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# AOGD BULLETIN

***AOGD Theme 2017-18***

'Optimizing Women's Health Through Enhanced Skills and Best Practices'

***Issue:***

**The Year that was: Best of 2017-18**

**AOGD SECRETARIAT**

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# AOGD BULLETIN
**Volume 17-12, April 2018**


# Contents






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# President's Message

Dear Friends

The time of the year has come to bid adieu and I thank all members and well-wishers for making it happen. Our successful tenure could not have been possible without the untiring efforts of AOGD team at GTB Hospital. Patrons Dr. SN Mukherjee, Dr. Urmil Sharma, Dr. Kamal Buckshee & Dr. Neera Agarwal are the very foundation on which AOGD has grown and I thank them for their unconditional support. We miss, this year, our patron Dr. SK Das whose contributions to AOGD have been immense and may she rest in peace. Our valued advisors Dr. Swaraj Batra, Dr. Shakti Bhan Khanna, Dr. Chitra Raghunandan are present at almost all clinical meetings and do add depth to the discussions. Special thanks to all Chairpersons and members of AOGD sub committees for active participation and bringing out much needed and appreciated AOGD good practice guidelines. Of the next generation Dr. Sangeeta Gupta of ESI hospital has not missed a single clinical meeting and she deserves special mention.

I congratulate Dr. Abha Singh for taking over as President AOGD, 2018-19, at a small but significant ceremony at GTB Hospital during the GBM on the 23rd March 2018. We wish her success during her tenure and also best wishes to dream big for AOGD. I congratulate the incoming Chairpersons of four committees whose posts fell vacant – Dr. Surveen Ghumman, Infertility Committee, Dr. Susheela Gupta, Breast and Cervical Cancer Awareness, Screening and Prevention committee (Breast and Cervical cancer are now merged into one committee), Dr. AG Radhika, Multidisciplinary committee and Dr. Abha Sharma, Rural health committee. All the best for a successful and happening tenure.

This last issue deals with the ***'Best of 2017-18'*** where we have tried to include practice changing research papers over the past year. As a gynaecologic oncologist, the most thought breaking paper of 2018 was the ***'Phase III randomised trial of laparoscopic or robotic versus abdominal radical hysterectomy in patients with early stage cervical cancer-LACC trial'*** presented at SGO conference, New Orleans, March 2018. This multicentric trial conducted by MD Anderson Cancer Centre was closed prematurely as the recurrence rates (Hazards ratio: 3.74) and poorer survival (Hazards ratio: 6.00) were far higher in the MIS group. This finding must be communicated to patients before undertaking MIS for cancer cervix and as of now the open method for management of early stage cervical cancer is the standard of care. Details of study will be found in this issue. Other trials like ASPER, PORTEC III, TRUFFLE, Cascade testing and WHO guidelines are addressed in this issue.

Cheers and Thank you once again for allowing me to serve you as President AOGD, 2017-18!

**Shalini Rajaram**
President, AOGD (2017-18)

# Vice President's Message

Dear Friends

This issue of AOGD Bulletin is last in the series contributed by our superbly talented editorial team from UCMS & GTB Hospital.

'Trials and Guidelines' are the scientifically paved roads to a better and improved "patient – centric" quality care. This is the best focussed and targeted approach to keep ourselves updated with "what's latest and best for the patients."

The current issue gives insight into the major clinical trials, molecular tests and guidelines released during 2017 in the field of Obstetrics & Gynaecology. I am sure this issue will benefit lot of our readers.

So Goodbye from UCMS & GTBH AOGD team

& Cheers to the new AOGD Team!

**Kiran Guleria**
Vice President AOGD (2017-18)

# From the Secretary's Desk.....

Dear AOGDians

Hello!

The last issue from current AOGD office is in your hands, a glorious journey of twelve months, twelve issues. It was a fantastic time made memorable by your enthusiastic participation in all events organized by us. I will take this opportunity to thank the lovely people who made last year possible. Notably the skills workshop chairperson Dr A.G. Radhika & her team Dr Richa Sharma, Dr Sanjeeta Behera & Dr Bhanupriya. They made tremendous effort to organize these workshops on relevant topics.

