cells/mm3 and continued through pregnancy, delivery and breastfeeding as per national guidelines (dose-double strength tablet-1 tablet daily)with folate supplementations
- The recommended first line regimen for HIV infected pregnant women in India is Tenofovir (TDF) (300 mg)+ Lamivudine (3 TC) (300 mg)+ Efavirenz (EFV) (600 mg) (if there is no prior exposure to NNRTIs (NVP/ EFV) at any gestational age even in first trimester of pregnancy) (EFV is safe in pregnancy as per WHO2012, NACO 2015)
- If prior exposure to NVP or EFV (NNRTIs) in prior pregnancies, then better to shift on protease inhibitors: TDF+3TC+LPV/r (lopinavir/ritonavir)
- Infant of mothers, who are on ART who are exclusive breastfeeding or doing exclusive replacement feeding should receive at least 6 weeks of infant prophylaxis with Syp Nevirapine daily
- EID(early infant diagnosis at 6 weeks,6 months,12 months(or after 6 weeks of stopping breast feeding completely and final test at 18 month(3 rapid test)
- Alternate regimen are-if she cannot tolerate first line regimen

  AZT+3TC+EFV

  AZT+3TC+NVP

  TDF+3TC+NVP





National guidelines of NACO for PPTCT

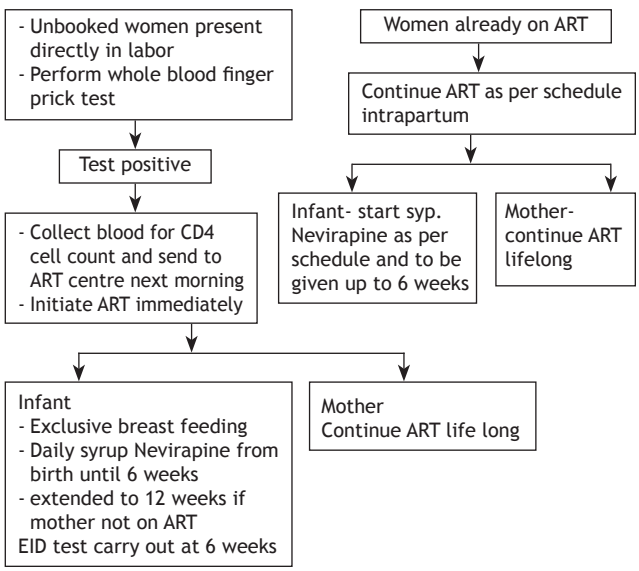
BHIVA guidelines (British HIV Association) regarding ART-

- Women should commence ART as soon as they are able to do so in the second trimester, but within the first trimester if VL >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm3. All women should have commenced ART by week 24 of pregnancy.
- Women are recommended to start tenofovir disoproxil fumarate or abacavir with emtricitabine or lamivudine as a nucleoside backbone as recommended in the BHIVA adult antiretroviral treatment guidelines.
- Integrase inhibitor-based regimen is considered as the third agent of choice in patients with high baseline viral load (>100,000 HIV RNA copies/mL), where cART is being started late in pregnancy or where it is failing to suppress the virus.
- The viral load is unknown or >100,000 copies/mL a three- or four-drug regimen that includes Raltegravir is suggested.
- All women are recommended to commence lifelong ART.

Assessment of mental health-assessment of antenatal and postnatal depression should be undertaken at booking, 4-6 weeks after postpartum and 3-4 month postpartum in accordance with NICE guidelines. As per NACO postpartum depression may begin at delivery, or a month later; in some women, it may begin during the first post-natal menstrual period or weaning, so screening should be done just after delivery and during follow up visits. Postpartum blues present in almost 80% of women.

- The symptoms include crying, irritability, sleep problems (insomnia or sleeping all day), eating problems (no appetite or eating all day), persistent feelings of sadness, lack of desire or inability to care for self or baby, exaggerated concerns about the baby, and memory loss.

Care during Intra Partum Period



- Some women may feel extremely anxious or fearful, sometimes experience panic attacks including palpitations, chest pain, dizziness, cold flushes and shaking. More importantly, postpartum depression may reduce the adherence to ART especially the infant NVP prophylaxis for the first 6 weeks of life.

False labour-

In the case of false labour or mistaken ruptured membranes, for women taking ART should continue with normal dosing schedule of the combination regimen.

Cesarean sections in HIV positive pregnant women should be performed for Obstetric indications only as per NACO guidelines.

Safe Delivery Techniques

Mother-to-child -transmission risk is increased by the prolonged rupture of membranes, repeated P/V examinations, assisted instrumental delivery (vacuum or forceps), invasive foetal monitoring procedures (scalp/foetal blood monitoring), episiotomy and prematurity. Thus, when delivering HIV-infected women, Observe:

- Standard/Universal Work Precautions (UWP) to be followed.
- Do NOT rupture membranes artificially (keep membranes intact for as long as possible).Procedure reserved for cases of foetal distress or delay in progress of labour**.**
- Minimize vaginal examination and use aseptic techniques.
- Avoid invasive procedures like foetal blood sampling, foetal scalp electrodes.
- Avoid instrumental delivery as much as possible,unless required in cases of foetal distress or significant maternal fatigue to shorten labour .If indicated, low-cavity outlet forceps is preferable to ventouse, as it is generally associated with lower rates of foetal trauma than ventouse.
- Avoid routine episiotomy as far as possible.
- Suctioning the newborn with a nasogastric tube should be avoided unless there is meconium staining of the liquor.

Precautions at Caesarean Section

Safer surgical techniques are useful in conducting any operative procedures such as the Caesarean section, repairing wounds/lacerations etc.

- Use of 'dry' haemostatic techniques to minimize bleeding; i.e. good observation and following of surgical fascial planes during dissection, judicious use of electro-cautery during Caesarean section etc.
- During Caesarean section, wherever possible, the membranes are left intact until the head is delivered through the surgical incision.

- The cord should be clamped as early as possible after delivery;
- Use of round-tip blunt needles for Caesarean section;
- Do not use fingers to hold the needle;
- Use forceps to receive and hold the needle.
- Observe good practice when transferring sharps to surgical assistant eg. holding container for sharps.
- For disposal of tissues, placenta and other medical/ infectious waste material from the delivery of HIV-infected deliveries, standard waste disposal management guidelines should be followed.

Mode of Delivery as per Bhiva Guidelines- (2018)

For study point of view we should know that RCOG follows different guidelines in comparison to NACO guidelines-

For women taking cART, a decision regarding recommended mode of delivery should be made after review of plasma HIV viral load results at 36 weeks-

For women with a plasma viral load of <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications, a planned vaginal delivery is recommended	1C
For women with a plasma viral load of 50–399 HIV RNA copies/mL at 36 weeks, PLCS should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and the woman's views	1C
Where the viral load is ≥ 400 HIV RNA copies/mL at 36 weeks, PLCS is recommended	1C
In women for whom a vaginal delivery has been recommended and labour has commenced, obstetric management should follow the same guidelines as for the HIV-negativepopulation	1C
Vaginal birth after Caesarean section (VBAC) should be offered to women with a viral load <50 HIV RNA copies/ mL	1D
Where the indication for PLCS is the prevention of vertical transmission, PLCS should be undertaken at between 38 and 39 weeks' gestation	1C
In all cases of term pre-labour spontaneous rupture of the membranes (ROM) delivery should be expedited and mode to be opted as per viral load	1C
When P-PROM occurs at <34 weeks: • Intramuscular steroids should be administered in accordance with national guidelines • Virological control should be optimised • There should be multidisciplinary discussion about the timing and mode of delivery	1C
Intrapartum intravenous zidovudine infusion is recommended in women with a viral load of >1000 HIV RNA copies/mL plasma who present in labour, or with ruptured membranes or who are admitted for planned CS	1C

Care During Postnatal Period-

Within hour of delivery-

- Infants born to HIV-infected mothers should receive NVP prophylaxis immediately after birth.
- **Infants should be given exclusive breastfeeds for the first six months preferably. Exclusive replacement feeding may be done only if the mother has died or has a terminal illness or decides not to breastfeed despite adequate counselling. (NACO)**
- Involvement of men (husband/close male family members) is important so that the family support to the HIV-infected mother and infant is optimal.
- Continuation of breastfeeds for 1 year in EID negative babies, and up to 2 years in EID positive babies with initiation of Paediatric ART. Weaning foods should be introduced from 6 months onwards in all babies whether breast fed or replacement feeds fed.
- Insertion of Cu-T temporary contraceptive method) for HIV infected mother at 6 weeks if a post-partum IUD (PP-IUD) has already not been inserted within 48 hours in addition to the use of condoms will prevent unwanted pregnancies (dual protection)
- All HIV exposed infants and children regardless of HIV status will be followed-up until 18 months of age for care, monitoring and the final confirmatory HIV test at 18 months using 3 HIV Rapid tests (even if HIV-1 rapid test is negative).
- No DBS & WBS (DNA/PCR) testing to be done at or after 18 months.

  (NACO guidelines)
- In the UK and other resource rich settings the safest way to feed infants born to mothers with HIV is with formula milk, as this eliminates on-going risk of HIV exposure after birth
- In RCOG in low risk infants Zidovudin monotherapy is given up to 4 week and in high risk multiple regimen is preferred.
- Infant testing is done in first 48 hours and prior to hospital discharge, If HIGH RISK, at 2 weeks of age, at 6 weeks (at least 2 weeks post cessation of infant prophylaxis) at 12 weeks (at least 8 weeks post cessation of infant prophylaxis*). In breast feeding it is done monthly and then 4and 8 week after stoppage of breast feeding. In both cases final testing done at 18-24 month as per BHIVA guidelines.

ARV Prophylaxis and Feeding Practices in Infants as per NACO 2015

Babies receiving exclusive breast feeding (EBF) for the first 6 months

MOTHER

Lifelong ART should be initiated as soon as possible

INFANT

i) At Birth: Start Sy. NVP Prophylaxis immediately and give until 6 weeks (or more indicated, up to 12 weeks if mother ART started late)

ii) At 6 weeks:

a. Start CPT and continue until baby is 18 months of age

b. Immunization: Start 1st dose of DPT/OPV/Hep-B vaccine (2nd dose)

c. Early Infant Diagnosis (EID): Do DBS at 6 weeks for all babies; if positive do WBS. If WBS positive, start Paediatric ART irrespective of CD4% for babies less than 2 years.

d. EID negative ,stop breast feeding at 12 month and in EID positive can continue feeding up to 24 month with paediatric ART, then stop breast feeding gradually

e. NO MIXED FEEDING is to be done during the first 6 months i.e. (not to give along with Breastfeeds any other milk (tinned formula food or cow's milk or dairy milk), liquid juice or water.

Babies receiving exclusive replacement feeding (ERF) for first 6 months

MOTHER

Life-long ART initiated as soon as possible even though the baby is getting exclusive replacement feeding

INFANT-

I) At Birth: Start Sy. NVP Prophylaxis from birth until 6 Weeks

ii) At 6 weeks:

a. Start CPT and continue until baby is 18 months of age (and may be thereafter, if babies status is positive in the confirmatory test)

b. Immunization: Start 1st dose of DPT/OPV/Hep-B vaccine (2nd dose)

c. Early Infant Diagnosis(EID): Do DBS at 6 weeks for all babies; if positive do WBS. If WBS positive, start Paediatric ART irrespective of CD4% for babies less than 2 years.

d. EID negative and positive both we can give ERF up to 6 month

e. NO MIXED FEEDING is to be done during the first 6 month, no breast feed to be given within first 6 months

Care and follow up of HIV exposed infants-(source NACO guidelines)

Table 10: Activities at Each Follow-up Visit for HIV Exposed Infants and Children < 18 Months

Visit	Birth	6 wks	10 wks	14 wks	6 mths	9 mths	§12 mths	18 mths
Co-trimoxazole prophylactic therapy (CPT)		▮ Start CPT from 6 weeks (or first immunization visit) for all HIV-exposed infants and children ▮ Continue CPT for all babies up to 18 months irrespective of EID status and thereafter if confirms positive						
Counselling for Infant feeding	Exclusive breast feeds for first six months	✓	✓	✓	BF+complementary feeds	✓	If EID is –ve stop BF. Continue BF if EID is +ve after 12 months up to 2 yrs	✓
Growth monitoring	✓	✓	✓	✓	✓	✓	✓	✓
Developmental assessment	✓	✓	✓	✓	✓	✓	✓	✓
Immunization & Vitamin A supplements	BCG HBV0* OPV0	OPV 1 DPT 1 HBV 1*	OPV 2 DPT 2 HBV 2	OPV 3 DPT 3 HBV 3		Measles + Vit. A		OPV DPT and Measles (Booster doses) Vit.A
Clinical assessment	✓	✓	✓	✓	✓	✓	✓	✓
HIV testing (✓-if required)		✓ (DNA/ PCR)			✓ (Rapid Test + DNA/PCR)		+/- (12 months) ✓ Rapid Test + DNA/PCR)	✓ All 3 Rapid Tests(No DNA/PCR)

**HBV vaccines as per state approved schedules*

Source-NACO GUIDELINES; PPTCT,2013

CLINICAL AND LABORATORY FOLLOW UP OF ART-
(SOURCE-PPTCT guidelines NACO 2016)

Table 5: Recommended Clinical and Laboratory Follow-up of Pregnant Women Receiving ART

Assessment	Baseline	2 Weeks	4 Weeks	8 Weeks	12 Weeks	Every 6 Months	Comment
Clinical evaluation	✓	✓	✓	✓	✓	✓	Every month
Adherence counselling	✓	✓	✓	✓	✓	✓	Every month
Weight	✓	✓	✓	✓	✓	✓	Every month
*Haemoglobin	✓	✓	✓	✓	✓	✓	Re-check at 28-32 weeks
ALT (LFT)	✓	✓	X	X	X	✓	As and when required clinically
Urinalysis*	✓					✓**	**Specifically for TDF-based regimen. Urinalysis dipsticks is routinely done in follow-up
CD 4 count	✓	Thereafter every 6 months as per guidelines					
Blood Urea / Sr. Creatinine	✓					✓	
Blood Grouping and Typing	✓						
HBV, HCV screening	✓						Screening should be performed in States where ANCs are being tested routinely or based on the risk profile (e.g. IDUs, through blood transfusion)
RPR/ VDRL*	✓						
Blood Sugar*	✓						Repeat every 6 months if started on LPV/r based regimen
Lipid profile	✓						

Essential Gynaecologic Care for HIV Infected Pregnant Women-

During the long term follow-up of HIV infected pregnant women, apart from ART and pre-ART care, key areas which must be discussed, are:

- Cervical screening
- Family planning and birth-spacing
- Contraception

Cervical Screening: Women infected with HIV are at higher risk of developing cervical dysplasia leading to cervical cancer. The Human Papilloma virus (HPV) infection is more common in HIV infected pregnant women, particularly Genotypes 16, 18 and others incriminated to be carcinogenic being IARC (WHO) 31,33,35,39,45,51,52,56,58,59 & 68. In the National ART Guidelines for adults and adolescents, cervical screening eg. Pap smear or trichloro-acetic acid screening of the cervix should be done annually for all HIV infected pregnant women.

Family Planning and Birth-spacing; With ART and PPTCT being increasingly available, HIV infected pregnant women and men are now living longer and healthier lives and desiring to have children. Accordingly, reproductive plans including pre- conception counselling, and counselling regarding reversible methods of contraception should be discussed with HIV infected pregnant women of child bearing age.

Pre-conception counselling- The goals are improve the health of the woman before conception and to identify risk factors for adverse maternal and foetal outcomes. These include:

- Safe sex practice
- Prevent test and treat STI.
- Reproductive history including numbers of pregnancies and outcomes of pregnancies.
- Length of relationship with current partner, HIV status of partner and couple's sexual history including condom use and sexual decision-making or control of reproductive choices.
- Patient's and partners reproductive desires and discussion of options.

- Reduce/avoid risky behaviour eg. smoking, substance abuse.
- Take folic acid before conception.

Family planning counselling- information includes:

- Information about effective contraceptive methods to prevent pregnancy, dual protection; the effects of progression of HIV disease on the woman's health
- The importance of family planning and birth planning;
- The risk of HIV transmission to an uninfected partner while having unprotected intercourse (for instance, when trying to become pregnant);
- The risk of transmission of HIV to the infant and the risks and benefits of Antiretroviral prophylaxis in reducing transmission;
- Information on the interactions between HIV and pregnancy, including a possible increase in certain adverse pregnancy outcomes.

Contraceptive Methods- • Condoms together with another effective method of contraception, including emergency contraception can be used.

Hormonal contraception: is safe in women living with HIV. These may be either:

- Oral contraceptives
- Depot medroxyprogesterone acetate (DMPA.

DMPA is safe to use in women living with HIV as well as those on ART. There is no hormone-drug

interaction with several ARV drugs commonly used such as NVP, EFV and Nelfinavir

Intra-Uterine Contraceptive Device (IUCD) is a good contraceptive method for HIV infected pregnant women. IUCD8 Copper T 380A is recommended by MoHFW as a long term reversible method of contraception up to 10 years. PP IUD (Cu- 'T'A-380) to be inserted within 48 hrs of delivery.

PP IUD - Postpartum IUD requires specialised training before the healthcare personnel undertake the same

Lactational Amenorrhoea Method (LAM) does not protect against STIs, pregnancy and HIV. Correct and consistent condom use should be adopted at every sexual encounter.

Male sterilization (NSV): Males should be motivated at every mother-baby pair follow-up visit to undergo sterilization. No Scalpel Vasectomy (NSV) when the baby attains 18 months/2 years of age (at 18 months confirmatory test, irrespective of the baby's HIV status). However, after NSV operation, male should continue to use a condom at every sexual encounter.

Special Considerations

Pregnant Women with Active TB

The risk of active TB is approximately 10 times higher in HIV-infected pregnant women compared to HIV uninfected women. All HIV-infected pregnant women presenting with a cough, fever, night sweats and weight loss should be evaluated for TB and started on TB treatment when indicated. The tuberculosis treatment should be started first, and followed by ART as soon as feasible (usually after 2 weeks). Drug interactions between Rifampicin and some of the antiretroviral drugs, including NVP complicate simultaneous treatment of the two diseases. EFV is the preferred NNRTI for pregnant women which can be used in those with concurrent TB treatment also.

Pregnant Women with HIV-2 Infection

HIV-2 has the same modes of transmission as HIV-1 but has been shown to be much less transmissible from mother-to-child (transmission risk 0-4%).

NNRTI drugs, such as NVP and EFV, are not effective against HIV-2 infection. Therefore, for women who are infected with HIV-2 alone should**:**

- Follow standard adult guidelines for HIV-2 treatment which consists of 2NRTIs + LPV/r.
- Prophylaxis NVP with AZT (instead of Syp NVP) to be given to babies in mothers with HIV -2

If a pregnant woman is detected to have BOTH HIV-1 and HIV-2 infections, she should receive standard first ART Regimen (TDF+3TC+EFV) recommended for women with HIV1 infection.

Pregnant Women with Hepatitis B or Hepatitis C Virus CO- Infection- An elevation in liver enzymes following the initiation of ART may occur in HIV-HBV co-infected women because of an immune-mediated flare in HBV disease secondary to immune reconstitution (IRIS) with therapy, particularly in women with low CD4 cell counts.

- HBV infection may also increase the risk of hepatotoxicity with certain antiretroviral drugs, specifically NVP and protease inhibitors.
- Pregnant women with HIV-HBV co-infection should be counselled about signs and symptoms of liver toxicity.
- For women who do not require HBV treatment, ART general recommendations for HIV-infected pregnant women should be followed.

For Women Co-infected with HIV and HCV-

- No specific changes in treatment are recommended in the adult ART treatment guidelines.
- Pregnant women co-infected with HIV and HCV should receive ART according to the general recommendations for HIV-infected pregnant women.
- Those women on ART require careful clinical and laboratory monitoring

VERY LOW RISK	1C
Two weeks' zidovudine monotherapy is recommended if all the following criteria are met: • Mother has been on cART for longer than 10 weeks AND • Two documented maternal HIV viral loads <50 HIV RNA copies/mL during pregnancy at least 4 weeks apart AND • Maternal HIV viral load <50 HIV RNA copies/mL at or after 36 weeks	
LOW RISK	1C
• Extend to 4 weeks' zidovudine monotherapy: • If the criteria in 9.1.1 are not all fulfilled but maternal HIV VL is <50 HIV RNA copies/mL	
HIGH RISK	1C
Use combination PEP if maternal birth HIV VL known to be or likely to be >50 HIV RNA	

References

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RECENT ADVANCES

Congenital Zika Syndrome: Diagnosis and Management


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Introduction

Zika virus is an arthropod-borne flavivirus transmitted through infected mosquitoes. This virus was first identified in the Region of the Americas in early 2015 when local transmission was reported in Brazil.[1] Six months later a notable increase in the number of infants with congenital microcephaly was observed in northeast Brazil. Clinical, epidemiologic, and laboratory evidence led investigators to conclude that intrauterine ZIKA virus infection can result in microcephaly and serious brain anomalies in the fetus.[2,3]

Pathogenesis

The risk for vertical transmission exists throughout pregnancy. Prenatal infection especially during the first and second trimesters has been associated with serious consequences.[4] Placental transmission of Zika virus from infected mothers primarily destroys neural progenitor cells of the fetal nervous system, thereby disrupting the process of neuronal proliferation and differentiation. Besides causing multiple brain malformations, this virus has also been linked with increased fetal loss including stillbirths.

Clinical manifestations

Infection is likely to be asymptomatic in ≈80% of cases. All ages are susceptible (4 days–76 years), with a slight preponderance of cases in females. When symptoms occur, they are typically mild, self-limiting, and nonspecific, usually resolving within two weeks. Commonly reported symptoms include rash, fever, arthralgia, myalgia, fatigue, headache, and conjunctivitis.

Congenital Zika Syndrome

Clinical features of CZS (Table 1) are a consequence of direct neurological damage and severe intracranial volume loss.[5]

Table1. Clinical manifestations of CZS

Feature	
Cranial morphology	Microcephaly Fetal brain disruption syndrome Craniofacial disproportion Overriding cranial sutures Craniosynostosis Cutis gyrita
Brain anomalies	Intracranial calcification Ventriculomegaly Pachygyria / polymigrogyria Reduced brain volume Delayed myelination Hypoplasia of brainstem & cerebellum Hypogenesis of corpus collasum
Ocular abnormalities	Focal pigmentary mottling Chorioretinal atrophy Cataracts Optic nerve abnormalities Microphthalmia
Hearing loss	Sensorineural hearing loss
Congenital contractures	Arthrogryposis Clubfoot
Neurologic sequelae	Hypertonia / spasticity Hyperreflexia Dysphagia Feeding difficulties Seizures
Small for gestational age	Birth weight < 10th percentile

Diagnosis

For the purpose of recommendations, the definition of possible Zika virus exposure has not changed and includes travel to, or residence in an area with risk for mosquito-borne Zika virus transmission or sex with a partner who has travelled to or resides in an area with risk for mosquito-borne Zika virus transmission. These areas can be found on the CDC "Zika Travel Information" webpage.

Laboratory diagnosis is challenging since, so far, there are no "gold standard" diagnostic tools. The low and short viremia in the acute phase, and together with the high cross-reactivity among the members of flavivirus genus are the most challenging aspects to be overcome.

During the first 7 days of these illnesses, viral RNA can often be identified in serum, and RTPCR is the preferred test for Zika virus. Because viremia decreases over time, a negative RT-PCR collected 5-7 days after symptom onset does not exclude flavivirus infection and serologic testing should be performed.