My editorial team Dr Rashmi, Dr Bindiya, Dr Richa Aggawal & Dr Sruthi made these bulletins such prized possessions. They have set a high benchmark & current issue is one of the best, dealing with latest advances over last year. Our web editors Dr Rachna and Dr Anshuja took extra care to keep the website updated with current events and bulletin.

I wish to acknowledge my backbone my joint secretaries, Dr Sandhya & Dr Himsweta who worked tirelessly by my side. My money worriers were ably handled by Dr Alpana & Dr Archana. Dr Vishnu Bhartiya & Dr Shweta Prasad kept meticulous record of clinical meetings. The hospitality and public relations were handled adroitly by Dr Seema Prakash & Dr Rashmi Gupta. Last but definitely not the least, I wish to thanks my elders Dr Gita Radhakrishnan, Dr Amita Suneja, Dr Shalini Rajaram & Dr Kiran Guleria whose unstinting support & guidance made my work easy & enjoyable.

Dear readers I wish you all success in life .Happy doctoring,

A heartfelt **"Thank you"** to all !!

Signing off, Adios Amigos!!

**Abha Sharma**
Secretary AOGD (2017-18)

## Monthly Clinical Meet

Monthly Clinical Meet will be held at Apollo Hospital, Sarita Vihar
on **Monday, 23rd April, 2018** from 4:00-5:00pm.

# From the Editorial Board

Respected Seniors and Dear Friends,

In the month of April which marks the time of new beginnings & Hindu New year, the journey of AOGD also takes a new turn with a new team of Lady Harding Medical College taking over from us. At this time, our editorial journey is also coming to an end and we are bringing out this last issue for you all.

***"There is no real ending. It's just the place where you stop the story" ……Frank Herbert***

But we saved the best for the last and we bring out the last bulletin on "***Best of 2017-18".*** Some of the largest trials published their results in last year like TRUFFLE, ASPRE, PORTEC 3, WOMAN trial and it's important for everyone to know these results and incorporate in our clinical practice. These cover such important topics like Post partum hemorrhage, Fetal Growth Restriction, Pre eclampsia and endometrial carcinoma. New recommendations issued by WHO on Intrapartum care and ASRM guidelines on Embryo transfer have also been included. A lot of research is being done on molecular level in both obstetrics and gynecology …. Be it prenatal diagnosis or genetic mutations in malignancies. Also in the era of minimal invasive surgery, the boundaries are being pushed and results of trials for early cervical cancer should make one cautious. All this have been covered in this bulletin.

***"Whatever good things we build, end up building us."***

The editorial journey had been a very fulfilling experience as we read and learnt a lot in the process. It still feels like yesterday when we were planning for our first bulletin and now the task is coming to an end. Hope you all enjoyed reading the bulletins (including the present one) as much as we did while putting these together.

"***Every new beginning comes from other beginning's end***". So the new chapter begins and we wish all the best to the new team.

Our heartfelt thanks to our seniors for supporting us, to our authors who took out time from their hectic schedules to write chapters for the bulletins and last, but not the least, the whole printing team of Mr Ahuja and especially Mr Satya Prakash who burnt their night lamps with us to bring out issues in time. Without these people, this would not have been possible.

And thanks to all our readers for being ever so encouraging and appreciating. Our parting words to you all……

***"A Lump in throat, An anxious drop of sweat, A tear in the eyes, A feeling of debt, The skip of heartbeat, Emptiness in the soul,***
***This is how I feel, As you leave your role, The feeling is of that, A friend going away, Who I will remember, Each and every day……"***

With Warm Regards

**The Editorial Team**
AOGD (2017-18)

# The World Maternal Anti-Fibrinolytic (WOMAN) Trial

**Amenda Davis[1], K Aparna Sharma[2]**
[1]Junior Resident, [2]Associate Professor, Dept of Obstetetrics and Gynecology, AIIMS

## Introduction

Post partum hemorrhage (PPH) is the leading cause of maternal mortality, accounting for 100,000 deaths per year, 34% of all maternal deaths[1]. The WOMAN Trial was a multi-centric trial which aimed to estimate the effect of early administration of tranexamic acid on death, hysterectomy, and other outcomes in women with post partum hemorrhage. This was an international, double blind, placebo controlled trial done in 193 hospitals in 21 countries from March 2010 to April 2016. 20,060 women above the age of 16 with established post partum haemorrhage were randomized to receive either 1 gm of tranexamic acid diluted in 100 mL normal saline at 1 mL per minute, or saline placebo, in addition to the standardized protocols for PPH. If bleeding did not stop after 30 minutes or restarted within 24 hours, a second dose was given. After randomization, 10,036 women received tranxexamic acid and 9985 women received saline placebo. 70% of the women had undergone vaginal delivery, with the causes of hemorrhage ascertained due to uterine atony (64%), placenta previa or morbidly adherent placenta (9%), or traumatic (7%). The randomization was done within 1 hour of delivery in 48%, in 1-3 hours in 27% , and more than 3 hours in 25%.

The primary outcomes analyzed were death due to various causes within 42 days post partum, and the incidence of hysterectomy. There were a total of 483 maternal deaths (2.4%), of which 77% occurred within 24 hours of randomization and 72% were attributable to post partum hemorrhage. There was a significant reduction in death due to bleeding, with 1.5% (n=155) and 1.9% (n=191) deaths in the tranexamic acid and placebo group respectively (p=0.045). This effect was more pronounced if tranexamic acid was given within 3 hours of delivery, with no risk reduction after 3 hours. The risk reduction was similar irrespective of the mode of delivery and the cause of post partum hemorrhage. Tranexamic acid did not reduce the deaths due to other causes such as eclampsia, sepsis, or organ failure. There were 709 hysterectomies performed (3.5%), 358 in the tranexamic acid groups and 351 in the placebo group, and tranexamic acid was not found to reduce the risk of hysterectomy (relative risk 1.02, p=0.84). The need for additional surgical interventions like intra uterine tamponade, manual removal of placenta, embolization, brace sutures, or arterial ligation was not reduced,; however, there was a significant in the overall laparotomies done for bleeding, with 0.8% and 1.3% of women requiring laparotomies in the tranexamic acid and the placebo group respectively (RR 0.64, p=0.002). There were no significant increase in adverse effects like thromboembolic events, medical complications, neonatal effects, or quality of life.

## Comment

Post partum haemorrhage is the single most important cause of maternal mortality and near miss mortality world-wide. An estimated 14 million women are affected by PPH and around 2% of them die every year.[1] The risk of PPH in all pregnancies is estimated to be 1.2%, with the most common cause being atony[2]. However, the deaths due to PPH are found to be due to atony in only 6.5%, & rest predominantly due to other causes like abruption, placenta previa, ruptured uterus, retained placenta, morbidly adherent placenta, vaginal and cervical trauma, inverted uterus, bleeding during and after caesarean section[3].

The WOMAN trial is the first of its kind in evaluating the effect of tranexamic acid in the treatment of established post partum haemorrhage, in contrast to previous trials which have evaluated its role in prevention. A Cochrane review by Novikova et. al[4] revealed that tranexamic acid used for the prophylaxis of post partum hemorrhage lead to a significant reduction in the incidence of both minor and major post partum hemorrhage, a mean reduction in total blood loss, with no significant increase in thromboembolic events or adverse side effects. A meta analysis by Li[5] et al found that tranexamic acid given prophlactically reduced intra delivery and post delivery blood loss significantly, irrespective of the mode of delivery. There has been only one study (Ducloy Buthers et. al)[6,7] prior to the WOMAN trial assessing the effect of tranexamic acid in the treatment of post partum hemorrhage. This study did not show any significant benefits, but the sample size was too small to make any meaningful conclusions. The introduction of time stratification in the WOMAN trial derived origin from the results of the CRASH-2 trial by Roberts et. al[8] which found that tranexamic acid given to patients of trauma led to a significant reduction in the number of deaths due to bleeding, but only if given within 3 hours of the inciting event.

Current practice guidelines incorporate the use of tranexamic acid in the protocol for management of post partum hemorrhage. The RCOG advises the use of tranexamic acid in addition to oxytocin during caesarean section in women at increased risk of PPH, a level A recommendation based on the findings of Novikova et. al[9]. The WHO in 2012 had recommended the use of

tranexamic acid for the treatment of PPH if uterotonics fail to control bleeding or the cause was partly due to trauma[10]. The level of evidence was moderate, with extrapolation from the findings of the CRASH-2 trial. The ACOG recommends considering the use of tranexamic acid when other medical therapy fails in the treatment of PPH[11].