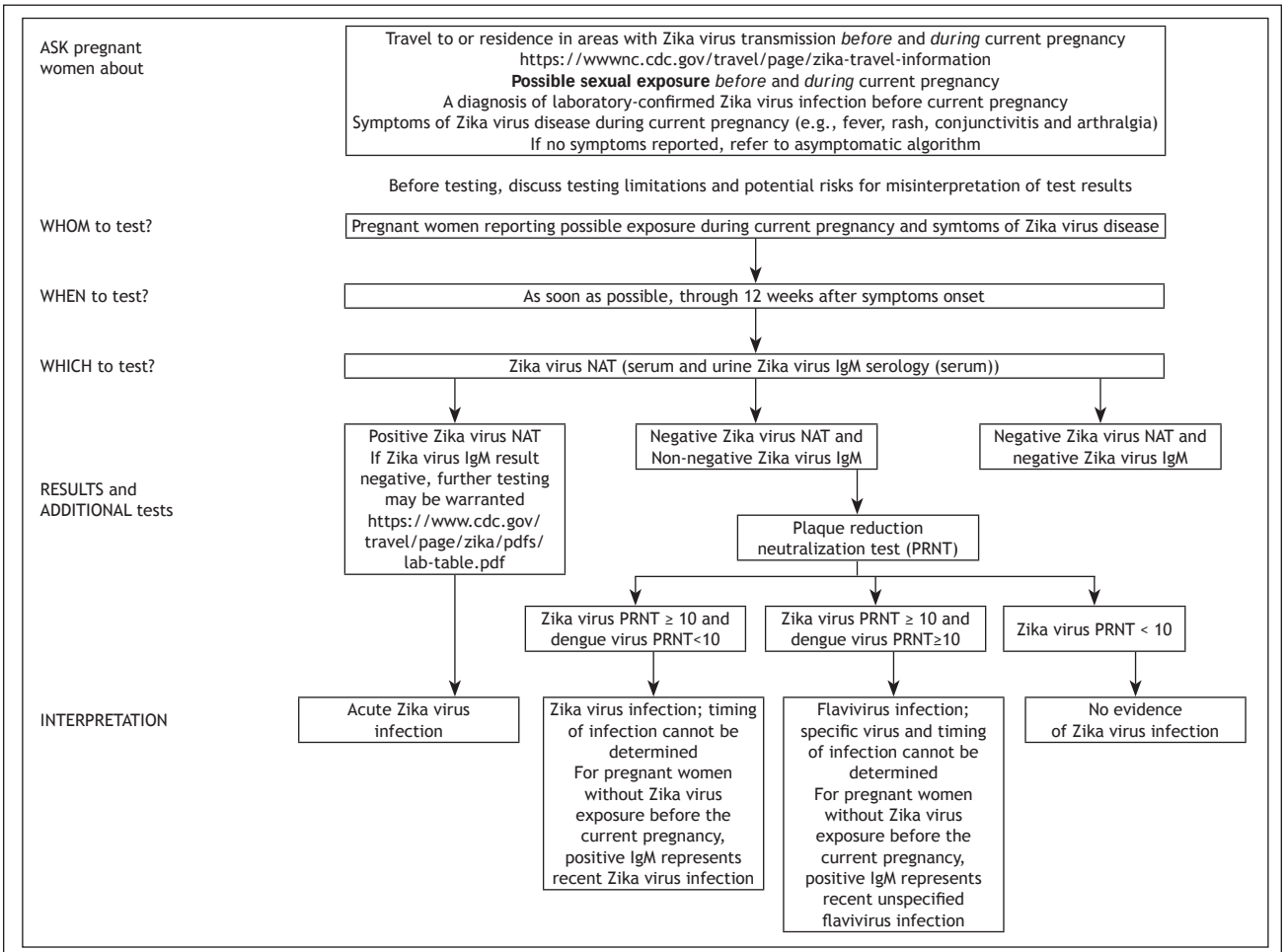
Serologic test interpretation is complex; a positive IgM result can be difficult to interpret since cross-reactivity can occur with related flaviviruses. Plaque-reduction neutralization tests (PRNT) may be able to discriminate between cross-reacting antibodies in primary flavivirus infections.

Serologic testing for Zika virus infection may be

performed on serum specimens from

Symptomatic and asymptomatic pregnant women (Algorithm I and II).[6]

Algorithm I: Algorithm I: Updated interim testing recommendations*,†,§,¶,,††,§§ and interpretation of results¶¶ for symptomatic pregnant women with possible Zika virus exposure***,†††**



Abbreviations: lgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

* Ask about type and duration of Zika viru exposure before and during the current pregnancy, Exposure before the current pregnancy might limit interpretation of Zika virus lgM result; pretest counseling can help inform testing decisions. Some patients may choose not to receive Zika virus lgM testing.

† Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus indection by either NAT or serology (positive/equivocal Zika viruw or dengue virus lgM and Zika virus PRNT ≥ 10 and dengue virus PRNT < 10 results)

§ This algorithm also apppies to pregnant women with possible Zika virus exposure who have a fetus with prenatal ultrasound findings consistent with congenital Zika virus syndrome.

¶ The duration of detectable Zika virus RNA in pregnant women following infection is not known. Preliminary data suggest that NAT might remain positive for several weeks after symptom onset in some pregnant women. Zika virus lgM antibodies are most likely to be detected within 12 weeks after infection; however, lgM antibodies might be detected for months after infection, limiting the ability to determine whether infection occured before or diring the current pregnancy.

** Dengue virus lgM antibody testing is recommended for symptomatic pregnant women. For laboratory interpretation in the presence of dengue virus lgM results, refer to https//www.cdc.gov/dengue/clinicallab/laboratory.html.

†† Non negative results include “positive”, “equivocal,” presumptive positive,” “possible positive.” These are examples of assay interpretation that might accompany test results; non negative serology terminology varies by assay. For explanation of a specific interpretation, refer to the instructions for use for the specific assay performed. Information on each assay can be found at https//www.fda.gov/medicalDevices/Safety/Emergency Situations/ucm161496.htm#zika under the “labeling” tab for the specific assay.

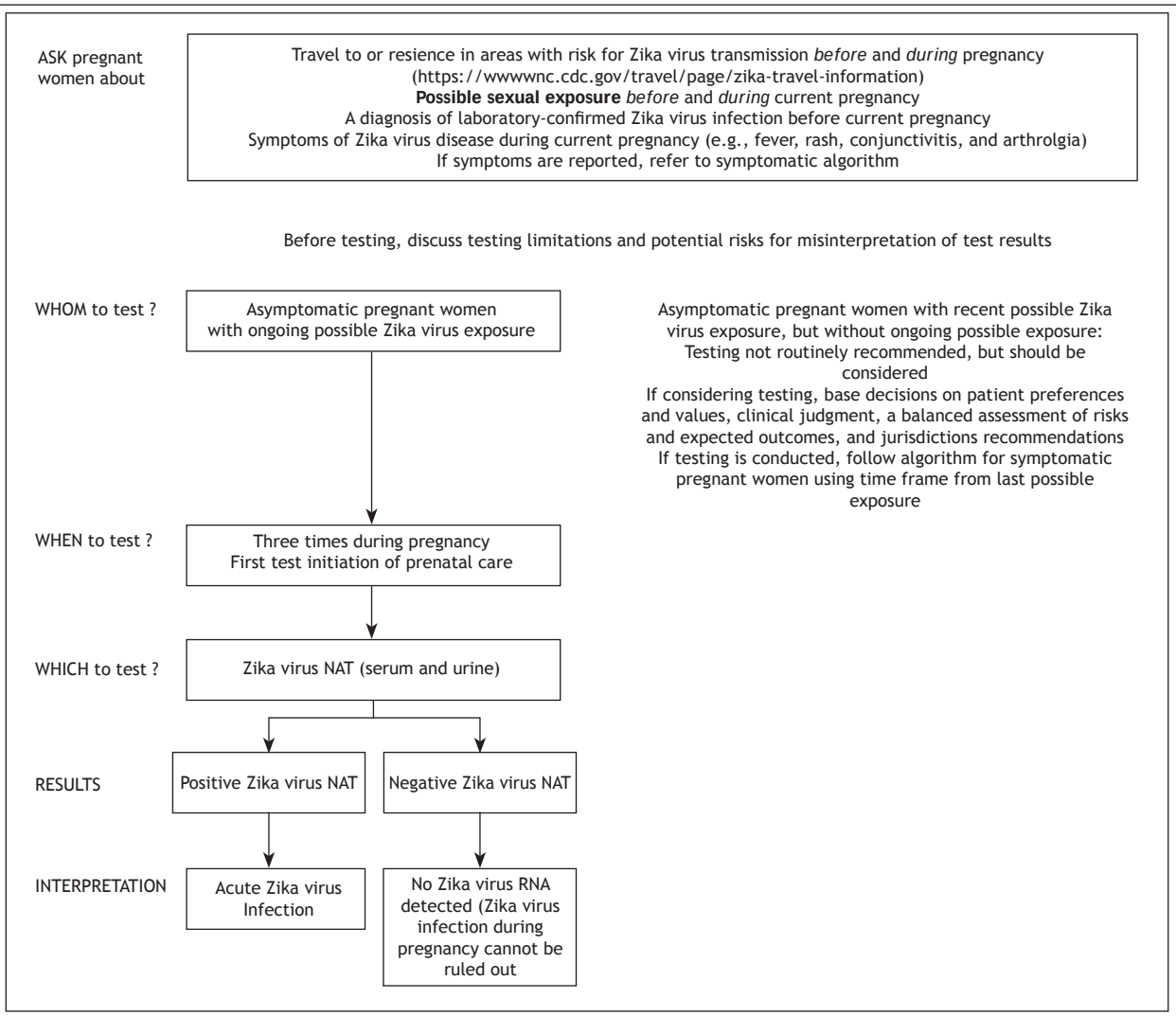
§§ Currently, PRNT confirmation is not routinely recommended for persons living in Puerto Rico. For laboratory interpretation, in the absence of PRNT testing, refer to https//www.cdv.gov/zika/pdfs/lab-table.pdf

¶¶ Despite the high specificity of NAT, false-positive NAT results have been reported, **If both serum and urine specimens are NAT-positive, interpretation should be acute Zika virus infection**. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. **If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection.** If repeat NAT testing is negative, results are indeterminate and health care providers should repeat Zika virus lgM antibody testing on a serum specimen collected ≥2 weeks after symptom onset. If subsequent lgM antibody test is positive, Interpret as evidence of acurt Zika virus infection, but if negative, interpret as no evidence of Zika virus infection.

*** Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https//wwwnc.cdc.gove/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period]), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

††† For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.

Algorithm II: Updated interim testing recommendations*,†,§ and interpretation of results¶, for asymptomatic pregnant women with possible Zika virus exposure††,§§,¶¶**



Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test; PRNT = plaque reduction neutralization test.

* Ask about type and duration of Zika viru exposure before and during the current pregnancy, Exposure before the current pregnancy might limit interpretation of Zika virus IgM result; pretest counseling can help inform testing decisions.

† Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus indection by either NAT or serology (positive/equivocal Zika viruw or dengue virus IgM and Zika virus PRNT ≥ 10 and dengue virus PRNT < 10 results)

§ The interval for Zika virus NAT testing during pregnancy is unknown. Preliminary data suggest that NAT might remain positive for several weeks after infection in some pregnant women. For women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the prenanancy coinciding with prenatal visits. The proportion of fetuses and infants with Zika virus-associated birht defect; is highest among women with first and early second trimester infections; therefore, conducting all NAT testing during the first and second trimesters might be considered to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester; therefore, testing every trimester might be consicered.

¶ Despite the high specificity of NAT, false-positive NAT results have been reported, **If both serum and urine specimens are NAT-positive, interpretation should be acute Zika virus infection**. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. **If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection.** If repeat NAT testing is negative, results are indeterminate and health care providers should perform IgM testing on a specimen collected ≥2 weeks after initial specimen collection. For laboratory interpretation, refer to https//www.cdv.gov/zika/pdfs/lab-table.pdf

** A negative Zika virus NAT result does not exclude infection during pregnancy because it represents a single point in time. Zika virus RNA levels decline over time, and the duration of the presence of Zika virus RNA in serum and urine following infection varies among pregnant women. Despite Zika virus IgM antibody test limitations (e.g., cross-reactivity with other flaviviruses and prolonged detection for months, presenting challenges in determining the timing of infection), which should be discussed as part of pretest counseling, patients may still choose to receive Zika virus IgM testing.

†† Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission (https//wwwnc.cdc.gove/travel/page/zika-travel-information) during pregnancy or the periconceptional period (8 weeks before conception [6 weeks before the last menstrual period]), or sex without a condom, during pregnancy or the periconceptional period, with a partner who traveled to, or resides in an area with risk for Zika virus transmission.

§ Persons with ongoing possible Zika virus exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk for Zika virus transmission.

¶¶ For the purposes of this guidance, recent possible Zika virus exposure or Zika virus/flavivirus infection is defined as a possible exposure or infection during the current pregnancy or periconceptional period.

Diagnosis of Congenital Zika Virus Infection

Recommended laboratory testing for congenital Zika virus infection includes evaluation for Zika virus RNA in infant serum and urine and Zika virus IgM antibodies in serum. In addition, if cerebrospinal fluid (CSF) is obtained for other purposes, NAT and IgM antibody testing should be performed on CSF because CSF was the only sample that tested positive in some infants with congenital Zika virus syndrome[7]. Testing of cord blood is not recommended because it can yield false-positive and false-negative test results[8].

Interpretation of results of laboratory testing of infant's blood, urine, and/or cerebrospinal fluid for evidence of congenital Zika virus infection[9].

Infant test result*		Interpretation
NAT	IgM	
Positive	Any result	Confirmed congenital Zika virus infection†
Negative	Nonnegative	Probable congenital Zika virus infection§,¶
Negative	Negative	Congenital Zika virus infection unlikely§,**

Abbreviations: IgM = immunoglobulin M; NAT = nucleic acid test. *Infant serum, urine, or cerebrospinal fluid.

† Distinguishing between congenital and postnatal infection is difficult in infants who live in areas where there is ongoing transmission of Zika virus and who are not tested soon after birth. If the timing of infection cannot be determined, infants should be evaluated as if they had congenital Zika virus infection.

§ Laboratory results should be interpreted in the context of timing of infection during pregnancy, maternal serology results, clinical findings consistent with congenital Zika syndrome, and any confirmatory testing with plaque reduction neutralization testing.

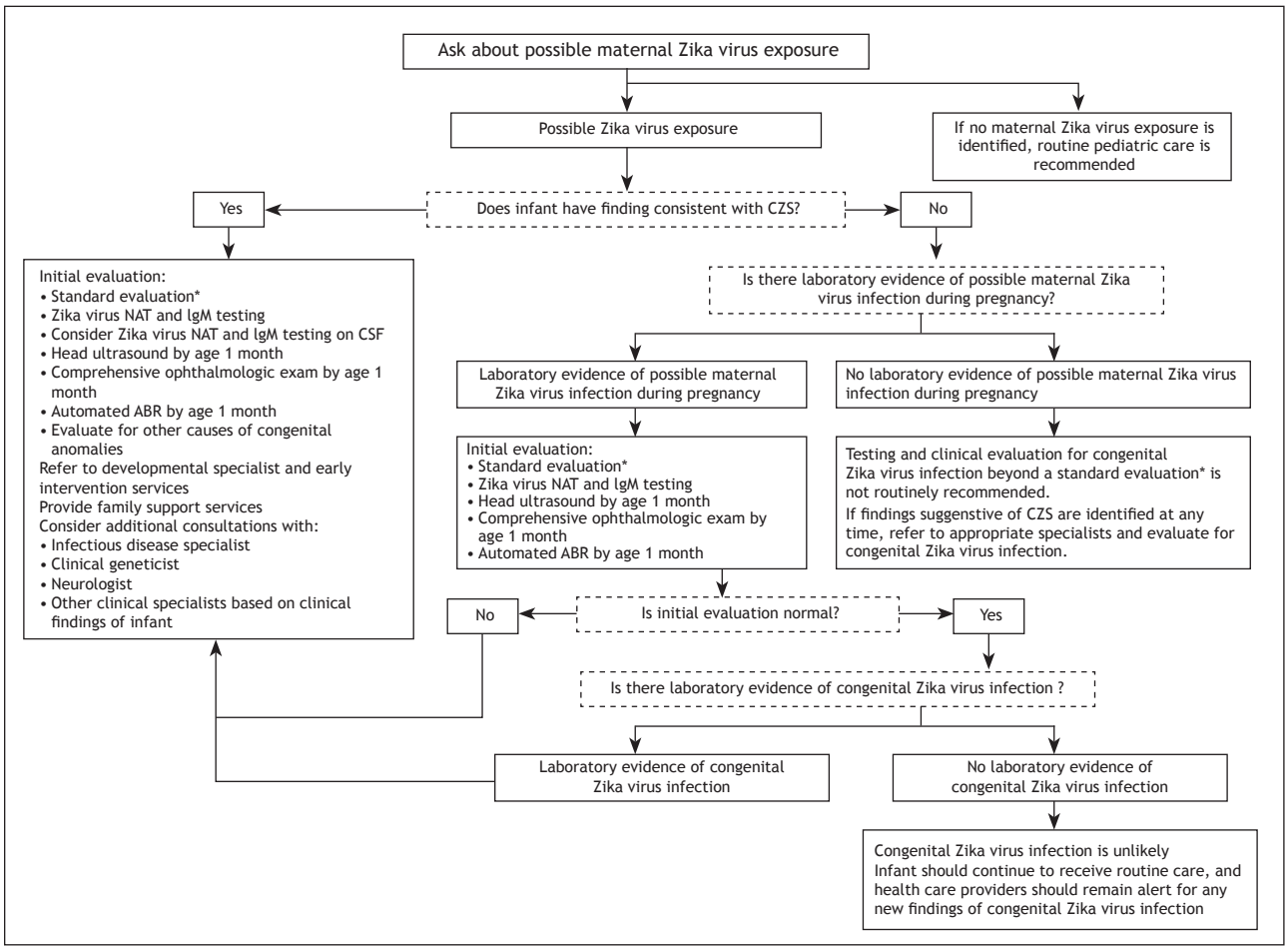
¶ If Zika virus plaque reduction neutralization test is negative, this suggests that the infant's Zika virus IgM test is a false positive.

** Congenital Zika virus infection is unlikely if specimens are collected within the first few days after birth and the clinical evaluation is normal; however, health care providers should remain alert for any new findings of congenital Zika virus infection.

Updated Recommendations for Diagnosis, Clinical Evaluation, and Management of Infants without Clinical Findings Consistent with Congenital Zika Syndrome

The clinical evaluation for infants with laboratory evidence of congenital Zika virus infection should follow recommendations for infants with clinical findings even in the absence of clinically apparent abnormalities. (Algorithm III)

Algorithm III: Recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings,*, †maternal testing results,§, ¶and infant testing results,††(6)**



Abbreviations: ABR= auditory brainstem response; CSF = cerebrospinal fluid; CZS = congenital Zika syndrome; IgM = immunoglobulin M; NAT = nucleic acid test;PRNT = plaque reduction neutralization test.

* All infants should receive a standard evaluation at birth and at each subsequent well-child visit by their health care providers including 1) comprehensive physical examination, including growth parameters and 2) age-appropriate vision screening and developmental monitoring

and screening using validated tools. Infants should receive a standard newborn hearing screen at birth, preferably using auditory brainstem response.

† Automated ABR by age 1 month if newborn hearing screen passed but performed with otoacoustic emission methodology.

§ Laboratory evidence of possible Zika virus infection during pregnancy is defined as 1) Zika virus infection detected by a Zika virus RNA NAT on any maternal, placental, or fetal specimen (referred to as NAT-confirmed), or 2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified flavivirus infection, timing of infection cannot be determined by serologic tests on a maternal specimen (i.e., positive/equivocal Zika virus IgM and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value;or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women, is not routinely recommended in Puerto Rico (https://www.cdc.gov/zika/laboratories/lab-guidance.html).

¶ This group includes women who were never tested during pregnancy as well as those whose test result was negative because of issues related to timing or sensitivity and specificity of the test. Because the latter issues are not easily discerned, all mothers with possible exposure to Zika virus during pregnancy who do not have laboratory evidence of possible Zika virus infection, including those who tested negative with currently available technology, should be considered in this group.

** Laboratory testing of infants for Zika virus should be performed as early as possible, preferably within the first few days after birth, and includes concurrent Zika virus NAT in infant serum and urine, and Zika virus IgM testing in serum. If CSF is obtained for other purposes, Zika virus NAT and Zika virus IgM testing should be performed on CSF.

†† Laboratory evidence of congenital Zika virus infection includes a positive Zika virus NAT or a nonnegative Zika virus IgM with confirmatory neutralizing antibody testing, if PRNT confirmation is performed.

Consultation with the following specialists is usually indicated:

1. A neurologist by one-month age for complete neurologic examination and deciding if tests such as neuroimaging and electroencephalogram are essential.
2. An infectious disease specialist to help in differentiation of Zika virus infection from other congenital infections (eg, syphilis, toxoplasmosis, rubella, cytomegalovirus infection, herpes simplex virus infection).
3. Clinical geneticist to assess for other causes of microcephaly and other anomalies, if present.
4. Early intervention and developmental specialists as affected children are at risk for developmental delay and disabilities.
5. Family and supportive services.

Follow-up of affected infants:

For infants with confirmed or probable congenital Zika infection, vital aspects of follow-up care include:

1. Monitoring growth parameters, including head circumference
2. Monitoring development using a standardized, validated developmental screening tool and referral to specialist for early intervention if needed.
3. Provide routine immunizations
4. Providing anticipatory guidance, psychosocial support and ensuring infants receive necessary testing and consultations.
5. Infants should be monitored for other clinical features of congenital Zika syndrome that may develop or worsen over the first year of life (eg, feeding difficulties, seizures, hydrocephalus):
6. Referral to specialists based upon need.

Special Considerations for the Prenatal Diagnosis of Congenital Zika Virus Infection

While much has been learned about congenital Zika syndrome, limitations of laboratory testing exist and the full spectrum of congenital Zika virus infection is not yet known. Current CDC guidance regarding prenatal diagnosis is reviewed below:

Ultrasound: Comprehensive ultrasound examination to evaluate fetal anatomy is recommended for all women at 18–22 weeks' gestation[10]. However, for the detection of abnormalities associated with congenital Zika virus infection, the sensitivity, specificity, and positive and negative predictive values of ultrasound are unknown. Prenatal ultrasound findings associated with congenital Zika virus infection include intracranial calcifications at the gray-white matter junction, ventriculomegaly, abnormalities of the corpus callosum, microcephaly, and limb anomalies [11,12]

Questions remain about optimal timing of ultrasound among pregnant women with possible maternal Zika virus exposure. Brain abnormalities associated with congenital Zika syndrome have been identified by ultrasound in the second and third trimesters in published case reports [13,14]. CDC previously recommended serial ultrasounds every 3–4 weeks for women exposed during pregnancy with laboratory evidence of Zika virus infection, based upon existing fetal growth monitoring for other maternal conditions (e.g., hypertension or diabetes). However, in absence of supportive data, clinicians may consider extending the time interval between ultrasounds in accordance with patient preferences and clinical judgment. Women with possible exposure but without laboratory evidence of Zika virus infection during pregnancy should receive ultrasound screening as recommended for routine prenatal care. Future data will be used to inform the optimal timing and frequency of ultrasound in pregnant women with possible Zika virus infection.