Based on the findings of the WOMAN trial, in 2017, the WHO updated the strength of its recommendations to include tranexamic acid in the standard of care for PPH[12]. They now recommend using intravenous tranexamic acid within 3 hours of birth in addition to standard care for all women with clincally diagnosed PPH, irrespective of the mode of delivery or cause of PPH. The fixed dose should be 1 gram in 10 mL saline over 10 minutes, to be repeated if bleeding continues 30 minutes after first dose or if bleeding restarts within 24 hours.

The WOMAN trial provides invaluable evidence that tranexamic acid given within 3 hours of delivery reduces maternal mortality due to post partum hemorrhage by nearly one third and reduces the need for laparotomy performed for PPH. These benefits are observed irrespective of the mode of delivery or the cause of PPH. It is not associated with an increased incidence of thromboembolic events or adverse effects.

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WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017; 389: 2105–2116

## Forthcoming Events

- Urogynaecology live workshop on 15th of April 2018 at Sunderlal Jain Hospital, Phase III, Ashok Vihar, Delhi - 110052. For any query contact Dr Uma Rani: 9811258731
- CME on "Medical Disorders in Pregnancy" on 15th April at Sir Ganga Ram Hospital. For any query contact Dr Mala Srivastav: 9811228336
- Next AOGD Clinical Meeting on 23rd April, 2018 at Apollo Hospital, Sarita Vihar
- Gynecological Endoscopy Video Workshop and Endotraining to be conducted at Department of Obs & Gyne Maulana Azad Medical College on 5th May, 2018 Saturday under the aegis of AOGD endoscopy committee from 10.30am - 4.00pm. Details are available on MAMC website. Registration fee Rs 1000/- For registrations please contact : Dr Pushpa Mishra 9868392729, Dr Niharika Dhiman 9968604420
- CME series in Maternal Fetal Medicine "being organised by Division of Fetal Medicine, Department of Obstetrics and Gynecology, AIIMS, New Delhi, under the Aegis of AOGD Fetal Medicine subcommittee on 13th May, 2018, in LT-1, AIIMS. Registration fee Rs 1000/-. For registrations please contact: Ms Rekha : 8587004239

FOGSI has recommended RUSH teams to be formed in the local societies. These local teams will help each other in case of any case of any mob attack or surgical emergency at Someone's Hospital. Volunteers please contact AOGD office for registration and further information.

# Trial of Umbilical and Foetal Flow in Europe: TRUFFLE study

**Sruthi Bhaskaran**
Assistant Professor, University College of Medical Sciences & GTB Hospital, Delhi

## Introduction

Advances in neonatal care over the last few decades have resulted in improved survival of preterm infants even at very early gestational ages. However, neurological impairment, and decreased intellectual and social performance are still strongly associated with lesser gestational age at birth.[1]

The situation becomes even more important if prematurity is associated with fetal growth restriction (FGR). Outcomes in later life relating to neurological impairment which are of greater importance than survival, are rarely reported, and cannot be inferred from whether or not complications occur in the neonatal period.[2] Most studies of early onset fetal growth restriction have focused on short-term neonatal outcomes.[3,4]

No targeted treatment exists for FGR, delivery is the only intervention that can prevent severe hypoxemia and acidosis, and eventually intrauterine death. Thus, optimal monitoring and timing of delivery remains crucial in the management of early-onset FGR.

The balance in early-onset FGR is between, on the one hand, prolonging pregnancy to reduce prematurity-related complications, and in the other, timely intervention, to prevent mortality and limit morbidity.

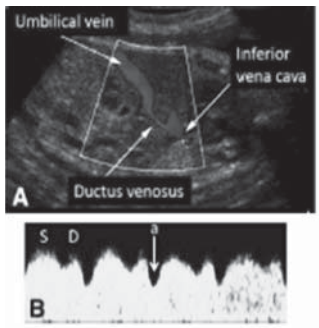
The issue of how to monitor and when to deliver in early-onset FGR has until recently been backed by little evidence. In the preterm growth restricted fetus, the decision to deliver is usually made only when signs of substantial worsening of the fetal condition are observed by visual or qualitative assessment of a cardiotocograph tracing or changes in biophysical status because these changes correlate with fetal hypoxaemia.[5]

Several methods exist for surveillance of the at-risk fetus—eg, cardiotocography, arterial and venous Doppler examination, and biophysical profiles.[6] No consensus exists for what is the best way to monitor growth restriction.