Amniocentesis. The role of amniocentesis for the detection of congenital Zika virus infection is unknown. Data regarding the positive and negative predictive values and optimal timing for amniocentesis are not available. Reports of the correlation between positive Zika test results in amniotic fluid and clinical phenotype or confirmatory infant laboratory testing are inconsistent [15]. Zika virus RNA has been detected in amniotic fluid specimens; however, serial amniocenteses have demonstrated that Zika virus RNA might only be present transiently[16]. Therefore, a negative test result on amniotic fluid cannot rule out congenital Zika virus infection. However, if amniocentesis is indicated as part of the evaluation for abnormal prenatal findings, NAT

testing for Zika virus should be considered to assist with the diagnosis of fetal infection.

Summary of prenatal diagnosis of congenital Zika virus infection. Given the limitations in the available screening modalities and the absence of effective interventions to prevent and treat congenital Zika virus infection, a shared decision-making model is essential to ensure that pregnant women and their families understand the risks and benefits of screening in the context of the patient's preferences and values. For example, serial ultrasound examinations might be inconvenient, unpleasant, and expensive, and might prompt unnecessary interventions; amniocentesis carries additional known risks such as fetal loss. These potential harms of prenatal screening for congenital Zika syndrome might outweigh the clinical benefits for some patients; therefore, these decisions should be individualized [17].

Prevention of Zika Virus Infection

CDC recommends that pregnant women avoid travel to any area with risk for Zika virus transmission. To prevent Zika virus infection during pregnancy, all pregnant women and their partners should receive counseling on prevention measures including strategies to prevent mosquito bites and sexual transmission of Zika virus [6]. If pregnant women must travel, CDC recommends strict adherence to strategies to prevent mosquito bites and sexual transmission. Pregnant women living in areas with risk for Zika virus transmission should also follow these strategies. Couples wishing to conceive should receive preconception counselling about how to minimize risks for Zika virus infection [18].

Prognosis

The outcome of this infection is uncertain. The reported mortality rate among live-born infants with confirmed and probable congenital Zika infection varied from four to six percent from a large case Brazilian study [19]. The combination of Zika virus-related microcephaly and severe cerebral abnormalities generally has been associated with poor prognosis, but little is known about the prognosis for congenitally infected infants with less severe or no apparent abnormalities at birth [20].

Where resources exist, pregnant women with ultrasound evidence of suspected fetal microcephaly and/or other brain abnormalities should be referred for specialized care, regardless of the underlying cause. If brain abnormalities are confirmed on ultrasound and a Zika virus test is positive in maternal serum or an amniocentesis specimen, then it is very likely that the abnormalities are related to Zika virus. As the head circumference gets smaller, the likelihood of other brain abnormalities and consequently a poorer prognosis increases. In such situations, the woman – and her partner if she wishes – should receive individualized counselling and care. Depending on the severity and certainty of the fetal brain abnormalities and associated prognosis, this could range from specialized antenatal care and serial ultrasound follow-up to monitor any progression of the abnormalities, to a discussion of the potential next steps in managing the pregnancy. It is important to ensure that an affected pregnant woman receives accurate and evidence-based information on the prognosis of the identified abnormalities. The woman – and her partner if she so wishes – should be offered non-directive counselling so that she, in consultation with her health care provider, can make a fully informed choice about the next steps in the management of her pregnancy. Women who carry their pregnancy to term must receive appropriate care and support to manage anxiety, stress and the birth environment. Plans for care and management of the baby soon after birth should be discussed with the parents during the pregnancy, in consultation with a paediatrician or paediatric neurologist where available. Women who wish to discontinue their pregnancy should receive accurate information about their options to the full extent of the law, including harm reduction where the care desired is not readily available. All women, whatever their individual choices with respect to their pregnancies, must be treated with respect and dignity

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Calendar of Monthly Clinical Meetings 2018-19

Months	Name of the Institute
December, 2018	Sir Ganga Ram Hospital
January, 2019	Dr RML Hospital
February, 2019	UCMS & GTB Hospital
March, 2019	LHMC
April, 2019	Apollo Hospital

CONTROVERSY

Perinatal Transmission of HPV Infection

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Dr Saritha Shamsunder

Introduction

Human papillomaviruses are small, double-stranded DNA viruses that infect the epithelium. More than 100 HPV types have been identified; they are differentiated by the genetic sequence of the outer capsid protein L1. Most HPV types infect the cutaneous epithelium and cause common skin warts,about 40 types infect the mucosal epithelium and these are categorized according to their epidemiologic association with cervical cancer. Condylomata acuminata or genital warts, is one of the most common sexually transmitted diseases caused by infection with the human papilloma virus (HPV), in particular, HPV types 6 and 11[1]. Diagnosis is mostly by visual inspection for the presence of lesions consistent with warts, and sometimes using pathologic confirmation[2]. The mode of transmission is sexual, however there are non-sexual modes of spread such as vertical transmission by delivery through the infected birth canal and horizontally through manipulation of the infant with infected hands, towels or fomites.

Screening in pregnancy: Screening recommendations for cervical cancer are same as in non- pregnant women. Co- testing is preferred in pregnant women ≥ 30 years with last screening test done > 5 years ago. HPV screening is not recommended in pregnant women with age less than 30 years[3].

Effect of pregnancy on HPV: The prevalence of warts gradually increases from first to third trimester. The risk of occurrence of warts increases to two fold in pregnancy compared to non-pregnant state[4]. There is a tendency of warts to increase in size and vascularity due to suppression of immunity and hormonal factors which may result in obstruction of the birth passage.

Effect of HPV on pregnancy: There is a risk of perinatal transmission of HPV to the neonate and an increased chance of caesarean delivery if there is obstruction in the outlet due to warts[5-8].

HPV transmission to the neonate: Transmission can occur even in the absence of clinically evident lesions. The classic method of transmission is when the fetus comes into contact with the infected maternal secretions during vaginal birth[5]. Detection rates of HPV infection by polymerase chain reaction (PCR) have ranged widely between 1% and 20% in newborns of pregnant women without apparent infection in their cervix[5-8] and between 5% and 72% in women with HPV-related cervical diseases diagnosed during pregnancy[9]. A clinical observation made by Xu and Favre et al showed that infants are exposed to HPV and infected during vaginal delivery[10,11]. In contrast, some investigators have suggested that vertical transmission is possible without evidence of contact of the fetus with vaginal or cervical secretion[12-14]. However, the number of women studied to confirm placental transmission of HPV has been limited. There is a risk of transmission even in newborns born by caesarean delivery due to ascending infection after premature rupture of membranes[15]. Lai and associates showed that there can be a risk of intrauterine transmission with infected sperm while passing through infected birth canal during fertilization. HPV cannot only infect human sperm cells, certain HPV genes are expressed actively in infected sperm cells. The virus-infected sperm cells conceivably can behave as vectors or carriers for the transmission of HPV, to sexual partner during sexual contact, to fetuses through fertilized eggs, or both[16]. Tseng et al proposed possible antenatal transmission through the transplacental route and the potential association of such transmission with the presence of human papillomavirus in peripheral blood mononuclear cells[13], proved by presence of HPV from amniotic fluid obtained before rupture of membranes[13]. A study conducted by Castellsague et al showed that 19.7% of infants born to HPV-positive mothers and 16.9% of those born to HPVnegative mothers tested HPV positive at some point during infants' follow-up. The most frequently detected genotype both in infants and mothers was HPV-16, after excluding untyped HPV infections. They found a strong and statistically significant association between mother's and child's HPV status at the 6-week post-partum visit[17]. Studies evaluating the risks of vertical transmission shows a wide range from as low as 9.4% for overall HPV infection and still low 2.8% for type specific infection[17]. Sarkola et al[18] studied the relationship between human papillomavirus in the placenta and umbilical cord blood. They concluded delivery mode did not predict HPV status of the neonate. HPV DNA is detected in placental trophoblasts and umbilical cord blood. The presence of HPV DNA at these sites increases the risk of a neonate testing HPV-positive at birth[18]. Laryngeal papillomatosis is the only disease to occur secondary to perinatal infection with HPV 6 and 11; however, this is a rare occurrence with a reported rate of around 1-4/100000 births[3]. Scoczyncski et al[19] showed that asymptomatic HPV infection of a pregnant woman rather than the mode of delivery or other obstetrical characteristics constitutes significant risk factor of vertical transmission[19]. Vertical transmission of HPV is associated with vaginal delivery and multiple HPV types in the mother; however, neonatal HPV infection through vertical transmission is thought to be a transient[20].

HPV transmission and mode of delivery: A meta-analysis done by Chatzistamatiou et al[21] showed that the risk of perinatal transmission decreases by 46% but there is still a risk of 15% transmission in neonates born by caesarean section. Potentially,7.5 caesareans done can prevent a single case of neonatal transmission[21]. Vertical transmission from an infected mother to the neonate increased when the infant was delivered through an infected cervix but the absence of persistent infection in infants at 6 months after delivery may suggest temporary inoculation rather than true vertical infection[22]. Although cesarean section may prevent the exposure of children to the HPV virus during childbirth, its effectiveness in preventing juvenile onset laryngeal papillomatosis(JOLP) is debatable and the procedure itself carries an increased risk of complications[23]. Deng et al[24] concluded that the maternal fetal transmission rate of HPV via genital tract as well as blood was 40.91% and 57. 89% respectively. It was concluded that besides the transmission route of genital tract and amniotic fluid, there was also transplacental transmission of HPV in utero. Therefore, the evidence does not suggest an absolute indication to perform caesarean delivery for pregnant women with asymtomatic genital HPV infection[24]. Silverberg et al[25] showed that a maternal history of genital warts in pregnancy is the strongest risk factor for respiratory papillomatosis in the child. But, future studies should examine the efficacy of genital wart treatment for the prevention of disease. In women with genital warts, delivery times of more than 10 hours were associated with a two-fold greater risk of disease. Cesarean delivery was not found to be protective against respiratory papillomatosis, and no other procedures or complications during pregnancy were observed to increase the risk of respiratory papillomatosis[25].

Treatment of warts in pregnancy: During pregnancy, vaginal secretions contacting the skin and mucous membranes are more abundant[26] , meaning that the vulva will remain in a moist and immersed state, which would be problematic for women with vulval warts. Several factors associated with pregnancy can promote the growth of HPV-induced lesions, for example, pregnancy hormones and reduced immunoresponsiveness. Warts increase in size and number during pregnancy which leads to reduced tolerance and poor compliance to treatment[27] . Only a small number of treatments have been tested and recommended in pregnancy; at present, bi- and tri-chloroacetic acid (BCA/TCA), cryotherapy, electrocautery and surgical excision, including laser treatment, are the only recommended treatments. In addition to high recurrence rates, significant side effects have been observed for these methods, including local ulceration and scar formation, which may reduce a patient's compliance with treatment requirements[28].

Conclusion

There is inadequate evidence to conclude that caesarean delivery reduces the risk of HPV transmission to neonates. Caesarean delivery should be limited to obstetric indications or there is anticipation of obstruction by giant condylomas in the vagina or vulva.

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Forthcoming Events

- Next Monthly Clinical Meeting on Thursday, 27th December, 2018, 4:00pm - 5:00pm at Sir Ganga Ram Hospital, New Delhi.
- Global Conference on Reproductive Health with Focus on "Occupational, Environmental & Lifestyle Factors" to be held on 22nd – 24th February, 2019 at JNU Convention Centre, New Delhi. Contact: Dr J B Sharma 9868138205

CASE APPROACH

Positive TORCH Test in Pregnancy- What next?

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Dr Monika Gupta

What are TORCH Infections?

TORCH infections involve Toxoplasmosis, Rubella, Cytomegalovirus (CMV), Herpes simplex (HSV) and others. The others include Treponema pallidum, Varicella zoster and parvovirus B19. These infections are unique in their pathogenesis and have potentially devastating clinical manifestations. In most cases, maternal infection is mild (fever with rash) but the impact on the developing fetus is enormous in terms of congenital infections, malformations, intrapartum or neonatal fetal affection depending upon gestational age of exposure. The relative predilection to in-utero or perinatal/postnatal affection of various TORCH infections is summarized in table 1.

Table 1: Prediliction to in-utero or postnatal affection

Infection	In-Utero	Perinatal
Toxoplasma	+++	+
Rubella	+++	+
Cytomegalovirus	+	+++
Herpes Simplex	+	+++
Treponema pallidum	+++	+
Varicella zoster	++	++
Parvovirus B19	++++	-

How are TORCH Infections Screened?

Routine full 'TORCH PANEL' screening is not recommended in low risk asymptomatic pregnant women. It is indicated in pregnancies suspected to be complicated with congenital infections, fetal hydrops, fetal brain lesions, unexplained IUGR or in pregnant women with non-vesicular rash with other signs and symptoms suggestive of systemic infection or in women with contact with a person of such illness.[1]

Women presenting with complaint of non-vesicular rash and fever requires a detailed history of demographic profile, any contact with person with rash illness and past history of infection or antibody testing or vaccination. This is followed by lab testing. Amongst the battery of test available ELISA is most cost effective. Paired serological tests can be done in which the first sample is drawn during clinical illness and the second is drawn 4 weeks later. The titers are compared and diagnosis is made.

Diagnosis of fetal infection is only possible by amniotic PCR. It is positive only after 4 weeks from the maternal infection and accordingly amniocentesis is done.

What if TORCH Test is Positive?

A positive test result means IgG or IgM antibodies were found for one or more of the infections covered in the screening. If a woman tests positive for IgM antibodies during pregnancy, more testing will be done to confirm an infection. The presence of IgG antibodies in a pregnant woman usually indicates a past infection (Table 1). Typically, a second blood test is done two weeks later so the antibody levels can be compared. A negative test result is considered normal. This means no antibodies were detected, and there's no current or past infection. The timing of the maternal infection can be found by Avidity test for the particular infection. A high avidity means that the infection has been there before 3 months and a low avidity would mean an infection within 3 months. The presence of infection in relation to gestational age is very crucial.

Table 2: TORCH Serology Interpretation

IgG - , IgM -	No Prior Exposure / Susceptible /Unvaccinated
IgG-, IgM +	Acute Primary Infection (Repeat serology will show IgM negative or absent with IgG positive)
IgG+, IgM -	Past Infection

Toxoplasmosis

How to counsel if Toxoplasmosis serology is positive?

Toxoplasmosis is a parasitic infection transmitted through the fecal matter of cat, eating raw meat, contaminated water and soil, and unpasteurized goat milk. Primary infection in pregnancy is usually subclinical but may cause chorioretinitis. Incidence of toxoplasma with adverse reproductive outcomes is 11-55%.[2]

Vertical transmission occurs 1-4 moths after placental colonization and risk of transmission increases with gestational age (table 3).

Table 3: Risk of vertical transmission of Toxoplasmosis[3]

Period of gestation	Transplacental transmission	Fetal damage
1st trimester	5-15%	60-80%
2nd trimester	25-40%	15-25%
3rd trimester	30-75%	2-10%

Congenital toxoplasmosis occurs in 25% to 50% cases.[1] 70-90% of these infants appears normal at birth but develop clinical illness by young adulthood especially in the form of chorioretinitis that can lead to permanent blindness, obstructive hydrocephalus and intracranial calcification. They may develop mental retardation, seizure activity and motor & developmental delays.

How to interpret the serology and further action?

Usually first step in diagnosis is serology for Toxoplasma. IgG and IgM levels are measured and they represent acute and chronic immune response to the infection. The interpretation and further action is outlined in table 4.

Table 4. Toxoplasma serology: interpretation and action

IgG	IgM	Interpretation	Further action
Negative	Negative	No past or recent infection	Education on prevention
Positive	Negative	Past infection (>12 months)	Immunity to Toxoplasmosis
Negative	Positive	Very early active infection or false positive	Repeat test in 3 weeks to see rising titre. (IgM may persist >1 year)
Positive	Positive	Active infection or false positive	• Repeat test in 3 weeks. (titres rising-active infection, titres stable or reducing-false positive) • IgG avidity testing (if low-recent infection, if high-infection >5 months)

When to do invasive testing for fetal infection of Toxoplasmosis?

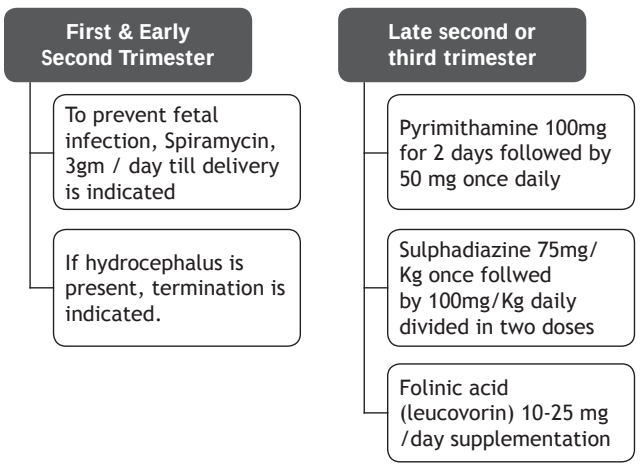
Fetal infection is ruled out by amniotic fluid Polymerase chain reaction (PCR). Amniocentesis should be done after 18 weeks. The specificity and positive predictive value of PCR is 100%.[4]

It should be offered if:

- Pregnancy <20 weeks and maternal primary infection is diagnosed.
- Abnormal ultrasound findings especially intracranial calcification, microcephaly, hydrocephalus, hydrops, hepatomegaly.
- Serological testing is not able to confirm or exclude infection in early pregnancy.

What is the Further Management?

Figure 1: Maternal treatment for reduction of congenital Toxoplasmosis[5]



Rubella

It is transmitted through direct contact or airborne droplets from the respiratory system. Prevention is the best option to a pregnant woman. This can be achieved by preconceptional vaccination and avoiding contact with rubella positive person. The period of infectivity is 7 days before to 7 days after the onset of rash.

How to counsel with positive serology?

Maternal infection in first trimester leads to 80% risk of fetal infection, late second trimester 25% and third trimester from 35% to nearly 100%.

The triad of congenital rubella syndrome (CRS) includes sensorineural deafness, eye-microphthalmia cataracts and congenital heart disease-patent ductus arteriosus especially. The fetus is at 90% risk of congenital abnormalities if affected in first trimester. Fetal growth restriction is the only sequela of third trimester infection.

Table 5: Interpretation of Rubella serological tests

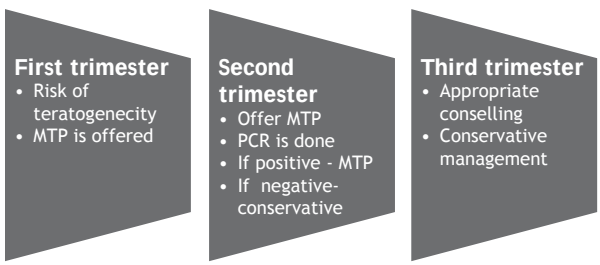
IgG	IgM	IgG avidity	Interpretation
Non reactive	Non reactive	Not applicable	Infection unlikely
Reactive	Non reactive	High	Past infection
Reactive	Reactive	Low	Primary infection
Reactive	Reactive	High	Reinfection, nonprimary infection

Fetal infection can be confirmed by ultrasound, amniocentesis, cordocentesis and chorionic villous sampling or fetal blood sampling. Virus isolation by tissue culture, molecular assays as PCR and ELISA IgM by immunofluorescence.

How to manage once serology is positive?

In cases of non-immune mothers >20 weeks and immune mothers >12 weeks no further tests are required and appropriate reassurance given.

Management depends on gestation at which infection occurred.



All women who are not immune (rubella IgG titre less than 10 IU/mL) should be offered MMR immunization before discharge from hospital after delivery.[6] Long term follow up of infants for developmental defects is required.

Cytomegalovirus

How to counsel once CMV test is positive?

It is the most common perinatal infection affecting pregnancy, transmitted to an infant during pregnancy, ingestion of infected human milk, direct contact with urine and saliva. In 90% cases mother is asymptomatic. Only 10% neonates are symptomatic. The classical triad of CMV is mental retardation, cerebral calcifications, microcephaly and chorioretinitis.

The main feature of this virus is a permanent state of latent infection in host throughout life after primary infection has occurred. Reactivation leading to reinfection can be induced by immunological or hormonal changes in the host. Despite presence of IgG antibodies, maternal reinfection or recurrence is not prevented nor does the fetal or neonatal infection get mitigated.[7]

About 2-2.5% of women seroconvert during course of pregnancy. Mother to child transmission is 30-50% out of which 90% are asymptomatic. Amongst the 10% who are symptomatic, 70% survive with 50% of infants having major sequelae. Thus, primary infection results in more of symptomatic neonates.[8] In case of non-primary reactivation of past CMV, risk of transmission is <1% ; hence reassurance can be done.

How to confirm intrauterine infection?

Discuss the option of diagnostic invasive test (amniocentesis) with all related risks for confirmation of fetus at risk of symptomatic disease. Quantitative PCR (Polymerase chain reaction) on amniotic fluid is recommended for diagnosis of fetal CMV infection. It takes around 5-7 weeks from presumed time of maternal infection for detectable quantities of virus to be secreted by fetal kidneys in amniotic fluid. Fetal blood sampling is not recommended to make this diagnosis.

What is the further management protocol?

- Amniocentesis, if opted for, after explanation of procedure
- Detailed scan for signs of ascites, periventricular and intracraial calcification, ventriculomegaly, microcephaly, hydrops, pleural, pericardial effusion, oligo or polu hydramnios.
- If the woman chooses termination of pregnancy – discuss about postmortem and placental histopathology
- If she wishes to continue pregnancy: serial growth scans at 4 week interval with regular ANC and pediatrician referral.
- Early induction or caesarean not indicated for CMV
- Women with confirmed fetal infection can be offered Valaciclovir oral 8gm/day
- Neonatal tests and investigations- viral culture in body fluid within first 3 weeks of life.
- Affected neonate can be offered Ganciclovir.
- Long term follow up is required.

Herpes Simplex Virus Infection

What are various types of HSV infection?

Primary –Absence of type-specific IgG antibodies with multiple painful vesicular eruptions on vulva and perineum. Rarely symptoms like flu, hepatitis, pneumonia and encephalitis

Non primary First infection- first genital HSV outbreak with heterologous antibodies; fewer systemic symptoms and shorter duration of lesions.

Recurrent infection- genital HSV outbreak with homologous IgG antibodies; may be asymptomatic or have pain, itching or vaginal discharge

How to counsel the patient?

Primary infection and recurrent infection each account for 50% of neonatal morbidity. The infection spreads primarily through direct contact with infected lesions. Neonates acquire infection through an infected vaginal canal during birth. Of all women with history of genital herpes, 25% have recurrence.[9] Risk of neonatal infection is as low as 1% if mother acquires infection in first trimester and it is due to formation of protective antibodies whereas the risk is highest almost to 30-50% if mother gets infection in last trimester.[10] In cases of active recurrent genital herpes the risk is around 4-8% and 0.3-3% in cases of subclinical viral shedding. About 10% of neonates acquire herpes postnatally through contact with infected parents or healthcare workers.

What next when serology is positive?

Type specific antibodies to HSV-1 and HSV-2 in mother guide to the diagnosis of primary or recurrent infection.

Current strategies of treatment[11]

- After confirmation of infection, tablet acyclovir 200 mg 5 times a day or 400 mg TDS for 10 days is started in cases of primary infection (uptill 28 weeks of gestation). This is followed by daily suppressive therapy with Acyclovir 400 mg BD from 36 weeks till delivery.
- In 3rd trimester suppressive therapy usually continues with 400 mg TDS until delivery.
- Active genital lesions over perineum, vagina and cervix or prodomal symptoms such as vulvar pain or burning during labor are an indication for Caesarean Section.
- In case of active recurrent genital herpes, suppressive therapy is given at or beyond 36 weeks.
- Local relief is provided by saline baths or analgesics.
- Vaginal delivery is allowed if there are no lesions.
- Neonatal cultures from eye, oropharynx, and skin and PCR of CSF are performed at birth and repeated after 24 hours.
- Breastfeeding is contraindicated in cases of active lesions on breast.

Parvovirus B19

What if serology for Parvovirus B19 comes positive in a pregnant woman?

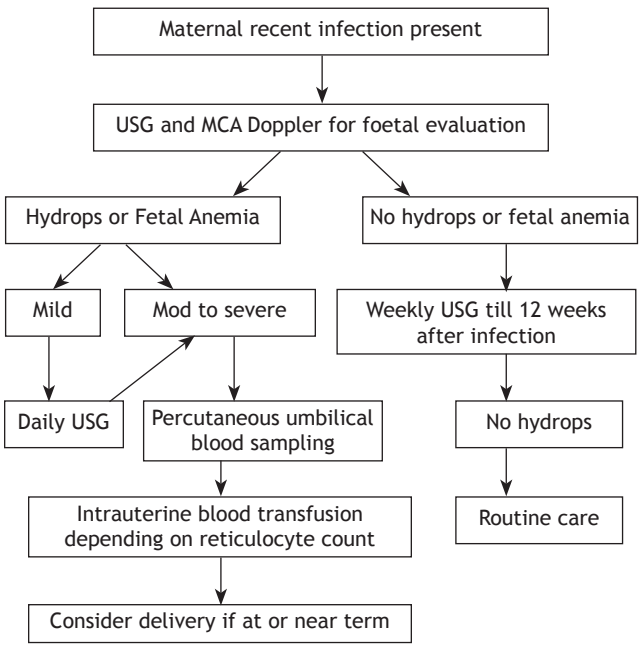
A pregnant woman exposed to or with signs and symptoms of Parvovirus B19, must undergo serological testing for specific IgG And IgM. IgM appears within 2-3 days of acute infection or 10-12 days of exposure and may persist for 6 months whereas IgG remains for lifelong.

This infection affects 1-5% of pregnant women and asymptomatic in 25% of them. The virus has a predilection for the haemopoeitic system thereby destroying the erythroid progenitor cells. The risk of infection is greater in first trimester but the affection of fetus is more between 16-28 weeks as during this period active erythropoesis occurs. It can lead to red cell aplasia and causes fetal anaemia, nonimmune fetal hydrops and fetal death. If the fetus gets the infection before 20 weeks of gestation spontaneous abortion occurs in 13%and hydrops in 4.7% whereas in cases of infection after 20 week spontaneous abortion occurs in <2% and hydrops in 2.3%

Neonates born can have hepatic disorder, transfusion dependent anaemia, CNS abnormalities. There are no long term sequalae.

What is the management plan?

If the mother has a likely past infection (IgG +, IgM-) or no past or recent infection (IgG +/-, IgM-), a reassurance or counselling is required. Parvovirus infection is usually self-limiting in mother.[12]



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DISTRESS TO DE-STRESS

Stress Free Living and Mental Health in Pregnancy


Dr Mohit D Gupta

Manju Gupta[1], Mohit D Gupta[2]

[1]Family Physician and consultant OBG, Co-Director, Nirogam Medicare, [2]Professor of Cardiology, GB Pant Institute of Postgraduate Medical Education and Research / Authors are Associated with Brahma Kumaris World Spiritual University

"You Never Understand Life, until it Grows Inside You"

Pregnancy is one of the greatest gifts of womanhood. It is interesting that at one minute, women is celebrating the impending motherhood and the very next she is terrified at the prospect or giving birth. While pregnancy is filled with excitement and many life changing moments and events, it is also a time when mums-to-be are unprepared for the challenges that come with being pregnant. It's important to remember that whatever you have to deal with, your baby has to deal with too. So, too much pressure can take a toll on your body and may give rise to problems in your baby.

Approximately 80% of women experience some level of stress and anxiety, that can range from mood swings, to often severe levels of depression. So what is an event and moment to celebrate and what is supposed to be a joyous journey often becomes and source of constant fear, emotional instability and mental agony. This takes a toll on the mind and body of both the mother and child.

It often leads to preterm delivery, complications during pregnancy and post natal mental and physical instability.

It is imperative to inculcate certain healthy practices to keep up good mental and physical health during pregnancy.

1. **Maintaining a sense of self:** One of the major problems that most women face is letting there original self-disappear. Women need to be mindful about how they're going to look after and make time for themselves. This includes time for personal health, nutrition and well being. The more one stays connected with self, the better is the outcome.
2. **Ignore and avoid negativity:** Pregnancy is the time when mind is showered with various negative emotions and questions. One often finds self surrounded with fear, anxiety and uncertainties. The golden rule to take care of these and steer safely is to inculcate positive and powerful thoughts. It is like creating Healthy boundaries while letting the healthy stuff in your life and mind. Positive thinking and anticipating a bright future is the essence of remaining happy.
3. **Don't be afraid to ask for Help:** Often, a feeling to let other know that we are perfect and not dependent on others takes a toll on the pregnant female. One must understand that seeking help and support from the partner and family is good for both mother and baby. The sooner one understands this, the better it is.
4. **Exercise.** The research keeps growing — exercise benefits your mind just as well as your body. We keep hearing about the long-term benefits of a regular exercise routine. But even a 20-minute walk, run, swim or dance session in the midst of a stressful time can give an immediate effect that can last for several hours.
5. **Smile and laugh.** Our brains are interconnected with our emotions and facial expressions. When people are stressed, they often hold a lot of the stress in their face. So laughs or smiles can help relieve some of that tension and improve the situation. Sitting with friends and family and talking about positive experiences, sharing a laugh is one of the finest ways to be mentally and physically healthy.
6. **Focus on the positives:** The more one develops the habit on focusing on the good, the better one trains mind to create a positive future. Dwelling in fear and uncertainty will destroy the present peace and take away our joy. It also harms the baby and brings instability.
7. **Get social support.** Call a friend, send an email. When you share your concerns or feelings with another person, it does help relieve stress. But it's important that the person whom you talk to is someone whom you trust and whom you feel can understand and validate you. If your family is a stressor, for example, it may not alleviate your stress if you share your works woes with one of them.
8. **Just breathe:** There are many breathing techniques you can use to calm your nerves whenever you feel overwhelmed. Sit in a comfortable position, relax your shoulders, and focus on your breathing:
   - Breathe in slowly for four counts.
   - Retain the breath for two counts.
   - Breathe out slowly for four counts.
   - If you're feeling comfortable, slowly increase the length of inhalation and exhalation up to six or seven counts, but always keep the retention at two counts.
9. **Meditate:** Meditation and mindful prayer help the mind and body to relax and focus. Mindfulness can help people see new perspectives, develop self-compassion and forgiveness. When practicing a form of mindfulness, people can release emotions that may have been causing the body physical stress. Much like exercise, research has shown that even meditating briefly can reap immediate benefits.

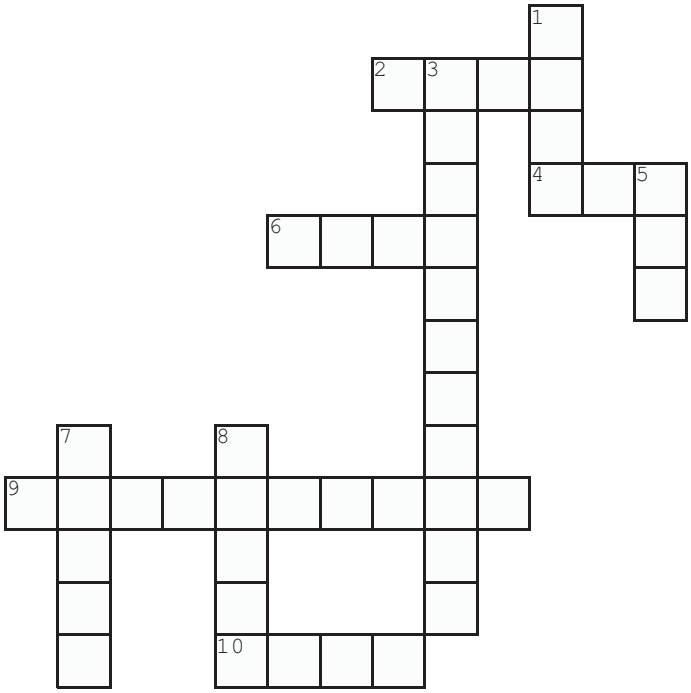
Wishing you a happy, peaceful and rightful life.

CROSSWORD

The Maze of Knowledge

Swati Agrawal
Associate Professor, Department of Obs & Gynae, LHMC & SSK Hospital, New Delhi


Dr Swati Agrawal



Down

1. Virus responsible for causing microcephaly in the neonates
3. Treatment for pituitary prolactinomas
5. Most common sexually transmitted infection
7. Program initiated to prevent mother-to-child transmission of HIV
8. Virus responsible for non-immune hydrops

Across

2. Treatment for severe male infertility
4. Marker for ovarian reserve
6. preferred method for sperm aspiration in men with non obstructive azoospermia
9. Drug used to reduce the risk of congenital toxoplasmosis
10. Iatrogenic complication of assisted reproductive technology

PICTORIAL QUIZ

A Picture is Worth a Thousand Words

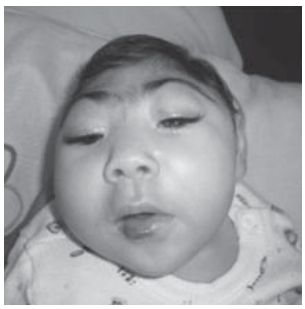


Figure 1:

Q1. Identify the condition

Q2. Name any one infectious cause for this condition

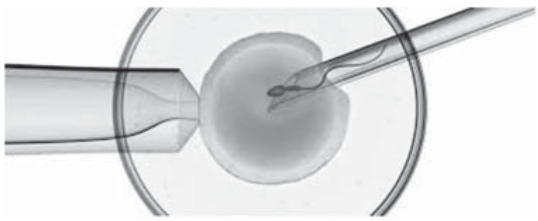


Figure 2:

Q1. Identify the procedure being done in the picture

Q2. Name any 1 absolute indication for this procedure.

WhatsApp your answers to 9953938995.
The names of first three correct entries will be mentioned in our next issue.

Refer page 61 for previous answer key.

40th Annual Conference of AOGD 2018
Pre Conference Workshops at a Glance

- "Hysteroscopy" 22nd November, 2018 at AIIMS, New Delhi



- "Colposcopy" 22nd November, 2018 at UCMC & GTB Hospital, Delhi



- "Fetal Surveillance in Pregnancy" 22nd November, 2018 at Max Hospital, New Delhi.


- "Ovulation Induction and Follicular Tracking" 23rd November, 2018 at LHMC Hospital, New Delhi



- "Operative Obstetrics" 23rd November, 2018 at SGRH, New Delhi



- "Pelvic Reconstructive Surgeries" 23rd November, 2018 at Medanta Hospital, Gurugarm


Day 1 : 24th November, 2018



















ence of AOGD 2018

Day 2 : 25th November, 2018

Conference at a Glance









Events Held

- Public Awareness programme on "Diabetes in Pregnancy" on 13th-14th November, 2018 at LHMC, New Delhi



- Public Forum on the occasion of "World Vasectomy Fortnight" on 27th November, 2018 at LHMC, New Delhi



- Public Forum on "Prevention of Parent to Child Transmission of HIV" on 28th & 29th November, 2018 at LHMC, New Delhi



- Monthly Clinical Meeting on 30th November, 2018 at LNJP Hospital & MAMC, New Delhi


Appraisals and Accolades!! Congratulations on the Success.....

Wonderful Conference, it was an academic feast, very good topics, very well organised Congratulations team LHMC, Dr Abha, Dr Manju, Dr Kiran and the entire faculty.

– Dr S S Trivedi

Congratulations team LHMC! Especially liked the felicitation of all senior members of AOGD. It was heart warming to see all of them.

– Dr Shalini Rajaram

Congratulations to Team LHMC for a Wonderful Conference.

– Dr Kiran Guleria

Congratulations Team AOGD LHMC for the Wonderful Conference. Depicts the hard work put in. Great efforts.

– Dr Amita Suneja

Congratulations to the Team AOGD 2018 for Wonderful Conference and thanks for Felicitation of Senior Members including myself.

– Dr Shaktibhan Khanna

Wonderful Conference, it was an Academic Feast, very good topics, very well organised Congratulations Team LHMC, Dr Abha, Dr Manju, Dr Kiran and the entire faculty.

- Dr Nirmala Agarwal

Program was really good Congratulations.

– Dr Manju Khemani

LHMC gynae team, Great show beautifully organised I do feel proud, Congratulations.

– Dr Chitra R

Wonderfully arranged, organised and managed .. congratulations Team AOGD.

– Dr Sushma Sinha

Excellent conference, Congrats to Dr Abha and entire LHMC team, Great show.

– Dr Indu Chugh

Congratulations team LH, very good content and organization. Quiz Masters enjoyed the questions.

– Dr Abha Sharma

Thanks to dynamic team AOGD, from selection of topics to the execution. Privileged to be part of it.

– Dr Shakuntla Kumar

Congratulations team LHMC. Excellent conference. Well organized and well thought of topics. Dr Abha, Dr Manju, Kiran, Reena, Ratna, Pikee and the whole team. Have had excellent experience of LHMC organization with the pg training programs. Thanks for a lovely conference and the many thoughtful gestures.

– Dr Surveen Ghumman

Heartiest congratulations Dr Abha Singh and team for wonderfully organising the AOGD conference. It was a grand success. Every thing was wonderful. Again congratulations, Best wishes.

– Dr JB Sharma

Dear Abha and entire LHMC team heartiest congratulations for very well organised and greatly appreciated AOCD conference.

– Dr Usha Gupta

Well done team LHMC. Was pleasure addressing full hall.

– Dr Alka Kriplani

Congrats to Team LHMC. **– Dr M Gouri Devi**

Wonderful Conference.Thanks Dr Abha Dr Kiran Aggarwal for making me a part if this grand event. Very well organized and well appreciated conference. Congratulations team LHMC.

– Dr S L Kabra

Very well organised conference congratulation to whole team of AOGD My best wishes for your future endavours.

– Dr Neera Aggarwal

Great show Dr ABHA Dr Kiran and the whole LHMC team congratulations.

– Dr Achla Batra

Very well going AOGD team! Congratulations! Long live AOGD.

– Dr Sudha Prasad

Congratulations LHMC team on the successful completion of the conference.

– Dr Sunita Malik

Thanks Abha di, dr Kiran for involving me this Prestigious conference. Great personal touch. Congratulations LHMC team for wonderful conference.

– Dr Ragini Aggarwal

Congratulations to team LHMC. For the wonderful conference Great academic feast. We perfectly enjoyed the entire conference.

– Dr Mala Srivastava

Heartiest Congratulations Dr Abha, Dr Manju, Kiran, Pikee, Ratna, Sharda and the whole AOGD team. Superb Conf ! Thankyou.

– Dr Rupender Sekhon

Congratulations Dr Abha, Dr Kiran & Team! Very well organised academic treat ! Thank you so much for inviting me !!

– Dr Rashmi Vyas

Heartiest congratulations to all! The pix look great. Sorry that I could not be there. Man proposes God disposes.... But once again kudos for the splendid show.

– Dr Neerja Bhatla

Great conference Kiran. Congratulations to the LH team.

– Dr Chitra Setya

Congratulations Dr Abha Dr Kiran and team.

– Dr Vatsala Dadwal

Congratulations Abha, Manju, Kiran and the whole LH team for a great conference! You've held the LH flag high!

– Dr Sanjeevani Khanna

Congratulations team AOGD for the academic feast....Thanks for making me a part..

– Dr Anita Rajorhia

Congratulations Dr Abha, Dr Kiran, Dr Manju and entire LHMC team for a great conference and workshops.

– Dr Sohani Verma

Congratulations team aogd for the excellent conference & involving peripheral government hospitals.

– Dr Vijay Kadam

It was a matter of great pleasure to have been at AOGD 2018 on 24th. It indeed was a great academic meet with excellent deliberations and impeccable time management. Congratulations to all the members of LHMC.

– Dr Uma Singh

Hearty Congratulations for conducting successful conference with good academic feast and thanks again for involving me and making me a part of this endeavour.

– Dr Amita Jain

Hearty congratulations Dr Abha, Dr Manju Puri, Dr Kiran and team.

– Dr Sonal Bhatla

STANDARD OF CARE

Ovarian Stimulation Regimens in Oncofertility

N Mahajan
Director Mother and Child Hospital. Scientific Director Ferticity Fertility Clinics


Dr N Mahajan

Cancer survivorship is steadily increasing due to availability of improved multimodality treatments and early screening procedures. This has brought fertility preservation (FP) into focus as reproductive needs of young patients form an important aspect of the proposed 'quality of life'. European and US data suggest that long-term survival in children and adolescents diagnosed with cancer is around 80% (Hudson, 2010). A recent study estimated that 1 in 530 young adults between the ages of 20 and 39 years is a childhood cancer survivor (Ward et al., 2014). Fertility preservation has become the standard of care for cancer survivors and non-cancer patients on cytotoxic drugs that reduce ovarian reserve and shorten the reproductive window.

Embryo and oocyte cryopreservation are the standard procedures used for FP. Oocyte cryopreservation is the preferred procedure as it offers reproductive autonomy to the woman and circumvents future ethical, religious, and legal issues. Since these procedures require ovarian stimulation (OS) and oocyte retrieval, a period of approximately 12–14 days is required before chemotherapy (CT). In breast cancer patient's the time available between surgery and chemotherapy (CT) is about 4–6 weeks and allows the patient to undergo OS with conventional protocols. In other cancer's the window available for FP may be much shorter and one has to resort to non-conventional OS protocols. One should always bear in mind that FP procedures should be completed fast to start oncology treatment. This article summarizes the various protocols used in oncofertility highlighting the modifications for hormone sensitive tumours.

Screening before FP – Apart from general health screening, ovarian reserve testing is essential for counselling the patient. Ovarian reserve (OR) testing requires AMH and AFC evaluation.

OR Evaluation:

1. Clinical Parameters - Return of menses. Return of menses however does not indicate fertility.
2. FSH & Estradiol (E2) levels – to be checked on 2/3rd day of menses. An FSH >12mIU or E2 > 75pg/ml suggests a poor ovarian reserve. Serum E2 and thus FSH levels are affected by Tamoxifen use as tamoxifen raises the serum E2 levels.
3. Anti-Mullerian hormone (AMH) - Produced by early antral follicles < 6mm size. AMH has been accepted as a good marker for OR. Can be estimated on any day of the cycle and is also proving to be useful in pre-pubertal girls. Unlike FSH its levels are not affected by E2 and thus tamoxifen use.
4. Antral follicle count- is measured by transvaginal ultrasound in the early follicular phase preferably by day 5. In young girls and unmarried women AFC count may have to be done using a trans-abdominal ultrasound probe which is less accurate.

Concerns and constraints of FP-

1. Constraints of time – Haematological malignancies – urgency to start treatment Breast Ca – 4-6weeks available between surgery & chemo
2. Risk of complications – ovarian hyperstimulation syndrome (OHSS) is a dreaded complication of IVF. OHSS is to be avoided at all costs as it will delay cancer treatment and poses an increased mortality and morbidity risk in these patients.
3. High E2 levels – may be detrimental to hormone sensitive tumours.
4. State of Health & Age – cancer leads to a cachexic state and an increased risk of thrombosis. These risks further increase with age.
5. Anaesthetic risks
6. Surgical risk – increased risk of bleeding and infection.

Ovarian Stimulation Protocols: OS for oocyte collection and IVF requires the use of gonadotrophins (GT) to stimulate maximal egg production in the ovaries. *The premature LH surge* is suppressed by the use of GnRH agonist or antagonist. The OS protocols used in '*in vitro* fertilization' (IVF) are the long (luteal start) GnRH agonist or antagonist and OS with gonadotrophins (GT). Constraint of time in cancer patients may necessitate the need for an early start. A random start protocol can be used without compromising egg numbers, fertilization rate(FR) or subsequent pregnancy rates (PR). Use of natural cycle IVF or mild natural cycle IVF or mild IVF is not a good option in FP as there is generally a single opportunity to collect oocytes and maximizing the yield gives a better chance of pregnancy subsequently. Antagonist protocol with GnRH agonist trigger is preferred as it reduces the risk of ovarian hyperstimulation syndrome.

The ovarian stimulation protocols followed are-

1. *Conventional Stimulation Protocols(CS)*
   a) Long agonist protocol
   b) Antagonist protocol
2. *Random start protocol*
3. *Crash protocol*
4. *Protocols for Hormone receptor positive patients*
   a) Letrozole with gonadotrophins for OS
   b) Tamoxifen with gonadotrophins

Monitoring for ovarian response: a baseline pelvic scan is done on cycle day(CD) 2 to confirm absence of any cysts in the ovary and a thin endometrial lining. Baseline E2 and Progesterone (P) may be determined but are not mandatory. Serial follicular monitoring starts subsequently from day 5 of ovarian stimulation. GT dose adjustment is done based on follicular size and E2 levels. E2 and P are measured when follicles reach 17mm in size. This determines the day and time of HCG administration which is essential for egg maturity and oocyte retrieval.

Ovulation Trigger: Both HCG and GnRH agonist can be used to trigger final egg maturation. GnRH agonist offers protection from OHSS and also an early luetiolysis and is preferred to HCG. Dosage of HCG used is 5000 or 10,000 IU and dose of agonist varies with the product used. For Decapeptyl dose is 0.2mg s/c, for luperolide it is 2mg s/c. Some authors suggest that GnRH agonist gives more mature oocytes but others do not support this finding.

OS Protocols

Long agonist protocol: GnRH agonist is started from day 21 of the previous cycle till the day of HCG administration. OS starts from day 2 of menses, starting dose is based on the patients age, AMH, AFC and BMI and can vary from 150-450iu. Both recombinant FSH or HMG may be used. Once OPU is done ovarian quiescence and a quick decrease in steroid levels may be achieved by giving daily dose of GnRH antagonist 0.25mg s/c for 5-6 days. If E2 levels are not high and an early period is required, progesterone support in luteal phase may be withheld. 3 weeks are required for this protocol. (Fig 1)

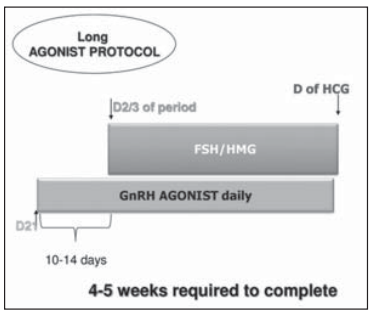


Figure 1.

Antagonist Protocol: GT stimulation starts on day 2 of the menstrual cycle. GnRH antagonist is added from day 5/6 of stimulation once the follicle size is 12-14 mm till and on the day of HCG. Follicular and hormonal monitoring follow the same standard pattern. 12-14 days needed to complete OPU. (Fig 2)

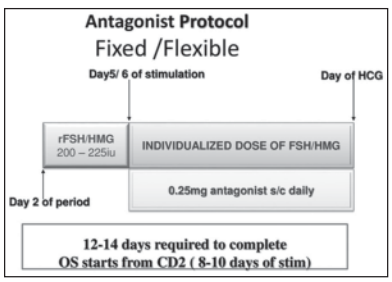


Figure 2.