Different umbilical artery Doppler patterns identify different degrees of impaired placental function. Absent end-diastolic velocities (AED) or reversed end diastolic velocities (RED) indicate impairment of the fetoplacental circulation and precede fetal deterioration.[7] The transition from AED to RED may be slow and gradual in early FGR. However, both AED and RED have been associated not only with increased fetal and neonatal mortality but also with a higher incidence of long-term neurological impairment.[8]

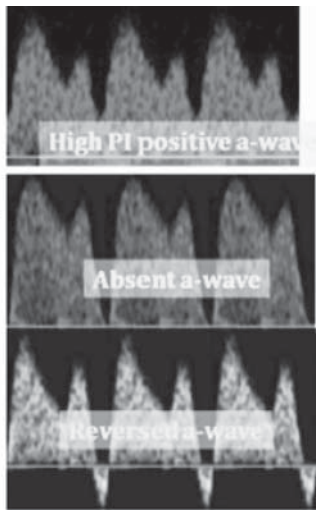
Since the early 2000s, attention has moved to assessment of the ductus venosus (DV) (Fig1, 2) and computerized cardiotocograph (cCTG) analysis of fetal heart rate short-term variation (STV) to guide timing of delivery in FGR.[6] Studies have found that mortality was higher if both DV and cardiotocography (CTG) were abnormal than when only one was abnormal.[3]

**Fig:1** Ductus Venosus imaging and waveform




**(A)** Two-dimensional and colour Doppler imaging of doctus venosus (DV), **(B)** Normal second trimester DV waveform, S-wave indicates systole, D-wave diastole and a wave denotes late dastole (artial contraction), Vertical arrow shows positive flow.

**Fig:2** Ductus venosus doppler velocimetry waveforms




Progression (from top to bottom) from increased pulsatility index (PI), to absent and reversed flow during a wave. Positive (forward) and negative (reversed) flow are dencted.

**The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE)** was designed to answer the question of which methodologies should be used to monitor and according to which criteria deliver foetuses with early-onset FGR.[9]

They postulated that changes in the fetal ductus venosus (DV) Doppler waveform, which generally develop after those in the umbilical artery, might be used as indications for delivery instead of cardiotocograph short-term variation.[9] The study compared 2 techniques in the monitoring and timing of delivery in early-onset (26-31$^{+6}$ weeks) FGR. These were **DV Doppler** and **cCTG for fetal heart STV(Short term variability)**.

## Methodology

The Trial of Umbilical and Fetal Flow in Europe (TRUFFLE)

study was a prospective, multicentre, randomised management trial done in 20 European tertiary care centres with a fetal medicine unit in five countries (Germany, Italy, the Netherlands, Austria, and the UK).

Participants were included from Jan 1, 2005 to Oct 1, 2010, which was extended to December 2013.[9]

The study was restricted to impaired fetal growth due to uteroplacental origin.

**The inclusion criteria** were singleton pregnancies with fetal abdominal circumference (AC) <10th percentile, gestational age between $26^{+0}$ weeks-$31^{+6}$ weeks, and UA Doppler pulsatility index >95$^{th}$ centile with or without reversed or absent end-diastolic flow.[9,10]

The $26^{+0}$ weeks-$31^{+6}$ weeks range was chosen as maximum uncertainty existed between this, given the uncertainty of outcomes at gestational ages <26 weeks and with a fetal weight <500 g and the low incidence of severe neonatal complications after 32 weeks of gestation.[11]

## Monitoring techniques and criteria for delivery

The aim of TRUFFLE was to compare the **outcome in the survivors of FGR pregnancies at 2 years of age when the timing of delivery was based on different monitoring techniques, namely cCTG STV or DV Doppler.**

The cCTG reflect changes in fetal sympathetic, parasympathetic activity and chemoreceptors occurring during the process of hypoxic deterioration in placental FGR.[12,13]

The increase in DV pulsatility index with progression to absent and reverse flow velocities of the a-wave (atrial contraction) is typically seen only in severe and early gestational age FGR fetuses.[3,6] After 32 weeks, abnormal CTG (late decelerations, reduced variability) almost invariably precede DV abnormalities.[3]

Hypoxemia and acidemia result in altered sympathetic and parasympathetic activity, hence in decreased fetal heart rate variation, reflected by a lower cCTGSTV.[12,13] Late (shallow) decelerations are indicative of a chemoreceptor-mediated response to fetal acidemia and of a direct depression effect of acidemia on myocardial tissue.