Crash Protocol: Aim is to achieve quick D/R. GnRh Antagonist is given as a 3mg bolus in luteal phase or daily dose 0.25mg s/c for 2-4 days. OS is started at the onset of menses. Total time for cycle completion is about 16 days.

Random start protocol: was introduced by Cakmak et al in 2013. This protocol allows GTs to be started on any day of the cycle by recruiting a second wave of developing follicles, without compromising oocyte yield and/or maturation. OS with GT's is started on the day the patients present for FP, in any phase of the menstrual cycle. Late follicular phase being defined as presence of a dominant follicle (>13 mm) after cycle day 7 and P level <2 ng/ mL. Luteal phase is the post ovulatory phase- P level >3 ng/mL. If patient presents in the peri-ovulatory period with a DF 18mm, ovulation is achieved by giving an agonist trigger and stimulation started once ovulation has occurred. Both the lead follicle in the follicular phase and corpus luteum (CL) in the luteal phase are discounted. Starting of GnRH antagonist is dependent on the size of the secondary follicles following the lead follicle. As soon as the secondary follicles reach 12mm GnRH antagonist is started in a daily dose of 0.25mg s/c- this could be before or after the spontaneous LH surge. Cakmak et al demonstrated that in both late follicular & luteal phase–start cycles, follicular development patterns & rise in E2 levels were similar to those in the conventional stimulation (CS) cycles. Spontaneous LH surge in late follicular start cycles did not alter subsequent development of follicles <12 mm, growth was similar to CS cycles (Fig 3).

Follicular development in luteal phase cycles was similar to CS cycles even in presence of a CL & high P levels. In luteal phase cycles, CL regression & < P levels was observed during OS. Some patients had P withdrawal bleeding during OS however continued follicular growth with rise of E2 was observed. GnRH agonist was able to mount an endogenous LH surge within 7 days after the spontaneous LH surge. Two endogenous LH surges within a week did not affect the oocyte yield and/or maturation. Length of OS was significantly longer in RS cycles than CS cycles (P<.001). Dose of gonadotrophin used was significantly higher in RS (P<.001). Length of COS was similar in late follicular phase–start and luteal phase–start cycles. No difference was observed in the number of oocytes recovered (OR), MII or FR.

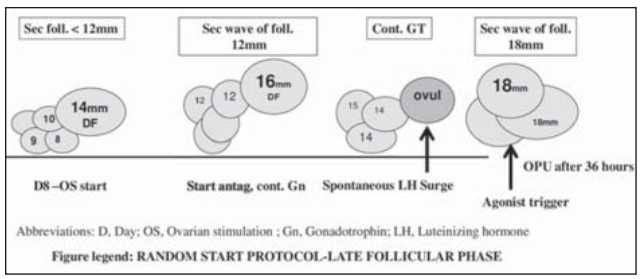


Figure 3.

Protocols for Hormone receptor positive patients: (Fig 4)

Use of Letrozole: High E2 levels achieved with OS are

of concern especially in ER+ve patients even though this increase is for a very short period of time. Addition of the aromataze inhibitor (AI) during OS with GT's- helps to reduce the E2 level significantly - by more than 50%. Letrozole is added in a dose of 2.5 – 5mg from day 2 of the cycle up to the days of HCG. It can be continued after OPU till E2 levels decrease. According to some authors letrozole reduces the number of mature oocytes available for cryopreservation (Revelli et al 2013)

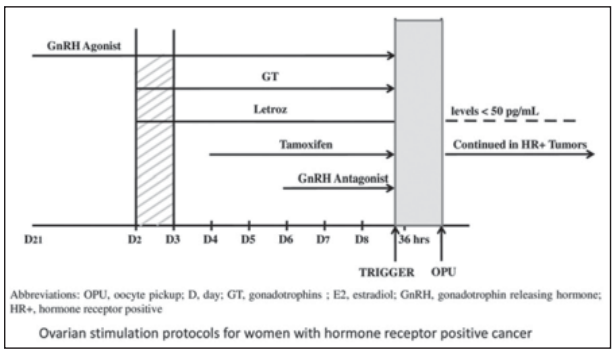


Figure 4.

Use of Tamoxifen: Tamoxifen is a selective estrogen receptor modulator and is used in HR+ve BC patients to prevent recurrence. It prevents proper binding of estrogen & the subsequent transcription of DNA to mRNA. In BC patients undergoing OS tamoxifen can be used in a dose of 20mg/day starting from cycle day D 2 or 4 once E2 levels start rising. E2 levels remain high with Tamoxifen but these do not seem to be detrimental as much higher E2 levels are seen in patients on Tamoxifen in pre-menopausal BC patients. A 3-10 yr follow up showed no increase in the risk of recurrence or late mortality (Meirow et al 2014).

Number of Oocytes retrieved: There is a controversy regarding the number of OR in cancer patients with some authors saying that they are similar to non-cancer patients with age being the only determining factor. while others suggest that the number is reduced. Poor ovarian response is seen in carriers of BRCA mutations and patients with lymphoma. A study by Alvarez et al 2016 looked at ovarian response in cancer patients undergoing OS for FP. Results of the study revealed that there were no differences in dose of gonadotrophins used & duration of stimulation between the groups, patients with haematological malignancies had the highest number of mature OR. Patients with gynaecological cancer had less mature OR compared with haematological and BC patients (P = 0.005 & P = 0.045, respectively). There was a significant difference in OR between age groups 31–35 (P= 0.026). The FR & the number of cycles cancelled were comparable between all groups.

Safety of Controlled Ovarian Stimulation: A Swedish register-based, matched cohort study (Rodriguez et al 2017) looked at the safety of hormonal stimulation in braeast cancer (BC) patients undergoing FP. It concluded that it was safe to practice FP in young women with BC. Women who received hormone stimulation did not have a higher relapse rate than unexposed controls adjusted for age and calendar period of diagnosis (incidence rate ratio (IRR), 0.59; 95% CI, 0.34–1.04). Results remained unchanged after adjustment for tumour size, ER status, affected lymph nodes, and CT treatment (IRR, 0.66; 95% CI, 0.37–1.17). A systematic review and meta-analysis looking at the safety of COS in BC (Rodgers et al 2017) also reported no decline in relapse-free survival rates in women receiving letrozole with GTs compared with women who did not undergo FP procedures (mean follow-up, 5.0 vs. 6.9 years; HR for recurrence, 0.77; 95% CI, 0.28–2.13). No significant relationship between the use of any fertility medication or IVF treatment (OR, 0.66; 95% CI, 0.18–2.33) and subsequent risk of ovarian cancer has been demonstrated (Gronwald et al., 2016).

Reproductive Outcome with Preserved Embryos/ Oocytes: An oocyte-to-baby rate of 6.5% is projected, the probability of achieving a baby increases progressively with the number of vitrified oocytes used, a plateau being reached at 25. Studies in cancer survivors have suggested an oocyte survival rate of 80-90% with a live birth rate of 44- 45%. SART data suggests that the likelihood of a live birth after ART among women with prior cancer using autologous oocytes is reduced and varies by cancer diagnosis but is similar to women without cancer when donor oocytes are used. LBR by Cancer status is 47.7% in patients without Ca vs 24.7% patients with Ca (P=0.0001), by cancer diagnosis it is 53.5% for melanoma patients to 14.3% for BC patients (P = 0.0001).

Women with BRCA Mutations: Fertility issues are extremely relevant as BRCA mutation carriers may require cancer treatment at a young age and prophylactic bilateral salpingo-oophorectomy could be advised. BRCA1 mutation carriers are at a 50%–80% lifetime risk of BC, 40%–50% risk of developing a second primary BC, and 40%–60% risk of ovarian cancer. Women with BRCA2 mutations also present a high risk of BC, although the risk of ovarian cancer is lower (10%–20%). Literature suggests a higher risk of POF, earlier menopause, and poorer response to OS among women with BRCA1/2 mutation. Fertility treatment has not been associated with increased risk of intraepithelial ovarian cancer in these patients.

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40th Annual Conference AOGD

24th - 25th November 2018

Prize Winners

Category	Award	Name	Institute	Topic
Dr Neera Agarwal's Medal for Best paper on theme topic of Obstetrics (Maternal Health)	Gold Medal (tie)	Dr Poonam Kashyap	MAMC	To Study The Clinical Profile, Prognostic Factors and Obstetric Outcome in Terms of Meternal and Neonatal Outcome in Pregnant Women with Peripartum Cardiomyopathy
		Dr Ruchi Bhatiyani	MAMC	Multidisciplinary Approach Resulting in Improved Maternal Survival in Eisenmenger Syndrome: Prospective study in a tertiary care centre
Dr Suneeta Mittal's Medal on Population Stablization	Gold Medal	Dr Nihita Pandey	LHMC	A Retrospective Analysis on Acceptability and Complications of PPIUCO Insertion
Dr U.P Jha & Raj Soni's Medal on best paper presentation in Endoscopy	Gold Medal	Dr Shruthi S.S	LHMC	Role of Ultrasound Based Soft Markers in the Evaluation of Women with Chronic Pelvic Pain
Dr U.P Jha & Dewan Balakram's Medal on best presentation on Gynae Oncology	Gold Medal	Dr Divya Singh	MAMC	Evalution of Visual Inspection byAacetic Acid, High Risk Human Papilloma Virus testing and Human Papilloma Virus 16/18 Genotyping to Screen for Cervical Cancer
Mr S. Bhattacharya & Dr Ganguli's Medal Free Paper (Miscellaneous Category)	Gold Medal	Dr K. Aparna Sharma	AIIMS	A Prospective Study of Aortic Isthmus Doppler Changes in Appropriately Grown and Small for Gestational Age Foetuses and Association with Perinatal Outcome
	Silver Medal	Dr Sukriti Malviya	IFC	Treatment of thin Endometrium with Autologous platelet rich plasma: A pilot study
Poster Presentation	Gold Medal	Dr Farhat Mazhari	HIMSR	Analysis of GDM Cases: Do all patients with abnormal OGTT need to be treated
	Silver Medal	Dr Sharmishtha	SGRH	Pregnancy Outcomes Post Bariatric Surgery
Slogan	First Prize	Dr Sandhya Jain	UCMS	
	Second Prize	Dr Neha Gupta	HIMSR	
Research Paper- Best Competition Paper	Gold Medal	Dr Vaishnavi Seshan	VMMC	Comparison of Lignocaine Spray Versus Lignocaine Gel for Pain Relief During Colposcopic Directed Cervical Biopsy
	Silver medal	Dr Megha Panwar	VMMC	Raised Neutrophil Lymphocyte Ratio and Serum beta hCG Level in Early Second Trimester of Pregnancy are Predictors of Development and Severity of Preeclampsia
	Bronze Medal	Dr Sonali Jain	LHMC	Association of Serum Placental Growth Factor with Severity of Preeclampsia and Fetomaternal Outcome
Dr Batra's Medal winning team of AOGD Quiz	Gold Medal	Dr Aayushi Rathore	UCMS	
		Dr Anushree	UCMS	
Dr S N Mukherjee Rotating Trophy	Best AOGD Monthly Clinical Meeting		UCMS	

RECENT ADVANCES

Endometrial Receptivity Array (ERA)

Tanya Rohtagi
Consultant Training Obstetrics & Gynaecology (Leeds Teaching Hospitals, NHS, UK), Principal Consultant IVF, Reproductive Medicine & Onco-Fertility, Max Super Specialty Hospitals, Saket and Panchsheel, New Delhi


Dr Tanya Rohtagi

Introduction

Human implantation is a highly enigmatic and dynamic process that requires a perfect synchrony between a developing embryo at the blastocyst stage and a well differentiated receptive endometrium.

It is known that **less than one-third of the human embryos** replaced in the uterus will **implant** and due to lack of objective and accurate methods of assessment, **Endometrial Receptivity (ER)** is rarely investigated.

Endometrial receptivity is the period of time during which the uterine lining is receptive to implantation of a fertilized embryo(blastocyst). Determining this period of peak receptivity **–"Window of Implantation" (WOI)** in a patient is necessary to synchronize embryo transfer during the optimal receptive period, a strategy known as **personalized Embryo Transfer (pET).**

Physiology of Implantation

The human endometrium is an intricate tissue that undergoes changes at multiple levels during the menstrual cycle in response to ovarian hormones and paracrine secretions. The principal regulators for the acquisition of endometrial receptivity are estradiol and progesterone. During the phase of receptivity, the endometrium undergoes morphological, cytoskeletal, biochemical, and genetic changes to become functionally competent to allow implantation of the embryo.

Lessey BA *et al*[1] demonstrated that the **"Window of Implantation" (WOI)** is **dynamic** and **not fixed** and opens on day 19 or 20 of the cycle and remains **open** for **just 4–5 days** at the time when progesterone reaches peak serum concentrations[1].

Markers of Endometrial Receptivity

The concept of endometrial receptivity and the existence of a WOI for the implantation of human embryos was first suggested by Hertig and Rock in 1956[2].

Histological, biochemical, and ultrasound markers of ER have been proposed but, most of these methods don't have good predictive value.

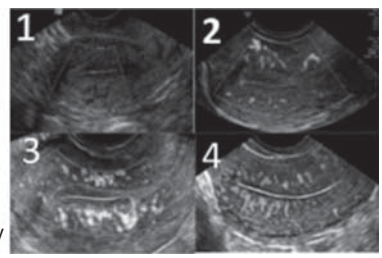
Ultrasound Markers- Applebaum Score

Ultrasound evaluation (TAS and TVS) offer a simple, quick and non-invasive way of assessing the endometrium.

Applebaum[3] came up with a unique scoring system- The Uterine Scoring System for Reproduction **("USSR")** to assess the endometrium and suggested that a USSR **"Perfect Score"** of **20** was associated with **100 % conception rate.**

The Uterine Scoring System for Reproduction **("USSR")** comprises evaluation and scoring of the following parameters:

Zone 1 - Myometrium surrounding the endometrium.
Zone 2 - Hyperechoic endometrial edge
Zone 3 - Internal endometrial hypoechoic zone
Zone 4 - Endometrial cavity



1. *Endometrial Thickness*
   a. < 7 mm = 0
   b. 7 - 9 mm = 2
   c. 10 - 14 mm = 3
   d. > 14 mm = 1
2. *Endometrial Layering*
   a. No layering = 0
   b. Hazy 5-line appearance = 1
   c. Distinct 5-line appearance = 3
3. *Myometrial Contractions (seen as wave-like endometrial motion high-speed playback from videotape)*
   a. < 3 contractions in 2 minutes (real-time) = 0
   b. > 3 contractions in 2 minutes (real-time) = 3
4. *Myometrial Echogenicity*
   a. Coarse/inhomogeneous echogenicity = 1
   b. Relatively homogeneous echogenicity = 2
5. *Uterine Artery Doppler Flow Evaluation*
   a. PI > 3.0 = 0
   b. PI< 2.5 - 2.99 = 0
   c. PI < 2.2 - 2.49 = 1
   d. PI < 2.19 = 2
6. *Endometrial Blood Flow within Zone 3*
   a. Absent = 0
   b. Present, but sparse = 2
   c. Present multifocally = 5
7. *Myometrial Blood Flow Internal to the Arcuate Vessels seen on gray-scale examination*
   a. Absent = 0
   b. Present = 2

The values assume a technically adequate ultrasound examination with no abnormalities of uterine shape or development, no other gross uterine abnormalities (e.g.,

significant masses) and a normal ovarian cycle (e.g., without evidence of ovarian-uterine dyscoordination).

However, consensus on the **perfect scoring system** and technique is still **lacking**.

Histological Markers

Noyes *et al*[4] established **morphological criteria** to evaluate endometrial development and receptivity. For years, these criteria remained the mainstay for defining ER despite the **huge inter** and **intra-cycle variability**, thus in recent years its accuracy to predict the WOI been questioned.

Pinopods are cytoplasmic projections of the luminal epithelial cells, abundant during the WOI, thought to promote blastocyst adhesion. The presence of pinopods was demonstrated in post receptive endometrium, and this precluded their potential use as a useful marker of ER[5]

Biochemical Markers

A number of molecules present during the mid-secretory phase have been studied as biochemical markers of ER. The ones which have shown significant association with the WOI are the integrins, leukemia inhibitory factor, homeobox A10, mucin 1, calcitonin, and cyclo-oxygenase 2[6].Many more are being investigated; however, none have found their place in the clinical setting.

Molecular Markers

The various molecular approaches for the study of biological samples are collectively called the "Omics" and include - genomics (study of genes), epigenomics (study of epigenetic DNA modifications), transcriptomics (study of gene expression), proteomics (quantification of proteins), metabolomics and lipidomics (composition and quantification of metabolites and lipids). Currently, **transcriptomics** is considered the **most established technology** available for evaluation of the endometrial factor.

Transcriptomics of the Human Endometrium

Over the last decade, the transcriptomics of the human endometrium have been widely researched. The transcriptome reflects the genes that are being actively expressed at any given time in a specific cell population. Transcriptomics also allows gene expression characterization at the messenger RNA level of a population, leading to a sample-specific molecular profile.

Haouzi *et al* [7]compared the gene expression profile of ER between natural and stimulated cycles for the same patients. They observed that the **gene transcription profile** of the endometrial WOI under **COS was defective** for biological functions such as transforming growth factor beta signalling, leukocyte trans-endothelial migration, and the cell cycle.

At a molecular level, the **pre-receptive/early secretory phase** is characterized by increased metabolic activity in preparation for implantation. This leads to a predominance of products related to cell metabolism (fatty acids, lipids, eicosanoids, and amino alcohols), transport, and germ cell migration[8]. There is an inhibition of mitosis during this phase as suggested by the downregulation of several growth factors[9].

The **receptive phase** witnesses a **"transcriptional awakening"** or upregulation of most gene expression. Apart from a high level of metabolic and secretory activity there is also an upregulation of genes involved in the activation of the immune response[9]. During the **late-secretory phase**, the **WOI closes** and in this phase genes related to immune response-both cellular and humoral, blood coagulation, steroid bio-synthesis, and prostaglandin metabolism are regulated[10]

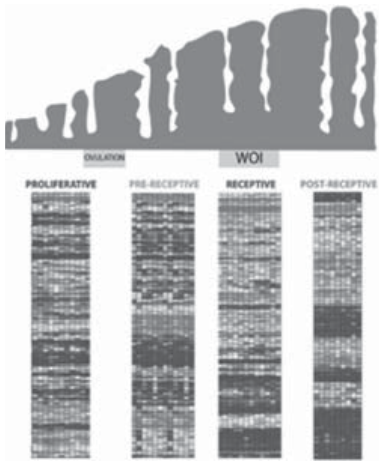


Figure 1. Endometrial transcriptomics profile[11].
Evolution of endometrial tissue over time and the gene expression profile at each given stage.
Heatmap showing the Endometrial Receptivity Array (ERA) gene expression profiles in each endometrial cycle stage (proliferative, pre-receptive, receptive, and post-receptive).

Endometrial Receptivity Array (ERA)

The ERA test **currently** it incorporates **248 genes** (Igenomix test)unique to the WOI.

Ruiz-Alonso *et al*[11] coined the phrase **"personalized embryo transfer" (pET)** or transferring an embryo based on the woman's personalized WOI to enhance success in ART independent of endometrial histology.

To perform ERA, messenger RNA **(mRNA)** is extracted from an endometrial biopsy, analysed by **NGS**, and evaluated by a **computational predictor**. The ERA predictor classifies the sample as receptive or non-receptive (this can be pre-receptive or post-receptive). A **non-receptive** result reflects the **displacement of the WOI** since the endometrium may require different timing of progesterone (P) administration than the

standard 5 days to reach receptivity. A **displaced WOI** can be **confirmed** by analyzing a **second endometrial biopsy** performed during the subsequent cycle at the specific day suggested by the first ERA result.

Standard Protocol to Obtain an ERA Sample

Prior to starting the procedure the **ERA cryotube** should be **labelled** with patient name and unique ID. To perform an ERA test[12], a small endometrial biopsy must be taken from the uterine fundus using a pipelle catheter (Cornier Devices, CCD Laboratories, France) or similar as a routine procedure. This requires 30-50 milligrams or approximately **1/5 of the pipelle**. If the inside of the uterus is not accessible with the pipelle, the biopsy can be taken with the same transfer catheter through syringe aspiration.

The endometrial biopsy must be **transferred immediately** to a **cryotube** that contains 1.5 mL of RNA-later (Sigma-Aldrich, St. Louis, MO), a solution that keeps RNA from degrading during shipment to the laboratory. The recommended **amount of endometrial tissue** is approximately 30–50 mg, which is equal to **1/3 of the volume of the cryotube (not beyond white line** on **cryotube)** and must be **shaken** vigorously for **at least 10seconds** so that the RNA later fully penetrates the sample.

The cryotube containing the sample must be kept **inside a refrigerator** at 4°C for at **least 4 hrs** until shipment, which can be at room temperature (<35°C). The sample can be kept in the fridge for 3 weeks until the time for shipment.

Protocols

Based on personal and/or clinical reasons, the endometrial biopsy can be obtained during either a natural or hormone replacement therapy (HRT) cycle.

If it is collected during a **Natural Cycle**[12]-it is recommended that ovulation be **triggered** by **hCG** once the **follicle** reaches 18 mm (hCG+0), and then the endometrial biopsy should be taken seven days later on hCG+7 (Figure 2a).

It is recommended that a dose of 400 mg/day of progesterone be administered in two doses of 200 mg: one in the morning and one in the afternoon. If the biopsy is taken at hCG+7 in the afternoon, the administration of P should start at hCG+2 at night; if the biopsy is taken at hCG+7 in the morning, the administration of P should start at hCG+2 in the morning.

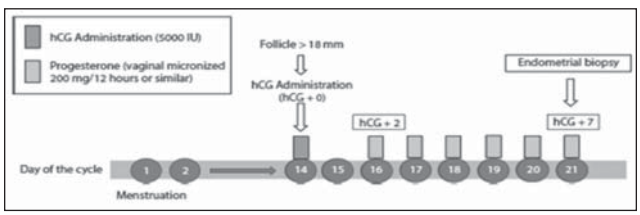


Figure 2(a)[12] The endometrial sample for an ERA test in a **Natural Cycle** must be taken 7 days after hCG injection.

- **HRT (Hormone Replacement Therapy) Cycle**[12]-is the preferred choice due to its simplicity, and consistency involving hormonal treatment with estrogen and progesterone. The classic endometrium build-up preparation protocol begins with estradiol valerate at a dose of 6 mg/day or estradiol hemihydrate patches delivering 150 µg every 48 hours between the first and third day of menstruation if an ultrasound reveals ovaries without functional follicles. Between days 7 and 10 of HRT priming, if ultrasound assessment reveals a **tri-laminar endometrium > 6.5 mm** and **serum progesterone < 1 ng/ml**, then **progesterone administration is started**. Vaginal micronized progesterone (or similar) should be administrated at a dose of 400 mg/12 h for five complete days (120 hours). The day on which the progesterone treatment begins is referred to as P+0 and the biopsy must be taken on day P+5, five days after progesterone administration or after approximately 120 +/- 3 hours (Figure 2b).