## Randomization arms

Participants were randomly assigned to one of three groups in a 1:1:1 ratio to establish the timing of delivery:

1. Abnormal cCTG-STV (<3.5 milliseconds at 26-$28^{+6}$ weeks and <4 milliseconds at 29-$31^{+6}$ weeks).
2. Early DV Doppler abnormalities: pulsatility index >95th percentile.
3. Late DV Doppler abnormalities: absent or reversed a-wave.

Abnormal measurements were confirmed by a second measurement at least 24 h later (measurements were repeated as often as needed). Monitoring in all groups included umbilical artery Doppler and CTG was recommended at least once a week, but was done more frequently according to local policy.

In cases where corticosteroids had been given for fetal lung maturity, no decision regarding delivery was made on the grounds of reduced variation from 24 h to 72 h after the first intramuscular dose because corticosteroid administration is known to lead to transient reduced STV.

## Safety-net criteria for delivery

In cases randomized to DV changes, the trigger for delivery was a cCTG-STV <2.6 milliseconds at 26-$^{+6}$ weeks and <3 milliseconds at 29-$31^{+6}$ weeks. Spontaneous repeated persistent decelerations on CTG represented a safety-net criterion in all 3 trial arms. At gestations >32 weeks, the policy for delivery was based on local protocols. RED in the UA was recommended as a reason to deliver the fetus >32 weeks but was permissible >30 weeks; AED, >34 weeks but permissible >32 weeks.

## Maternal indications for delivery

Maternal indications for delivery were considered as independent of fetal condition, randomization arm, and gestational age.[9,10]

## Primary outcome

Survival without cerebral palsy or neurosensory impairment, or with a Bayley III developmental score[14] of >85, at 2 years of age.

## Secondary outcomes

Secondary outcomes were perinatal mortality, and neonatal and infant morbidity and mortality.

## Patient characteristics

The study cohort consisted of 511 women recruited of 542 eligible for inclusion. The mean maternal age was 31 years, 63% were nulliparous, 84% were Caucasian, with a mean body mass index of 25 kg/m$^2$. No differences in demographic features were reported in the 3 trial arms. Hypertensive disorders of pregnancy were either already present at recruitment or developed during the observational period in 50% of cases with no difference between the 3 randomization arms and complicated 73% of the pregnancies by the time of delivery. Hypertensive disease, preeclampsia, and severe FGR is strongly associated with abnormal uterine artery Doppler velocimetry, although this parameter was not required for study inclusion.

# Results: fetal and neonatal risks of early FGR

## Mortality

The mean gestational age at delivery was 30.7 weeks and neonatal weight was 1019 g.[9] Antenatal death occurred in 12 cases (2.4%), including 5 cases where parents declined consent to delivery. In spite of the severity of FGR, 92%(463/503) babies survived to discharge. These results are more favorable than those previously reported from observational studies. No significant difference in baseline variables or short-term fetal and neonatal outcomes between the three study groups were noted.

## Morbidity & Mortality

Severe morbidity among live births was present in 24% of infants and 5% of neonates died in the perinatal period.

## 2-year Survival and neurodisability

There were no significant differences in survival without infant neurodisability at 2 years: 77% for the cCTG group, 84% for the early DV group, and 85% for the late DV group (P ¼ .09); this analysis included all deaths. However, among the survivors in a predefined primary analysis, the percentage of infants without neurodevelopmental impairment at 2 years of age, corrected for prematurity, was significantly higher (95%) in the late DV group compared to the cCTG arm (85%). In the same arm (late DV changes, ie, 0 or reversed a-wave) the better neurological outcome was associated with a small and nonsignificant excess of antenatal deaths.[10]

## Middle cerebral artery Doppler and outcome

Normalized for gestation using z-scores, middle cerebral artery (MCA) pulsatility index and umbilico cerebral ratio at inclusion were associated with 2-year survival with normal neurodevelopmental outcome (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.03e1.72, and OR, 0.88; 95% CI, 0.78-0.99, respectively) as were gestation at delivery and birthweight p50 ratio (OR, 1.41; 95% CI, 1.20-1.66, and OR, 1.86; 95% CI, 1.33-2.60, respectively).[15]

## Safety-net deliveries <32 weeks

The TRUFFLE protocol applied up to 32 weeks. In those delivered <32 weeks, the safety-net criteria triggered delivery in 38% of cases: 52% of 106 cases in the late DV group, 37% of 99 cases in the early DV group, and 25% of 105 cases in the cCTG-SVT group. Other fetal or maternal indications accounted for 30% of all deliveries <32 weeks.[16]

# Discussion

Overall, outcomes for very preterm foetuses with FGR were much better than previously assumed: 82% of children with known outcome survived without neurological impairment. With the exception of cerebral ultrasound abnormalities, commonly used neonatal morbidity criteria are poor markers of later neurodevelopmental outcome. Indeed, 2-year neurodevelopmental impairment was not preceded by any component of composite neonatal morbidity in 56% of cases.[17] Gestational age at both study entry and delivery were strongly related to morbidity and mortality. Thus, specific morbidity/ mortality tables in relation to gestational age at entry in the study and gestational age at delivery can be used for accurate parental counselling. The most important independent determinants of the composite adverse outcome (death or severe morbidity) were the presence of maternal hypertensive disease, low gestational age, and a low EFW at study inclusion.

# Clinical Implications

***Optimal timing of delivery of the early FGR fetus is achieved by monitoring with both DV and cCTG-STV. In those randomized to the late DV group there was better neurological outcome in surviving children, with nonsignificant higher antenatal mortality.***

**Hence, delivery should be undertaken when the a-wave in the DV reaches the 0 line (absent a-wave) or when there is a pathologically low STV.** This lower cCTG-STV cut-off was chosen assuming that STV of 2.6 milliseconds is the lowest cut-off clinically appropriate given the high chance of hypoxemia/acidemia below this level.

The presence of spontaneous, repetitive fetal heart rate decelerations or maternal indications should trigger delivery independently of DV and cCTG-STV evaluation.

Monitoring frequency of DV Doppler evaluation and cCTG was not established by the study, however it is reasonable to suggest frequent monitoring of cCTG and DV Doppler with a sliding scale from at least every 2-3 days to daily, based on the severity of FGR and UA Doppler abnormalities.

A subanalysis of babies delivered <32 weeks' gestation, in other words those whose management was strictly defined by the protocol, showed that more than one third delivered based on safety-net criteria, and another one third for other fetomaternal reasons.[17] Hence, in clinical practice, a significant proportion of fetuses will be delivered because of cCTG-STV abnormalities, even before DV changes occur. However, overall data from the TRUFFLE trial[9,10] and subanalyses[16] show a better outcome by the integrated use of both DV and cCTG-STV.

It is also recommended that Doppler measurements should be performed by experienced clinicians and the pulsatility index should be repeated at least 3 times at each assessment to verify uniformity of findings. In the case of maternal hypertension and/or HELLP syndrome, it is advised repeating assessments more frequently, since fetal deterioration may occur very rapidly.

### Delivery >32 weeks

TRUFFLE did not investigate which Doppler criteria should be used for delivering foetuses >32 weeks. However, Doppler evaluation of the UA becomes increasingly more important with advancing gestation. Reverse end diastolic flow may always prompt delivery >32 weeks and AED >34 weeks. Beyond 34 weeks delivery is often then triggered by other fetal criteria.

Apart from gestational ages the decision regarding timing of delivery should take into account the maternal condition, fetal growth, and EFW and should be left to the clinical judgment of the managing team.

Given the current interest in the fetal adaptive response to chronic hypoxemia assessed by Doppler of the MCA pulsatility index and its ratio with the UA (cerebroplacental ratio), a secondary analysis of MCA Doppler in the TRUFFLE cohort was undertaken. MCA Doppler did not add useful information for clinical management of these pregnancies.

**TRUFFLE 2 trial** - To address the issue of optimal monitoring and thresholds for delivery in late-onset fetal growth restriction, from 32-36 weeks gestation TRUFFLE 2 FEASIBILITY STUDY(started in 2017, likely to complete in early/mid 2018) is being conducted.