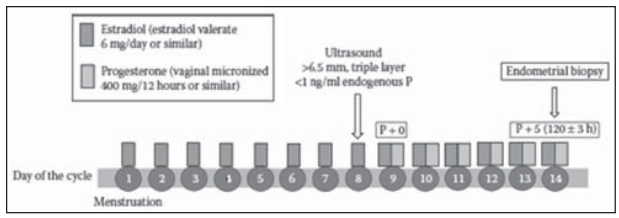


Figure 2 (b)[12] The endometrial sample for an ERA test in an **HRT Cycle** obtained after 5 days (120 h) of progesterone

The **reproducibility** and **consistency** of the **ERA** test have been demonstrated using **second endometrial biopsies** obtained from the **same patient** under the **same conditions** as in the first study cycle. The reproducibility set comprised four endometrial samples obtained during the WOI in a natural cycle (LH+7) and three samples outside the WOI (2 in the proliferative, n = 2/Post-receptive, n = 1). These second biopsies were obtained in a subsequent cycle between 29 and 40 months after the first[13] and showed no variations between cycles. Moreover, several patients have undergone successful embryo transfers consistently in the same pWOI that was detected up to **two years prior** and resulted in a second live birth, supporting the idea that **ERA predicted pWOI** is **maintained** over the course **of several years**.

Interpretation of ERA Results

ERA test has different diagnostic results[12], depending on which, the day of implantation of the embryo will be recommended.

Day 3 embryo should be transferred **2 days earlier** than the day the **ERA test** comes **receptive** for **blastocyst stage** embryo.

- *Receptive:* A receptive endometrial profile is divided into three sub-signatures: optimal receptive, early receptive, and late receptive.

1. An **Optimal Receptive Profile** indicates that the gene expression profile is concordant with a normal receptive endometrium. In this case, it is recommended to proceed with the embryo transfer in the same type of cycle and on the same day in which the endometrial biopsy was performed.
2. An **Early Receptive Profile** indicates that the window of implantation is slightly delayed. The endometrium is entering the receptive phase but needs 12 more hours of P administration in an HRT cycle to acquire an optimally receptive profile.
3. A **Late Receptive Profile** indicates that P administration should be reduced by 12 hours in a further cycle to achieve optimal receptivity since the window of implantation is advanced 12 hours.
4. The **early** and **late** receptive profiles are **considered transitional profiles** and it is recommended that personalized embryo transfer be performed after following the indicated treatment with P (12 more or less hours) **without need** of **further 2nd ERA** verification.

- *Non-receptive:* A non-receptive patient can show a pre-receptive or a post-receptive profile.

1. A **Pre-Receptive Diagnosis** indicates that the transcriptional activation necessary to achieve receptivity has not yet occurred, so the WOI is delayed. The patient needs 1 or 2 more days of P administration from the day of cycle in which the biopsy was taken to reach the receptive state.
2. A **Post-Receptive Diagnosis** indicates that the endometrium has already passed the ideal window for embryo implantation in the day of the cycle when the biospy was performed, so 1 or 2 days less of P administration is required to achieve receptive status because the WOI is advanced.

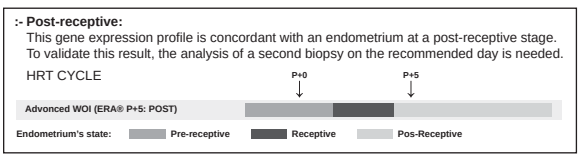


Figure 3. Post-receptive ERA

3. Finally, a **Proliferative Profile** generally indicates that the endometrium has not been exposed to endogenous or exogenous progesterone.
4. Whether to take a new endometrial biopsy following the progesterone timing indicated by the ERA report will vary if it is necessary to validate the displacement and to guide the pET (figure 3). The **blastocyst** stage embryo should be transferred according to the personal WOI identified by ERA, that is, under **exactly the same conditions** of type of cycle and on the same day as when the **receptive ERA** result was obtained, and providing a personal embryo transfer (pET) for every patient.

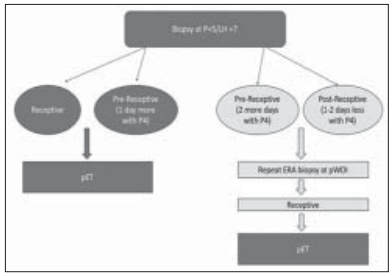


Figure 4. Clinical Algorithm to identify the receptivity of an endometrial sample

ERA, endometrial receptivity analysis; pET, personalized embryo transfer; pWOI, personalized window of implantation, WOI: Window Of Implantation.

Limitations

Despite the clinical applicability and accuracy of the ERA test, it is not exempt from limitations[12]:

- Transcriptomic analysis uses mRNA, a **highly sensitive** genetic material that can be **degraded** if high temperatures during shipment and storage, use of RNAse inhibitors, and sterile conditions are not applied.
- It is an **invasive** test and endometrial biopsies could present **difficulties** during **collection** leading to **too much blood admixed** with the **sample**.
- **No Result** may also be obtained in some cases **not suitable** to **process** because it is not possible to obtain **enough RNA** or it is degraded.
- Since ERA has only been tested during HRT and natural cycles, it is **not possible** to extrapolate to **fresh controlled ovarian stimulation** cycles.
- The protocol also currently only **allows** to perform **pET with frozen embryos from the same patient** or **fresh embryos in ovum donation cycles**.
- ERA assessment only accounts for the assessment of the endometrium at the transcriptional level. However, other possible changes may be present, such as an **altered uterine microbiome**, that **may impair the clinical results of an otherwise receptive endometrium.**
- **Cost** of test and need for vitrification for frozen embryo transfer cycle are additional factors that need to be looked at.

Clinical Efficacy

Díaz-Gimeno *et al* demonstrated ERA to have a sensitivity and specificity of 0.99758 and 0.8857, respectively[14]. Garrido-Gómez *et al*[15], in their study demonstrated the **robust reproducibility** of the transcriptomic profile of the mid-secretory phase endometrium between cycles or over relatively long periods (3 years). They also established that the concordance for ERA endometrial receptivity (ER) dating against the LH peak was 0.922 (0.815–1.000), and the reproducibility was 100%. Comparison between the histologic dating performed

by 2 pathologists against a LH peak reference yielded the kappa index values of 0.618 (0.446–0.791) and 0.685 (0.545–0.824), respectively. Inter-observer variability was 0.622 (0.435–0.839). These observations endorse the **clinical superiority** of **ERA over histological dating**.

The **clinical efficiency** of **pET** has also been assessed according to its **specificity** and **sensitivity.**

Ruiz-Alonso *et al* [16] analysed clinical outcomes of pET in a group of 205 ERA receptive patients and compared to frozen embryo transfer (FET) on a day after the determination of non-receptive status in 52 patients. To calculate specificity and sensitivity, the "positive" condition was considered to be non-receptive and the "negative" to be receptive; pregnancy achievement was the gold standard. After proper analysis, a **specificity** of **0.91** and a sensitivity of 0.33 were obtained. The **positive predictive value** obtained was **0.77** while the **negative predictive value** was **0.60[16].**

Indian Data

Mahajan *et al*[17] performed a retrospective ERA analysis to study the endometrial factor in patients with 1 previous IVF failure and patients with persistent thin endometrium <6 mm. They found that 27.5% women with RIF showed a significantly displaced WOI. The **pregnancy rate (PR)** and **implantation rates (IR)** in the **RIF group improved after Personalized ET** with values similar to those seen in our fresh non-RIF IVF cycles. In the sub-group analysis done on 33 RIF patients wherein 1 FET with the transfer of 2 good quality blastocysts had been done, they found that **one-third** of the patients had a non-receptive(**NR) endometrium**.

In women with **thin endometrium** they found that **after pET** the **PR** and **IRs** were also **similar** to **fresh non-RIF** IVF**.** However**,** the **numbers** in their study are **not high** enough to draw definite conclusions.

ERA in RIF

Ruiz-Alonso *et al* [11] in a prospective multi-centric trial investigated patients with RIF who had more than three IVF or IVF-OD failures. Controls were patients with no previous IVF failure. RIF and control patients underwent ERA-either on day LH + 7 in a natural cycle or on day *P* + 5 in an HRT cycle. The authors eliminated the effect of endometrial injury leading to increased IRs.

The results showed that a **displaced** or **asynchronous WOI** existed in **25.9% of RIF** patients[11]. This suggests that an endometrial factor exists in a quarter of patients with RIF and could contribute to their failed cycles. Correcting the WOI by doing a **pET improved** the **reproductive outcome**. A pregnancy rate (PR) of 50.0% and an IR of 38.5% were achieved which was similar to the control group.

Thus suggesting that **rescue** of **non-receptive RIF** patients by **pET results** in **normalized pregnancy** rates.

This initial study has been further validated by the report of a **clinical case** of successful personalized embryo transfer after **seven previous IVF failed** attempts (four with her own oocytes and three with oocyte donation) [18] This case report was accompanied by a pilot study of 17 oocyte donation (OD)cycles in patients who suffered multiple failed implantations with routine embryo transfer but were subsequently treated with pET after determining their pWOI resulting in normalization of their reproductive outcome[18].

Analysing above data, we must ponder on whether RIF results from inaccurate timing of ET when the individual woman's endometrium is non-receptive ?

ERA in Endometriosis

The effects of endometriosis on ovarian reserve and the quality of retrieved oocytes seem obvious.

However, lower implantation rates raise the question of whether this is due to poor embryo quality or oocyte numbers or whether it compromises endometrial receptivity (ER) as well.

Simon C *et al* [19] in a prospective functional study looked at this question using ERA to assess the endometrial gene expression during the WOI in endometriosis and healthy patients[19]. Non-differentially expressed genes (DEG) were found among the different endometriosis stages (minimum, mild, moderate, and severe) and clustering analysis showed that **gene expression** was **linked** more closely to the **day** when the **biopsy** was **performed rather** than to the **stage** of **endometriosis**. They found only 13 DEG were found in women with and without endometriosis on day 18 compared to days 19–20 of the cycle, indicating that, **according** to **ERA** diagnosis, the **transcriptomic signature** during the **WOI** is **similar** in infertile patients **regardless** of whether **endometriosis** was present.

Thus, concluding that it's the **endometriotic oocytes** that are the **main culprit** causing the **poorer reproductive outcomes rather than the endometrial receptivity.**

However, further studies are needed to evaluate this aspect further.

ERA in Obese

The molecular mechanism connecting obesity to reduced fertility remains poorly understood. However studies have highlighted the idea that **obesity** poses an **increased** risk of a **displaced WOI.**

Bellver *et al*[20] established a significant endometrial gene expression alteration during the optimal WOI in obese subjects (BMI>30).

Conclusion

Much of the implantation process still remains to be deciphered and in the era of personalized medicine,

a “one size fits all” policy is no longer acceptable. **ERA** is the most **objective** and **reproducible** test currently available for **diagnosing ER** and establishing a **personalized WOI** for each patient.

ERA has a **potential role** in various clinical settings including **RIF, obese** women**, patients** with **thin endometrium**, etc to improve ART success where endometrial factor could be the contributory cause.

In **future** we face the **challenges** of assessing the **cost effectiveness** of this diagnostic test as a **routine first-line checkpoint** during **infertility work-ups** and the **transition** to a **non-invasive cost-effective ERA** test that can analyse endometrial fluid in the **same cycle** thus **enabling fresh embryo transfer**.

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CONTROVERSY

IUI or IVF: Current Status

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Infertile couples are usually advised to start their investigations after 12 months of trying to conceive or after 6 months if the female partner is more than 35 years old or immediately if there is an obvious reason to investigate (Table 1)

Table 1

In women	In men
Age <35 yrs. with >12 months infertility.	History of: Genital pathology
≥35 years with > 6 months infertility	Uro-genital surgery
Length of menstrual cycle: < 21 days.	Sexually-transmitted infections
> 35 days	Varicocele
Menstrual abnormalities: Amenorrhea	Cryptorchidism
Oligomenorrhoea	Systemic illness
History of: Ectopic pregnancy	Chemotherapy/Radiotherapy
Pelvic infections (PID)	
Endometriosis	
Pelvic surgery (ruptured appendix)	Two abnormal results of semen analysis:
Developmental anomalies	Sperm count < 15million/ml
Abnormal P/V findings on examination	Total Sperm motility < 40%
Mid-luteal progesterone < 20 nmol/l	Progressive Sperm motility < 32%
FSH > 10 IU/l early follicular phase	Sperm morphology < 4% normal
LH > 10 IU/l early follicular phase	Abnormal findings on genital examination
Patient request or Anxiety. Patient request or Anxiety	

Each couple undergoes a physical examination and a structured battery of investigations. In females this comprises of hormonal profile, tests for ovarian reserve and ovulation, test to rule out tuberculosis, test for tubal patency and assessment of uterine cavity, infectious screen for HIV, Hepatitis B and Hepatitis C. Similarly, in males if semen examination is abnormal on repeat examination, he is further investigated with hormonal profile, scrotal ultrasound and infectious screen for HIV, Hepatitis B, Hepatitis C. FNAC of testes is performed if indicated. A diagnosis based on these investigations as to the cause of infertility is reached thereafter and treatment planned.

Treatment options available will depend also on the duration of their infertility, which partner is affected, the age of the female partner, any previous live birth, the underlying pathology and whether the treatment is covered by insurance and if not the cost involved.

There is a tendency of couples to change doctors once treatment does not appear to be bearing results and any previous assessment and treatment of infertility availed should be thoroughly reviewed.

One of the most important achievement unarguably of the 20th century has been the birth of first baby by IVF in 1978 and the techniques of IVF-ET have progressively evolved over time since then. Contrary to this IUI, since its introduction in 1962 has not made much progress and has remained static.

Counseling, ovarian stimulation, follicular monitoring and semen preparation are steps common to IUI and IVF. First line treatment is an enigma for the treating doctor.[1]

IUI involves insemination of prepared semen in the uterine cavity and fertilization in the female genital tract whereas IVF involves fertilization in culture dish and transfer of embryo in the uterine cavity. IUI is less intrusive, more patient friendly, less stressful and a very safe procedure.

Indications of IUI

1. Ejaculatory failure
   Anatomical (hypospadias)
   Neurological (Spinal cord injury)
   Retrograde ejaculation
   Psychological (Impotence)
2. Cervical Factor
   Poor cervical mucus
   Cervical mucus hostility
3. Male Factor
   OAT (oligoasthenoteratozoospermia)
   Oligospermia
   Asthenozoospermia
   Teratozoospermia
   Azoospermia -AID
4. Unexplained Infertility
5. Endometriosis
6. Immunological
   Male antisperm antibodies
   Female antiserum antibody (cervical, Serum)
7. Serodiscordant couples.

As against IVF (ART) there has been lack of prospective randomized trials and large prospective cohort studies caused by the low budget linked to IUI when compared to the budget associated with other methods of assisted reproduction such as IVF and ICSI. Multiple births consequent to ovarian stimulation has been a single reason pitched against IUI. This prejudice is based on historical practices involving the irresponsible induction of high numbers of follicles during IUI procedures.[2] Its effectiveness in terms of pregnancy rate is ▫10–14%

per cycle reaching cumulative values of 40% after 3 treatment cycles. Monitoring of follicles has reduced the absolute rate of multiple pregnancies to 0.3% after mono follicular growth and 2.8% after multi follicular growth.[3] Furthermore, IUI does not involve the cost required with embryo culture and cryopreservation facilities.

Indications of IVF/ICSI (Dutch Society of Obstetrics and Gynecology)

1. Tubal pathology-
   If tubal surgery is not a realistic option
   Following tubal surgery or non occlusive tubal pathology, no success for 2 years,
2. Unexplained infertility of 3 years duration or earlier if female >36years
3. Male infertility
   TMC<1 million, first treatment of choice is ICSI.
   TMC>1 and<10 million, IVF can be performed if infertility is 2 years or more.
   TMC >10 million, treat as unexplained infertility.
4. Endometriosis
   In case of mild or moderate endometriosis, treat as unexplained infertility.
   In case of severe endometriosis, treat as in tubal pathology.
5. Cervical factor /immunological Infertility
   After infertility duration of 2 years, IVF is indicated. This may be considered sooner if the woman is >36 years.
6. Hormonal disturbances – Anovulatory cycles are indicated for IVF if 12 cycles of treatment with ovulation induction have been unsuccessful.
7. Fertility preservation
8. Gestational Surrogacy
9. Pre implantation genetic diagnosis and screening.

Certain indications mentioned above are not absolute indications and IUI may be performed first as discussed later.

Indications for ICSI

1. TMC< 1 million
2. <4% normal morphology and TMC< 5 million
3. No or poor fertilization in two IVF cycle when TMC>10 million
4. Epididymal or testicular spermatozoa.

Indications for Oocyte Donation

Premature ovarian failure

Gonadal dysgenesis

Bilateral oophorectomy

Ovarian failure following chemotherapy or radiotherapy

Certain cases of IVF treatment failure.

There are clinical, economic, financial, and ethical realities which have been the basis for selecting one procedure over other. In countries where funding bodies dictate the treatment guidelines there have been disparities in treatment policies (NICE 2013). Excess embryos created through IVF procedures are frozen, possibly never used, and these monetary and emotional costs are not factored in when presenting the merits of IVF procedures.

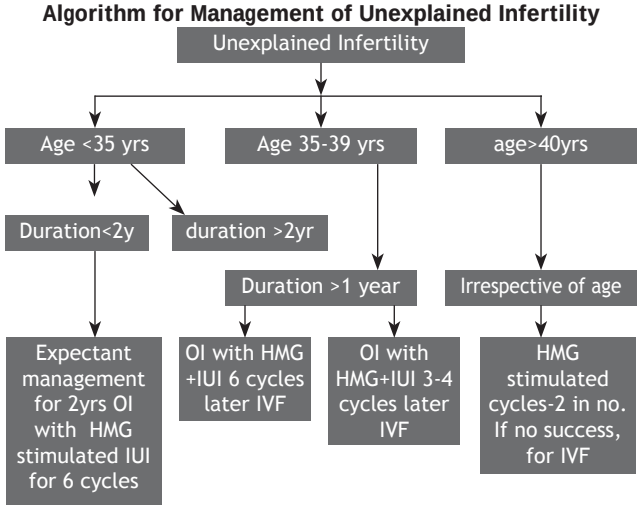
Recent reports also highlight possible concerns from cancers to mothers who have undergone IVF and the need to be vigilant of risks.[4] The potential increased risk of central nervous system (CNS) tumors in patients undergoing ART has been interpreted with caution[5], while long- term risk of ovarian and uterine cancers need careful follow-up.[6] The long-term health of children conceived after IVF also require careful studies.[7] Although most of the studies regarding safety of ART for mother and children conceived are reassuring yet the long-term effects associated with ART are yet to be determined.[8] Large international multi center cohort studies are required to find whether there is risk associated with ART procedures. **There has been renewed interest in IUI due to the above reasons and the latest studies reinforce the place of IUI in certain indications which were dismissed by NICE 2013. (NICE 2013 recommended IVF directly after 2 years of expectant management for unexplained infertility)**

Unexplained Infertility

An estimated 28% of all couples seeking reproductive assistance may have normal findings on their clinical evaluation, making the unexplained infertility a more common provisional diagnosis.

IVF is a widely accepted successful but invasive modality for treatment of unexplained infertility.It increases the number of oocytes available for fertilization and also helps in evaluating the embryo quality. IVF procedures may be associated with side effects like OHSS (Ovarian Hyper Stimulation Syndrome), ectopic pregnancy, and increased perinatal morbidity and mortality. However, few studies have shown the usefulness of IUI versus IVF cycles when matched equitably.

Algorithm for Management of Unexplained Infertility



In a study on women with unexplained infertility FSH stimulated IUI cycles had a pregnancy rate of 28% per couples whereas clomiphene citrate (CC) had 19% pregnancy rate. (OR 1.8, 95% CI 1.2 to 2.7).[9] The risk of multiple pregnancies was thwarted by strict cancellation criteria i.e. a cycle was cancelled when three or more dominant follicles developed. In a RCT performed in the Netherlands in vitro fertilization with single embryo transfer and in vitro fertilization in a modified natural cycle were non-inferior to intrauterine insemination with controlled ovarian hyper stimulation in terms of the birth of a healthy child (52%,43%and 47% respectively) and showed comparable, low multiple pregnancy rate.[10,11,12,13] Without any significant difference in efficacy, the IVF procedure was significantly more expensive when compared with stimulated IUI.

Endometriosis

There is no role of medical therapy for infertility associated with endometriosis.

On first laparoscopy itself aim should be to clear all the endometriosis lesions especially the peritoneal and cystectomy should be done in endometrioma >3 cm. This increases the chances of spontaneous pregnancy. It is very important that ovarian reserve be assessed before and after surgery and patient informed accordingly.

In infertile women younger than 35 years with AFS/ ASRM Stage I/II endometriosis, expectant management or superovulation with or without IUI may be offered after laparoscopy. [14]

In women > 35 years superovulation with IUI may be done and if does not conceive within 4 -6 cycles than IVF should be offered, since pregnancy rates are similar to those achieved in unexplained infertility.[14,15]

In infertile women with AFS/ASRM Stage III/IV endometriosis IUI has no role.

Repeat surgery should be avoided as it depletes the ovarian reserve unless large endometrioma are likely to come in the way of follicular aspiration.

SART (Society for Assisted Reproductive Technology) in a meta-analysis, found that infertile women with endometriosis had substantially lower success with IVF compared with tubal factor infertility, including lower ovarian response, reduced implantation rate and pregnancy rate. In addition, a more advanced disease was related to increasingly inferior outcome .[18] In two more recent meta-analyses on outcome of IVF in endometriosis, live birth rate was found to be similar in minimal/mild endometriosis and other indications for IVF, where as in patients with moderate/ severe endometriosis, the results were inferior, including fewer oocytes retrieved, lower implantation rate, and lower birth rate. ASRM during the period 2010–2013, observed that women with endometriosis undergoing ART had a marginally higher cancellation rate and more embryos transferred compared with the tubal factor group, but achieved a comparable live birth rate per cycle.

In a Cochrane review, the authors concluded that down-regulation for 3–6 months with a GnRH agonist in women with endometriosis increases the odds of clinical pregnancy by > 4-fold in ART cycles.[19]

Infertility associated with adenomyosis - There is very limited data confined to case reports on this condition. Medical management includes GnRH for 3-6 months followed by trial for spontaneous conception. For a well-defined adenomyoma surgical removal may be undertaken after 3 months of GnRH analogues.

Male Factor Infertility

Poor semen Quality is the single cause of infertility in 20% of infertile couples and is an important contributing factor in another 20-40 %. Semen analysis is universally used to assess quality. In 2010, WHO (World Health Organization) defined new reference value for sperm parameters to differentiate between normal and abnormal. However, it does not have good prognostic value. TMSC (Total motile sperm count) has been found to be of value to prognosticate couple undergoing IUI and also in conventional IVF in predicting fertilization failure. It also has a good correlation with spontaneous ongoing pregnancy rate.

TMSC = Semen volume × concentration in millions/ml × percent progressive motile sperms ÷100. TMSC can be calculated in either pre wash or post wash sample.

A pertinent explanation for this discrepancy is that TMSC considers absolute sperm parameter value simultaneously, while the WHO criteria treats sperm parameters discreetly. A validated classification is missing; the following groups are accepted according to the degree of male infertility:

Group 1 TMSC <1 × 10^6 spermatozoa,

Group 2 TMSC 1–5 × 10^6

Group 3 TMSC 5–10 × 10^6

Group 4 TMSC 10–20 × 10^6.

A TMSC of >20 × 10^6 is considered normal.

A guideline as to the management in case male infertility is the only cause is-

Group 4 - 6 months of expectant treatment, if no pregnancy, 6 cycles of IUI with ovarian stimulation.

Group 3 - 6 cycles of IUI with ovarian stimulation followed by IVF.

Group 2- direct IVF.

Group 1- direct ICSI.

For mild to moderate male factor infertility, stimulated IUI is cost-effective.

The average IUI success rates of around 13% per cycle typically translate to around 20–25% of the cohort for most clinics. Best results with IUI are achieved when the total motile sperm count in the insemination specimen exceeds 10 million and 14% or more of sperm have normal morphology.[23] It is also surprising that

spontaneous pregnancies occur even in the presence of extremely poor sperm quality.

Overall chance of a live birth following IVF treatment decreases with rising female age, increasing number of unsuccessful cycles, increased BMI of the woman and increases if there has been a previous pregnancy.

Results of ART are also decreased if female consumes=>1 unit of alcohol per day, smokes and with caffeine consumption.

Conclusion

With the given evidence couples especially < 35 years should be counseled that in mild endometriosis, mild to moderate male factor infertility and in unexplained infertility, ovarian stimulation along with IUI stands equal chance as IVF and hence a uniform policy of 6 IUI cycles followed by 3 cycles of IVF needs to be adopted. In case of blocked tubes, severe endometriosis, severe male factor infertility, poor ovarian reserve, where oocyte donation or surrogacy is indicated IVF/ ICSI is the only option. These are broad guidelines and treatment for each patient needs to be individualized. This is especially important for a country like ours where there is resource crunch and also strong economic reasons to delay IVF.

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CASE APPROACH

Current Trends in Workup and Management of Male Infertility


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There is a rise in incidence of male infertility, both real and apparent in the last two decades. Poor semen quality is the single cause of infertility in approximately 20% of infertile couples, and is an important contributing factor in another 20%-40% of them. The causes of apparent increase in incidence are due to greater diagnostic facilities and advanced treatment options. The real increase may be due to changing lifestyles, stress pollution etc. The evaluation includes history,examination and investigations.

History includes anosmia [Kallman's syndrome], respiratory infections [Young's syndrome], endocrine disorders [diabetes], environmental toxins etc. Drugs having gametotoxic effects are antihypertensive, antipsychotic drugs, few antibiotics, steroids and statins.

Physical examination is indicated when semen analysis reveals abnormalities –especially azoospermia. Presence/ absence of testes, it's size, consistency, presence of varicocele and hypospadias is looked for on examination. Semen analysis is the primary investigation in workup of male infertility.

Seminal parameters and role of sperm function test:
The reference values for normal semen analysis as given by World Health Organization in 2010 are volume >1.5 mL, sperm concentration > 15 mill/mL, total sperm count > 39 million, total motility > 40%, progressive motility > 32%, vitality > 58%, pH 7.2, morphology > 4% (kruger strict criteria), leukocytes < 1 million/mL. Men with normal semen parameters may not require any specialized tests. But in the cases of fertilization failures, sample with low sperm count and poor sperm motility may require additional assessment of sperm function like sperm penetration assay (hemizona assay, competitive zone sperm binding), tests for acrosome reaction (acrosomal assay, gelatine assay), tests for sperm vitality (dye occlusion method, hypo-osmotic swelling test), sperm DNA fragmentation test (SCSA, SCD, TUNEL, Comet), antisperm antibody (mixed antiglobulin reaction, immunobead test), nuclear protein assay, mitochondrial activity index, semen biochemical tests. Out of the whole battery of sperm function tests there is a need for targeted testing as they are complex, expensive, do not always provide clinically useful information and typically do not affect treatment. Most of these test are not available and do not have much impact on planning of treatment however test like HOST and DNA fragmentation may be helpful in certain categories of patients and should be advised accordingly.

Relevant hormonal analysis FSH, LH, Prolactin, TSH and chromosomal analysis is done when indicated.

The sequential analysis of sperm functions could assist clinicians in planning the therapeutic approach and predicting the outcomes of treatments such as intra uterine insemination (IUI), in vitro fertilization (IVF), intra cytoplasmic insemination (ICSI).

Indications for IUI are unexplained infertility with duration < 3 years and total motile sperm count (TMC)> 10 million, ejaculatory dysfunctions, erectile dysfunctions, psychosexual disorders.

Indications for IVF are unexplained infertility with duration > 3 years, TMC between 1 and 10 million, previous 5-6 unsuccessful IUI.

Indications for ICSI are TMC < 1 million, TMC < 5 million and normal morphology < 4%, no or poor fertilization in first IVF when TMC < 10 million, no or poor fertilization in two IVF cycles when TMC > 10 million, epididymal or testicular spermatozoa.

Management of Azoospermic Male

Karyotyping and Yq deletion screening to analyse any therapeutic consequence and counselling. In non-obstructive azoospermia (NOA), Testicular sperm extraction (**TESE**) and in obstructive azooospermia (OA) microsurgical or percutaneous epididymal sperm aspiration [MESA/PESA] or TESE is recommended for retrieval of sperms followed by ICSI. The results of ICSI are better in OA as compared with NOA with higher birth rates 28% vs 19%, higher fertilization and implantation rates and lower miscarriage rates. In OA no significant difference is seen when ICSI is performed with testicular vs epididymal sperm. There is no difference in result of fresh vs thawed sperms.

Treatment protocol depends on:

a. FSH and testes size

b. Fructose in seminal plasma

Elevated FSH, small testis– azoospermia is NOA due to genetic or immunological causes .Recovery rate depends on FSH levels, testicular consistency and size. With FSH level < 15 IU, recovery rates are quite satisfactory (upto 70 %), as FSH level increases further, chances of recovery decreases. However upto 30 IU, procedure of TESA /TESE may be performed with guarded prognosis but with FSH >30 IU LOT OF COUNSELLING IS REQUIRED BEFORE attempting any procedure as recovery rates are very poor and TESA/PESA /ICSI may not be possible. Insemination with donor sperms may be suggested. Rarely immature sperms may be obtained and ICSI may be attempted in such cases.

Low FSH, small but firm testes or normal testes- hypogonadotropic hypogonadism. This is one of the few conditions which responds to medical management. gonadotropin replacement is possible but expensive and prolonged and counseling is required to continue for atleast 6 months and upto one year to be effective. Recovery of immature to mature sperms is possible for ICSI.

Normal FSH and testesl- suggestive of obstructive azoospermia – VEA [vasoepididymal anastomosis] or PESA/TESA results in almost 100% recovery and this is followed by ICSI. Take home baby rate are as good as ejaculated sperm and even better as there is no female factor involved and since these couples are young and otherwise healthy prognosis is good.

Treatment based on fructose

Azoospermic male with absent fructose –obstruction at seminal vesicle, vas deferens or ejaculatory duct. When vas is absent –PESA –ICSI after counseling [risk of cystic fibrosis] else donor IUI. If vas is palpable and seminal vesicle is dilated –cyst in prostratic utricle may be the reason for which cystectomy or ICSI are treatment options. When seminal vesicle is not dilated [absent seminal vesicle]-PESA /ICSI are the options.

Fructose positive with small testes , FSH low or high- testicular failure primary or secondary-TESA /ICSI or Donor –IUI

Role of Medical Management

Medical treatment is indicated in a limited and select group of male infertility. This limited group includes oligospermia due to endocrinopathy, semen or seminal tract infection and some cases of erectile and ejaculatory dysfunction. In the presence of excess or deficiency of hormones related to sperm maturation or development, endocrine substitution or regulation will help improve semen parameters.

Role of gonadotropins- FSH and LH exert a synergist role for spermatogenesis with LH acting on Leydig cells to produce androgens and FSH acting on Sertoli cells to produce androgen binding globulin (ABG) which carries androgen to the lumen of seminiferous tubules for development and maturation of spermatozoa. In hypogonadotropic hypogonadism there is hypoandrogenism (serum and intratesticular) affecting sperm production and maturation. Medical treatment consists of substitution of gonadotropins with HMG and HCG. HCG is a surrogate for LH and so it increases intratesticular testosterone. HCG injection [1500-2000 IU] sc/im is given three times a week for 3-6 months. If sperm count does not improve then HCG is followed with HMG [75-150 IU] sc/im three times a week for 3-6 months. Alternatively HCG 5000 IU can be started once a week along with HMG 75 IU thrice a week Clomiphene has also been used for milder grades of hypogonadotropic hypoandrogenic oligospermia. Clomiphene binds to hypothalmic and pituitary estrogen receptors blocking estrogenic central feedback inhibition of gonadotropin secretion. Ensuing release of gonadotropins from the pituitary increases intratesticular testosterone. In males taking exogenous testosterone or anabolic steroids there is low FSH and LH and excess of androgens. In these cases hyperandrogenism causes suppression of pituitary resulting in hypogonadotropism and consequent reduced intratesticular testosterone production suppressing spermatogenesis. Treatment includes cessation of anabolic steroids and androgens. If there is no improvement then HCG with or without HMG to increase intratesticular testosterone may be beneficial.

Role of thyroid hormone- Hypothyroidism causes decreased libido, erectile dysfunction, alter spermatogenesis by lowering bioavailable testosterone and increase in LH and sex hormone binding globulin. After achieving euthyroid state these deficits including semen are corrected.

Estrogen excess- causes hypogonadotropic oligospermia by inhibiting pituitary gonadotropins by negative feedback inhibition decreasing intratestosterone levels resulting in deficient spermatogenesis. Aromatase inhibitor (testolactone, anastrozole) increases androgens and reduces estrogen thus helping in spermatogenesis.

Prolactin excess- inhibits GnRH, decreases FSH, LH, intratesticular testosterone and so impairs spermatogenesis. Treatment consists of dopamine agonists –cabergoline and screening for microadenoma if prolactin is more than 50ng/ml.

I**nfection** –evidenced by WBC in semen or bacteria on semen culture is treated by antimicrobial therapy, anti-inflammatory medication, antioxidants to reduce oxidative stress.

Sexual dysfunctions is treated by medications

Surgical management: have limited role

Limited to –varicocelectomy

VEA-vasoepididymal anastomosis

VVA-vasovasal anastomosis

Resection of mullerian cyst

Ejaculatory duct dilatation

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Journal Scan

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The Origins and Emergence of Zika Virus, the Newest TORCH Infection: What's old is new again

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In early 2015, a widespread illness characterized by skin rash and fever was reported to be occurring in several states of northeastern Brazil. The disease was initially thought to be the result of dengue virus infection because its symptoms resembled those of dengue fever, but testing excluded that virus as well as others. On April 29, 2015, the Bahia State Laboratory reported that patient samples tested positive for Zika virus, which was soon confirmed by polymerase chain reaction in Brazil's National Reference laboratory on May 7, 2015. On July 17, 2015, Brazil reported the occurrence of neurologic disorders associated with a history of infection, primarily from the northeastern state of Bahia. Among these reports, there were 49 cases of confirmed Guillain-Barré syndrome. In October and November of 2015, Brazil reported the occurrence of a large increase in the incidence of fetuses and infants with congenital microcephaly and other malformations, which led the Pan American Health Organization (PAHO) and the World Health Organization (WHO) to issue an epidemiologic alert to report cases of neurologic disorders including microcephaly. After many months of intensive collaborative research, during which pathology studies had a prominent role, on April 13, 2016, the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, issued a statement that Zika virus was a cause of microcephaly and other severe fetal brain defects. The most recent reports have confirmed that Zika virus is highly neurotropic, infects the placenta, is hematogenously transmitted to the developing fetus via a transplacental mechanism, and is potentially teratogenic, producing fetal malformations collectively termed the *congenital Zika syndrome* (CZS)

THE ORIGINS OF ZIKA VIRUS—A BRIEF HISTORY

Where did the Zika virus come from? In the early decades of the 20th century, it was yellow fever, another mosquito-borne flavivirus disease, that was one of the most-feared epidemic infections in many regions of the New and Old Worlds. After World War II, the Rockefeller Foundation investigators, looking for a new location to study yellow fever transmission, came across the Zika Forest, an isolated area of dense vegetation and swampland in Eastern Uganda (*ziika* means *overgrown* in the Luganda language; the second *i* was dropped by Europeans). They used captive monkeys, which were placed into 6 cages and suspended among the jackfruit and mango trees of the forest where mosquitoes bred. On April 18, 1947, one of the rhesus macaques, named *Rhesus 766*, developed a fever of 39.7°C, about 2°C higher than reference range. The monkey was sent to the laboratory at Entebbe, Uganda, where a blood sample was taken and injected via the intracerebral and intraperitoneal routes into Swiss albino mice and, subcutaneously, into an uninfected ("clean") rhesus macaque named *Rhesus 771*. The mice inoculated intraperitoneally and Rhesus 771 failed to develop symptoms; however, mice injected via the intracerebral route developed illness beginning 10 days after inoculation. A small virus (then termed a *filterable agent*) was recovered from brain tissue of the inoculated mice. Although Rhesus 766 never developed any symptoms, except fever, the same filterable agent was isolated from its serum.. The Rockefeller team named their "hitherto unrecorded virus" the *Zika virus*. In view of the recent autopsy pathology findings from microcephalic fetuses and infants infected with Zika virus an interesting and unusually prophetic conclusion from Dr Dick of Rockfeller team is his statement that "Zika virus is highly neurotropic in mice and no virus has been recovered from tissues other than the brains of infected mice.

Torch Infections

Exactly what is a TORCH infection? Although there is no universal definition of what constitutes a TORCH infection, it is clear that the various descriptions used for this term have many factors in common. The agents of TORCH infections all can infect women during pregnancy; typically, but not always, they are present in the maternal bloodstream as a viremia, bacteremia, or parasitemia, and often do not produce significant disease or even symptoms in the mother. They are also characterized by vertical transmission to the fetus, most often hematogenously, through the placenta before delivery or, less often, via the birth canal around the time of labor and delivery. Following fetal infection, TORCH agents can cause a variety of potentially severe complications, which can include microcephaly, multiorgan disease, congenital malformations, and intrauterine growth restriction. The TORCH agents can also cause miscarriages, stillbirths, and neonatal deaths. Several TORCH infections have a predilection for the central nervous system, causing severe pathologic changes in the brain that can result in neurologic, sensorial, and developmental abnormalities

Placental Pathology of Torch Infections

When transmitted from the maternal bloodstream to the fetus through the placenta, most TORCH agents result in recognizable placental abnormalities. These include the presence of acute, granulomatous or chronic villitis, intervillositis, intervillous microabscesses, viral

inclusions, villous endothelial cell abnormalities, villous necrosis, avascular villi, or necrotizing inflammation involving the villi, placental membranes, or umbilical vessels. Examination of placentas from second- and third-trimester infants having congenital Zika virus infection have shown a different pathologic spectrum. Villitis, which is the histologic hallmark of a maternal hematogenously transmitted infection, has not been a microscopic feature in placentas of fetuses with congenital Zika virus infection. Inflammatory lesions of the umbilical cord (funisitis) and placental membranes (chorioamnionitis), characteristically the result of an ascending infection arising from the maternal cervicovaginal canal, are (as expected) similarly not a feature of congenital Zika virus infection. Thus, there is no evidence of a maternal inflammatory response or a fetal inflammatory response in second- and third-trimester placentas from fetuses with microcephaly that have been examined thus far. There is also an absence of necrosis directly attributable to Zika virus infection in any placental structure

Similar to placentas from infants with some congenital TORCH infections, placentas from second- and third-trimester infants with Zika virus infection demonstrate increased numbers of Hofbauer cells within the stroma of chorionic villi.. Some Hofbauer cells have been demonstrated to still be in the proliferation phase of the cell cycle indicating the terminal phase of a hyperplastic response to transplacental Zika virus infection by these fetal-derived macrophages. The Zika virus has been shown to be present in the chorionic villi in placentas from infected fetuses, where the virus has been localized within Hofbauer cells using both nucleic acid and antigenic techniques. These findings from naturally infected human placentas are consistent with a recent report in which Hofbauer cells have been shown experimentally to be permissive to Zika virus replication in isolated cultures in vivo and infected with Zika virus ex vivo in chorionic villous explants.

Zika Virus is the Newest Torch Infection

Is the Zika virus a TORCH agent? The clinical and pathologic spectra of the effects of Zika virus infection on the developing fetus continue to expand. Zika virus infection occurring in pregnant women and their fetuses satisfies all of the characteristics of a TORCH agent—it is transmitted vertically during pregnancy from mothers who have mild or absent symptoms, it infects the placenta,and after intrauterine fetal infection can produce poor obstetric outcomes, including microcephaly and other fetal malformations.

When compared with previously recognized TORCH agents, Zika virus appears most similar to the rubella virus, which was the prototypical TORCH virus. When occurring in nongravid persons, both rubella and Zika viruses may by asymptomatic or can produce a mild illness characterized by a rash. The most serious consequences of both viruses occur when pregnant women become infected. Both rubella and Zika viruses are teratogenic and produce a syndrome of fetal malformations—the CRS and the CZS, respectively. Microcephaly and destructive brain lesions are components of the malformation syndromes produced by both viruses. There are also similarities in the timing of maternal infection and risk for development of fetal malformations in these viruses. In the case of rubella, the most important factor affecting the transplacental transmission rate and severity of fetal infection is the gestational age at which a primary maternal infection first occurs. Although fetal infection with rubella can occur at any time during pregnancy, the probability of fetal infection and development of the CRS increases with maternal infection occurring at an earlier gestational age. The CRS occurs in up to 90% of fetuses when maternal infection occurs before 11 weeks of pregnancy, decreasing to 33% between 11 and 12 weeks, 11% at 13 to 14 weeks, 24% at 15 to 16 weeks, and 0% after 16 weeks of gestation. This relationship between maternal infection occurring earlier in gestation being associated with a greater risk of fetal infection and malformation is recently being recognized for Zika virus, further strengthening their similarities. In one Brazilian study, the production of fetal microcephaly by the Zika virus was found to correlate best with maternal viral infection occurring at approximately 17 weeks gestation—early in gestation, but somewhat later than malformations caused by rubella. In a study from Bahia, Brazil, Johansson et al found that the risk for the development of microcephaly was greatest when Zika infection occurred in the first trimester of pregnancy. They estimated that the probability of having a fetus with microcephaly varied from approximately 1% to 13% when a woman developed Zika virus infection during the first trimester. There was negligible risk for development of the CZS when maternal infection developed in the second and third trimesters.

Rubella, and especially the congenital malformation syndrome associated with it, was a major public health problem throughout the world before the licensing in 1970–1971 of live attenuated vaccines in the United State and Europe. Systematic vaccination against rubella, most often in combination with measles, has virtually eliminated both the acquired and congenital forms of the disease from some resource-rich nations, including the United States. In April 2015, the WHO Region of the Americas was declared the first in the world to be free of endemic rubella transmission. Similar to rubella, the occurrence of the congenital varicella syndrome is also now a rare event in resource-rich countries because of the widespread use of the varicella vaccine.

Rubella can be viewed as a model for a TORCH virus that has been controlled through the widespread distribution of an efficacious vaccine. It is hoped that, with the development of an effective vaccine for Zika virus, the same success will be reached for mothers and their infants in preventing this newest of the TORCH infections from causing fetal infection, congenital malformations, and further suffering.

Editor's Comment: It is interestimg to note that zika virus which is a flavivirus was first discovered in 1947 during research on yellow fever virus which is another flavivirus, though its potential to cause congenital infection was discovered much later in 2015 in Brazil. Yet another interesting aspect is that Congental Zika Virus Syndrome has a resemblance to TORCH infections and it most closely resembles the Congenital Rubella Syndrome in its transmission rate and manifestations. Much like the rubella vaccine we are awaiting an effective Zika Vaccine to get rid of this scourge.

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Double Stimulation in the Same Ovarian Cycle (DuoStim) to Maximize the Number of Oocytes Retrieved From Poor Prognosis Patients: A multicenter experience and SWOT analysis

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A panel of experts known as the POSEIDON group has recently redefined the spectrum of poor responder patients and introduced the concept of suboptimal response. Since an ideal management for these patients is still missing, they highlighted the importance of tailoring the ovarian stimulation based on the chance of each woman to obtain an euploid blastocyst. Interestingly, a novel pattern of follicle recruitment has been defined: multiple waves may arise during a single ovarian cycle. This evidence opened important clinical implications for the treatment of poor responders. For instance, double stimulation in the follicular (FPS) and luteal phase (LPS) of the same ovarian cycle (DuoStim) is an intriguing option to perform two oocyte retrievals in the shortest possible time. Here, we reported our 2-year experience of DuoStim application in four private IVF centers. To date, 310 poor prognosis patients completed a DuoStim protocol and underwent IVF with blastocyst-stage preimplantation-genetic-testing. LPS resulted into a higher mean number of oocytes collected than FPS; however, their competence (i.e., fertilization, blastocyst, euploidy rates, and clinical outcomes after euploid single-embryo-transfer) was comparable. Importantly, the rate of patients obtaining at least one euploid blastocyst increased from 42.3% (n = 131/310) after FPS to 65.5% (n = 203/310) with the contribution of LPS. A summary of the putative advantages and disadvantages of DuoStim was reported here through a Strengths–Weaknesses–Opportunities–Threats analysis. The strengths of this approach make it very promising. However, more studies are needed in the future to limit its weaknesses, shed light on its putative threats, and realize its opportunities.

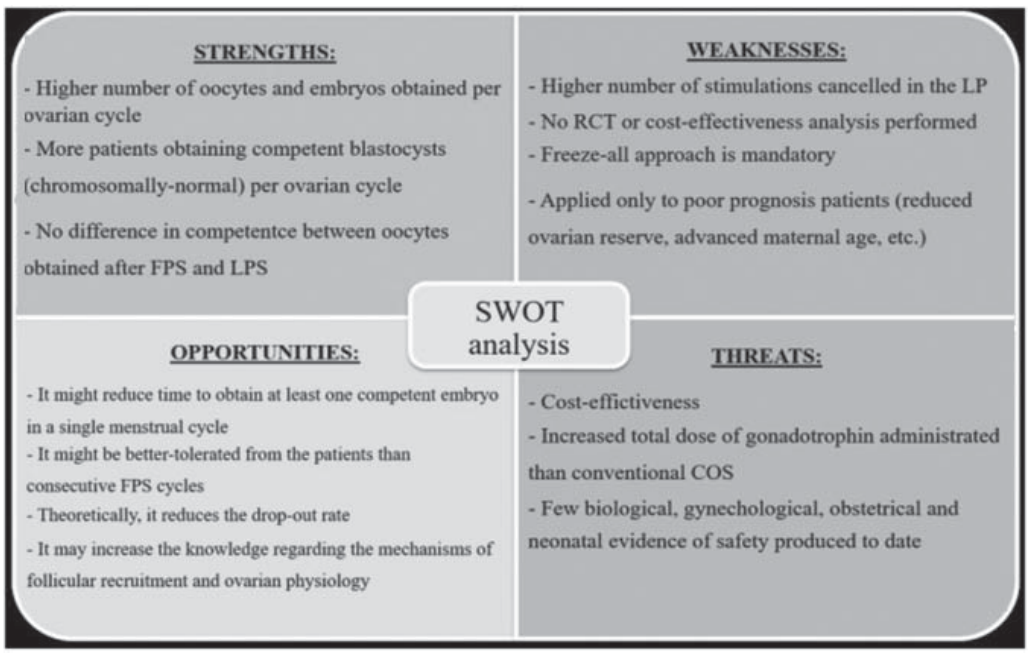

Figure 2
DuoStim SWOT analysis. Abbreviations: FPS, follicular phase stimulation; LPS, luteal phase stimulation; RCT, randomized controlled trial; COS, controlled ovarian stimulation.

Conclusion

The evidence that multiple waves of follicle recruitment may arise during a single ovarian cycle in women opened important clinical implications for the treatment of poor prognosis patients. LPS in general has become a promising protocol for patients who need to collect the highest number of oocytes in the shortest possible time (e.g., oncological patients). DuoStim approach conjugates FPS to LPS with very successful results reported to date. Still, any stimulation protocol, which exploits anovulatory waves of follicle recruitment should undergo a thorough biological and clinical investigation before it can be generally implemented. To this regard, DuoStim still needs a more extensive and wider validation to testify its safety. Interesting future perspectives to investigate its clinical efficacy/efficiency would entail (i) a RCT comparing double-FPS versus DuoStim; (ii) the application of DuoStim in cancer patients for fertility preservation; (iii) as well as in prospective analyses focused on patients clustered according to either the Bologna criteria or the Poseidon stratification. Until such evidence would be produced, DuoStim should be clinically applied only to a

population of patients of poor prognosis and/or to whom time represents a critical issue.

Editor's comment: Duostim protocol is based on the principle of double stimulation in the same cycle.ie. stimulation in both follicular and luteal phase of the same cycle to retrieve maximum number of oocytes. This has especially been used in oncofertility where time is a constraint.

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Insights from Clinical Experience in Treating IVF Poor Responders

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Introduction

In the field of IVF, the term 'poor responder' refers to a subpopulation of patients, typically with diminished ovarian reserve, that experience heightened problems in conceiving with IVF. The identification of poor responders is important to help determine the patient's appropriateness for IVF, guide selection of protocols to maximize ovarian response, and identify patients who may particularly need counselling to set expectations and minimize distress during IVF; however, there is no standard definition of a 'poor responder'. The Bologna criteria suggest that classification as a poor responder requires two of the following features: (i) advanced maternal age (≥40 years) or other risk factors for poor ovarian response, (ii) a previous poor ovarian response (≤3 oocytes with a conventional stimulation protocol), and (iii) an abnormal ovarian response test (antral follicle count <5–7 or anti-Müllerian hormone <0.5–1.1 ng/ml [< 3.6–7.9 nmol/l]) . However, published studies suggest a variety of alternative or additional criteria to define poor responders. It is therefore important to consider each patient's IVF history and clinical characteristics.

Despite the heterogeneity of this patient group, there are some characteristics and needs that are common to many poor responders, such as synchronization of early follicular development, IVF protocols tailored to poor responders, guidelines for the use of alternative medicine and nutritional supplements, and suggestions for the successful management of patient distress and anxiety. Addressing these needs through a holistic approach may help to improve the overall management of poor responders.

Synchronizing Early Follicle Development

Ovarian follicles mature over a period of approximately 2–4 months. Ovarian stimulation in IVF cycles has traditionally focused on the stimulation of antral follicles, which develop during the last 2 weeks of this maturation process, to increase the number of mature follicles for oocyte retrieval. However, successful ovarian stimulation with gonadotrophins is limited by the requirement of the presence of multiple antral follicles The stimulation and synchronization of earlier follicles prior to traditional ovarian stimulation may thus further improve IVF outcomes, particularly for poor responders.

In some patients, diminished ovarian reserve may essentially be an androgen deficiency state and, in these women, androgen supplementation via testosterone or dehydroepiandrosterone (DHEA) may help stimulate early follicle development and improve functional ovarian reserve.

DHEA administration is increasingly becoming the preferred method of androgen supplementation over testosterone because it is taken up and metabolized by organs as needed, whereas testosterone floods the body with a steady amount across organs. The follicles require about 6–8 weeks after the initiation of androgen supplementation to achieve synchronization and become mature enough to respond to ovarian stimulation with gonadotrophins. Based on this, many patients could potentially benefit from androgen supplementation beginning weeks or months prior to starting their IVF cycle.

Human growth hormone (HGH), either directly or indirectly via insulin-like growth factor 1 (IGF-1), also regulates oocyte maturation by increasing the sensitivity of the ovaries to gonadotrophins and promoting early follicle development. A Cochrane Review demonstrated improved clinical pregnancy (odds ratio [OR] = 3.28 [95% confidence interval (CI), 1.74–6.20]) and live birth rates (OR = 5.39 [95% CI, 1.89–15.35]) in poor IVF responders who received HGH supplementation. Minimal side effects, such as peripheral oedema and joint pain, have been reported in women taking HGH supplements

IVF Protocols for Poor Responders

Follicle development is a complex process that involves the regulated expression and interaction of multiple reproductive hormones at different stages of the development. As noted previously, poor responders may benefit from the synchronization of basal antral follicles with DHEA supplementation for a few weeks or months prior to initiating their IVF cycle. We recommend that subsequent ovarian stimulation protocols for poor responders should try to mimic and enhance the natural developmental process of single follicle growth, but in a multi-follicle approach. In general, we believe it is important to refrain from overriding the patient's natural cycle with the use of high-dose exogenous gonadotrophins, which can be associated with side effects and safety concerns, often without an improvement in response. However, stimulation dosages may be individualized, with special attention paid to the fact that higher gonadotrophin dosages can increase transferable embryo numbers and, therefore, cumulative pregnancy chances. Any form of suppressive therapy on the ovaries, including luteal phase (long) gonadotrophin-releasing hormone (GnRH) agonists, GnRH antagonists and oral contraceptives, should, if possible, be avoided in poor responders.

Each patient's clinical characteristics (e.g. basal antral follicle number, luteal synchronization), treatment history and past stimulation outcomes should be carefully considered when selecting stimulation protocols for poor responders For example, premature luteinization occurs frequently in older patients (e.g. aged ≥43 years) and some other poor responders. In these patients, earlier ovulation trigger (i.e. when the leading follicle is 16 mm) may improve the number and quality of embryos, as well as clinical pregnancy rates ,Often the optimal treatment approach is not clear until the patient visits on Day 2 to 3 of her cycle and all relevant baseline bloodwork/testing has been performed. Examples of protocols recommended for poor responders include a low-dose gonadotrophin protocol, low-dose clomiphene/gonadotrophin protocol and augmented natural cycle protocol.

Although controversial, some authorities advocate low-dose (or 'mild') stimulation in poor responders. The low-dose gonadotrophin protocol involves initiating highly purified human menopausal gonadotrophin (HP-HMG) 150 IU/day and recombinant follicle-stimulating hormone (rFSH) 150 IU/day on Day 2 for 9 days; inclusion of HP-HMG is important to provide some LH activity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, followed by ovulation trigger with leuprolide or human chorionic gonadotrophin (HCG) 10,000 IU when the lead follicle is 16–17 mm.

The low-dose clomiphene/gonadotrophin protocol involves administration of clomiphene citrate 100 mg/day for 5 days beginning on Day 2 to obtain pituitary output. A low dose of HP-HMG (150 IU/day) is given on Days 2, 4 and 6, followed by daily dosing until the follicle reaches maturity. A GnRH antagonist is administered when the lead follicle is ≥12 mm in diameter, which is intentionally a little early to help avoid breakthrough ovulation; if the patient's LH level begins to rise, the GnRH antagonist can be given twice a day. Ovulation is triggered with HCG 10,000 IU or leuprolide when the lead follicle is approximately 18–19 mm. Low-dose clomiphene/gonadotrophin protocols may be a good treatment strategy for patients who have previously responded to clomiphene, but did not have a successful cycle due to other factors. A clinical study in 31 poor responders compared a low-dose clomiphene/gonadotrophin protocol with a full stimulation protocol (FSH 300 IU/day and HMG 150 IU/day SC starting cycle Day 3 + ganirelix acetate 0.25 mg/day SC starting on cycle Day 8 for an average of five doses)). Patients who received the full stimulation protocol used significantly more vials of gonadotrophins and had a higher number of mature oocytes retrieved (3.8 versus 2.4 with the minimal protocol), but the clinical pregnancy rates per cycle (36% versus 38%) and per transfer (47% versus 42%) were similar between groups and the low-dose protocol had fewer patient cancellations.

Augmented natural cycle protocols are designed to provide continued gentle cycle support for women who have slow follicle development. In our experience, the timeline is not as important as observing the important developmental milestones in natural cycle protocols. Patients are monitored for oestradiol production >20 pg/ml and/or the presence of 3- to 4-mm sized basal antral follicles; in these patients it may take 7–10 days for these characteristics to be observed. Once the follicles are present, ovarian stimulation is initiated with a low-dose combination of HP-HMG and rFSH 75 (e.g. 75 IU/day of each) and continued for approximately 6 days, depending on continued follicle development; a GnRH antagonist is added when the lead follicle reaches ≥12 mm. Ovulation is triggered with HCG 10,000 IU or leuprolide. This protocol may particularly benefit patients who have not had a positive response (no mature follicles) to past stimulation protocols

Debate remains about whether Day 3 or Day 5/6 embryo transfers provide the best IVF outcomes, with the relative benefit possibly due to patients' clinical characteristics. A randomized controlled trial found no overall difference in implantation and pregnancy rates between Day 3 and Day 5 embryo transfers (However, the study also showed that patients without good-quality embryos on Day 3 still benefited from proceeding with embryo transfer on Day 3 (pregnancy rate of 33%), but were unlikely to become pregnant with a Day 5 transfer. Some embryos do not persist in culture to Day 5/6, so patients with very low embryo counts may also benefit from Day 3 transfer to ensure they have an embryo(s) to transfer. Conversely, in some cases it is predicted that a patient's uterus will be in better condition on Day 5, and for these patients it may be better to plan for a Day 5/6 embryo transfer.

Segmentation of the IVF cycle through embryo cryopreservation and deferred (i.e. cryopreserved) embryo transfer has been proposed as a possible strategy to accumulate greater numbers of embryos over several stimulation cycles in poor responders. This segmentation of the IVF cycle is thought to improve clinical outcomes in poor responders by allowing for the selection of only high-quality embryos for transfer and ensuring that the embryos are transferred to a more receptive endometrium (). Segmented treatment cycles were associated with lower dropout rates compared with fresh cycles and resulted in comparable cumulative success rates to those seen in normal responders. As in normal responders, progesterone supplementation during the luteal phase improves cycle outcomes in poor responders. There is some evidence to suggest that the addition of oestradiol to progesterone for luteal phase support may improve implantation rates in women undergoing IVF; however, this approach has not been shown to improve pregnancy outcomes in poor responders.

Conclusions

Poor responders are a heterogeneous population of IVF patients with unique needs.. Stimulation during the earlier stages of follicle maturation may help to synchronize the follicles for improved response to later gonadotrophin ovarian stimulation. We recommend that IVF protocols for poor responders should complement the patient's natural cycles, rather than override them with high doses of exogenous gonadotrophins, and avoid suppressive hormonal treatments. Because of the heterogeneous nature of the poor responder population, protocol selection should consider the patient's clinical characteristics, treatment history and goals.

Clinical Proceedings of AOGD Clinical Meeting held at Maulana Azad Medical College, New Delhi on 30th November, 2018

Successful Pregnancy Outcome in a Woman with Multiple Connective Tissue Disorder (MCTD)

Anjali Tempe, Niharika Dhiman, M Tanuja, Pushpa Mishra, Devender Kumar

Autoimmune diseases (ADs) represent chronic and complex group of disorders involving multiple systems with significant morbidity and poor quality of life as the disease progresses. There are only few cases of successful pregnancy outcomes in women with multiple autoimmune syndrome.

Case Presentation- 40 years old $G_{11}P_1L_0A_9$, 35+3 weeks with bad obstetric history, IVF conceived (in vitro fertilisation by donor embryo), complete placenta previa, FGR (fetal growth restriction), hypothyroidism, chronic hypertension, rheumatoid arthritis (K/C/O since 14 years) with ANA+ vasculitis. She had one induced abortion followed by 8 spontaneous complete abortions. At present she has complaint of cough with expectoration not associated with dyspnoea and fever. There is no history suggestive of any flare of RA during this pregnancy. On examination, she was afebrile, blood pressure (BP) of 130/80 mm of hg, left tibial artery was not palpable. There was reduced air entry on the right infra-axillary region. Features of RA were present. Amputated stumps of left great toe and right second toe seen and appears to be healthy. On per abdomen, uterine size was less as compared to the period of gestation- 30 weeks with transverse lie with good fetal heart rate. Erosive arthritis with severe vasculitis is not a common finding with RA hence she was planned for further workup of any other connective tissue disorder. A diagnosis of $G_{11}P_1L_0A_9$ with 35 weeks 3 days POG with transverse lie, central placenta previa, FGR with Multiple Connective Tissue Disorder (RA, SLE ? APS) with deforming and debilitating arthritis and gangrenous auto-amputation of digits and toes with extra-pulmonary kochs with RPL was made.

Workup for MCTD – ANA was positive,pleural effusion S/O Pleuritis/Extrapulmonary Koch's, ECHO revealed mild left ventricular dysfunction (myocarditis/chronic hypertension)with arthritis was suggestive of SLE(4 criteria present). Anti Rho/LA were negative suggesting no active disease and less chances of foetal / neonatal affection. A physician and Rheumatologist opinion was sort- Low molecular weight heparin and ecospirin was started. In view of high BP records she was started on tablet labetalol 100mg thrice daily. In view of ?Diagnosis of extrapulmonary tuberculosis after pleural fluid analysis, she was started on ATT (anti tubercular therapy) category II by withholding streptomycin. She delivered a male child of 1559 grams by elective lower segment caesarean section done at 37+2 weeks. Patient post-operative period was uneventful. During the postpartum period she was started on tab. Ecosprin 75mg daily and Inj. Methotextrate 10 mg subcutaneous once a week.

Discussion: Entities satisfying classification criteria of at least two connective tissue diseases (CTDs) occurring at the same or at different times in the same patient is defined as MCTD. Incidence- 3.1 per 100,000 population among females. F:M- 5:1. MCTD is associated with hypertension / preeclampsia, premature delivery, wound sepsis, thrombosis, HELLP syndrome (APS), GDM, PPROM, placental abruption and placenta previa, ↑Caesarean rate. Foetal Risk- Fetal loss, FGR, prematurity, low birth weight, neonatal lupus syndrome (Rho/LA +, ACHB of 2%). RA-60%- 90% improve during pregnancy and 47% relapse postpartum within 3 months. Variable flare has been seen with SLE 25-65% during pregnancy. Drugs like –hydroxychloroquine (HCQ), Prednisolone (low doses), Sulfasalazine (<2gm/day), Tacrolimus and Cyclosporine can be given safely during pregnancy. Multiple (overlap) CTD is a rare entity. Pre-pregnancy counseling and conception during remission phase is advisable to improve maternal and neonatal outcome.

Spontaneous Vaginoperitoneal Fistula: A rare complication of carcinoma ovary

Tarang Preet, Sangeeta Bhasin, Asmita M Rathore, Latika Sahu, Preeti Singh

INTRODUCTION: A fistulous communication between the vagina and bladder, urethra, ureter or rectum is commonly implicated when there is continuous vaginal discharge or urinary leakage following abdominal/ pelvic surgery. However, to the best of our knowledge, spontaneous development of vagino-peritoneal fistula in a case of carcinoma ovary has never been reported. Here, we report a case of stage IV B ovarian cancer with spontaneous vaginoperitoneal fistula.

CASE PRESENTATION: A 55 yr old, P5L5 postmenopausal lady presented with chief complaints of anorexia and easy fatigability for last 1 month, abdominal distention, decreased urine output and constipation for last 10

days. She also had complaint of something coming out of vagina for last 10 days. On clinical examination, patient was thin built and had cachectic facies. Her general physical examination was unremarkable. On abdominal examination, she had tense ascites due to which no abdominal mass was appreciated. Second-degree cervical decent, cystocele and rectocele were present on local examination. On per-speculum examination, cervix and vagina appeared healthy. On per-vaginum examination, uterine size was not made out well and all the fornices were full due to tense ascites. Biochemical investigations revealed raised levels of tumor markers such as CA-125 = 225.0 mIU/L, CEA = 146.5 ng/ml making her RMI score 2025 (suggestive of malignancy).

USG and CECT revealed presence of gross ascites with 10.2*10.7*12.5 cm solid-cystic mass arising from bilateral ovaries. It was extending to POD abutting rectum and sigmoid posteriorly and pelvic wall laterally with maintained fat planes. There were hypodense soft tissue deposits in subcapsular location in liver and pancreas and in gastro-esophageal junction likely metastasis. CECT was suggestive of ovarian neoplasm with metastasis. Ascitic fluid examination for malignant cytology was suggestive of mucin secreting neoplasm. USG guided FNAC from the mass was suggestive of adenocarcinoma. Upper and lower GI endoscopies were unremarkable. On the basis of a diagnosis of stage 1V ovarian malignancy, she was planned for neo-adjuvant chemotherapy followed by interval debunking followed by adjuvant chemotherapy.

She received her first cycle of paclitaxel and carboplatin based chemotherapy uneventfully. During her second cycle, she experienced spontaneous painless sudden gush of fluid coming out per vaginum while she was ambulating. On examination, she was hemodynamically stable. Her ascites had disappeared and a large irregular fixed lower abdominal mass could now be appreciated. On local examination a defect measuring 3*3cm was observed in posterior vaginal wall 1 cm from external os. It had necrotic margins and fluid with mucus flakes was seen draining out from the hole. Patient was planned for exploratory laparotomy on semi-emergency basis in collaboration with gastrosurgeons. Per-operatively, left and right ovarian masses measuring 9*6*4 cm each and multiple omental deposits were observed. A defect with necrotic margins was confirmed in the posterior vaginal wall which measured 3*3 cm. There was no mass in the pouch of Douglus. Patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy with omentectomy with appendectomy with omental patch repair of the posterior vaginal wall rent. Intra-bdominal drain was left for 15 days postoperatively to avoid ascitic fluid build-up and impact on fistula healing. Leak per-vaginum continued postoperatively and stopped on 3rd postoperative day. Adjuvant chemotherapy (paclitaxel and carboplatin) was started 3 weeks postoperatively and 4 cycles were given. Clinically patient appears tumor free and is healthy. She is currently under follow up.

DISCUSSION: Vaginoperitoneal fistula is a rare entity in itself and its spontaneous formation in a patient of carcinoma ovary has never been reported. Hence, there were no set protocols that we could follow in managing her. Neither was there any definite pointer as to the cause of the development of this fistula. We hypothesised various causes that could have led to the formation of this spontaneous vaginoperitoneal fistula. Firstly, malignancy per-se could have contributed to it. A metastatic tumour deposit in the Pouch of Douglus could have progressed and eroded through the vagina or a tumour deposit in the POD could have undergone lysis under the effect of chemotherapy, thus giving way and leading to vaginoperitoneal fistula formation. Secondly, it may have occurred as a complication of paclitaxel and carboplatin chemotherapy. Ischemic colitis and neutropenia-related necrotizing enterocolitis leading to bowel perforation have been reported as an uncommon complication with paclitaxel chemotherapy. By extrapolation, the same mechanism of necrosis and perforation could have led to the formation of the vaginoperitoneal fistula. Thirdly, it could have resulted from the intense pressure of the gross ascites on the weak postmenopausal prolapsed tissues.

Our basic aim in presenting this case is to highlight, that though very rare, the possibility of such an occurance should be kept in mind while treating patients of ovarian cancer with ascites..

A Case of Acquired Uterine Arteriovenous Malformation Post Uterine Curettage

Ashok Kumar, Poonam Kashyap

A case of 29 year female P2L2A1 with previous 2LSCS presented with complaints of intermittent heavy vaginal bleeding for 4 months. She took medical abortion after her urine pregnancy test was positive after one and half months of amenorrhea. She had undergone D&C twice for retained products of conception. She had the same complaints of intermittent heavy vaginal bleeding after D&C also. She got another USG done which showed suspicion of uterine Arteriovenous malformation and was referred to higher centre. In Lok Nayak Hospital, Patient had undergone various investigations including pelvic USG, Dynamic contrast enhanced MRI, and CT angiography which confirmed the diagnosis of uterine arteriovenous malformation. She was managed with transcathetral uterine artery embolization by Cardiologist in GB Pant Hospital. Patient recovered and started having regular menstrual periods after the procedure.

Uterine AV Malformations Presenting as Broad Ligament Haematoma A Rare Presentation

Ankita Srivastava, Gauri Gandhi, Poonam Sachdeva, Deepti Goswami, Krishna Agarwal

Uteine AV malformations are rare but can cause fatal complications. We present a case of previous caesarean haematoma due to an acquired AV M.AVM can be either acquired or congenital, latter is more common,these are due to previous uterine surgeries.

Second gravida with previous one caesarean section underwent an emergency caesarean for non- progressive labour. The caesarean was uneventful, bleeding was normal. One hour later she had atonic PPH Which was controlled by uterine massage and oxytocin. Despite that, tachycardia persisited. Patient was given blood transfusion but tachycardia worsened. Uterus was contracted and deviated to right side. PV examination and ultrasound confirmed a left sided braod ligament hematoma (10x 8cm). UAE was done, a uterine AVM was identified at the side of hematoma. Ipsilateral internal iliac artery (IIA) embolization was done just at the site of uterine artery origin.Blood flow decreased, post operative period was uneventful, size reduced to 5x3cm. Patient has been on follow up for 10 months and has normal menstruation.

IIA embolizaton has a higher success rate 90-95% as compared to IIA ligation (40-85%), as the bleeding vessels are easier to identify. It is a good method to conserve the uterus for patients who desire future fertility.

Congratulations

Dr Shivani Agarwal & Dr Anita Rajohria for successfully answering the quiz and crossword of November issue correctly!!

* * * * *

Answer to Quiz: November Issue

Answers of Crossword - November Issue

Down: 1. RMI, 2. Swede, 5. HOMA-IR, 8. DIPSI

Across: 3. HIPEC, 4. Sheehan, 6. Myxedema coma, 7. BIRAD, 9. PTU , 10. Meig

Answer of Pictorial Quiz - November Issue

Figure 1: Ans 1. Insulin pump

Ans 2. Advantages- precise insulin delivery & tight blood sugar control

Disadvantages-

- Risk of skin infections at the catheter site.
- Risk of diabetic ketoacidosis (DKA) from pump malfunction or absorption problems.
- Cost

Figure 2: Ans 1. HIPEC

Ans 2. Ovarian cancer

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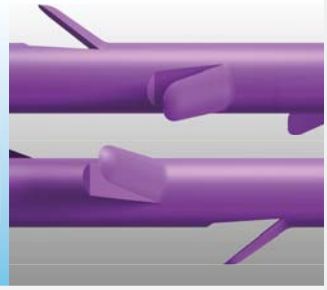
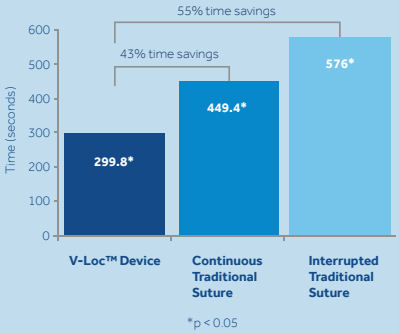
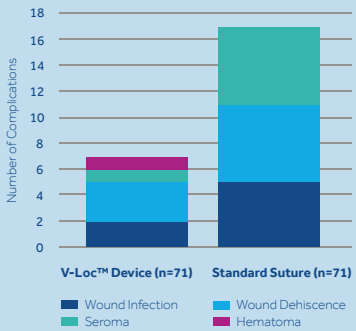


Closure Time for 9-Inch (23 cm) Incision[1]



*p < 0.05

DIEP Flap Reduction in Overall Complications[2]



† When compared with traditional suture

1. Ramakrishnan, V. & Withey, S. Comparison of Wound Closure Time Using Conventional Techniques & Knotless, Self-Anchoring Surgical Sutures. St. Andrew's Centre for Plastic Surgery & Burns. Broomfield Hospital, Chelmsford, UK, 10.2011.
2. De Blacam et al. "Early Experience With Barbed Sutures for Abdominal Closure in Deep Inferior Epigastric Perforator Flap Breast Reconstruction" Presented at the New England Society of Plastic and Reconstructive Surgeons Meeting, Brewster, MA June 2011. Published: Eplasty.com, 5.2012.

*compared with previous generation

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