## Conclusion

The optimal management of early FGR fetuses should integrate clinical, Doppler, and cCTG parameters to ensure safe delay in delivery or a timely intervention.

Severe anomalies in the DV, when they precede cCTG abnormalities, are an indication for undertaking delivery. When the DV is still normal, delivery can be deferred, provided the cCTG-STV remains above the safety-net cut-off level. Although TRUFFLE did not specifically investigate monitoring frequency, cCTG-STV and Doppler of UA and DV should be undertaken with increasing frequency after the onset of AED in the UA, with more intensive monitoring in case of rapid deterioration. A predefined and agreed-upon protocol, based on or similar to that of TRUFFLE, is likely to lead to optimal perinatal and infant outcome.

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# Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia: ASPRE trial

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## Summary

This was a double-blind, placebo-controlled trial, in which aspirin at a dose of 150 mg per day was compared to a placebo that was administered from 11 to 14 weeks of gestation until 36 weeks of gestation in women with singleton pregnancies who were at high risk for preterm preeclampsia. The trial was conducted at 13 maternity hospitals in the United Kingdom, Spain, Italy, Belgium, Greece, and Israel.

All women who had a routine prenatal visit at 11 weeks 0 days of gestation through 13 weeks 6 days of gestation in the participating hospitals were offered screening for preeclampsia by means of an algorithm that combined maternal factors, mean arterial pressure, uterine-artery pulsatility index, and maternal serum pregnancy-associated plasma protein A and placental growth factor. Inclusion criteria for the trial were the following: age of 18 years or more, singleton pregnancy, live fetus at the time that scanning was performed at 11 to 13 weeks of gestation, and a high risk (>1 in 100) for preterm preeclampsia according to the screening algorithm. Exclusion criteria were the following: unconscious or severely ill status, learning difficulties or serious mental illness, major fetal abnormality identified at the time that scanning was performed at 11 to 13 weeks of gestation, regular treatment with aspirin within 28 days before screening, bleeding disorder such as von Willebrand's disease, peptic ulceration, hypersensitivity to aspirin, long-term use of nonsteroidal anti-inflammatory medication, and participation in another drug trial within 28 days before screening.

Eligible women were randomly assigned, in a 1:1 ratio, with the use of a Web-based system (Sealed Envelope), to receive either aspirin or placebo. After randomization, the participants were prescribed the assigned trial product and received instructions to take one tablet every night throughout the trial and to stop taking tablets at 36 weeks of gestation or, in the event of early delivery, at the onset of labor. The primary outcome measure was delivery with preeclampsia before 37 weeks of gestation. Secondary outcomes were adverse outcomes of pregnancy before 34 weeks of gestation, before 37 weeks of gestation, and at or after 37 weeks of gestation; stillbirth or neonatal death; death and neonatal complications; neonatal therapy; and poor fetal growth.

A total of 26,941 women with singleton pregnancies underwent screening[1] of whom 2971 (11.0%) were found to be at high risk for preterm pre-eclampsia of which 1776 were eligible and underwent randomization. Of these, 878 were assigned to receive aspirin and 898 to placebo. Preterm preeclampsia occurred in 13 of 798 participants (1.6%) in the aspirin group, as compared with 35 of 822 (4.3%) in the placebo group (adjusted odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004). There was no significant between-group difference in the incidence of any secondary outcomes, but the trial was not powered for these outcomes.

## Comment

Hypertensive disorders of pregnancy, including preeclampsia, complicate up to 10% of pregnancies worldwide. Preeclampsia is a major cause of maternal mortality and morbidity. According to ACOG, preeclampsia is defined as blood pressure elevation >140/90 mm Hg on two occasions, 4 hours apart after 20 weeks of gestation with proteinuria or any other severe features of preeclampsia such as impaired liver function, thrombocytopenia, new development of renal insufficiency, pulmonary edema, cerebral or visual disturbances. The fetal and neonatal outcomes are also jeopardized. The complications are more severe if the disease has an earlier onset in pregnancy resulting in preterm delivery and consequent complications.

Prediction of preeclampsia and instituting an intervention for prophylaxis of preeclampsia has been a topic of extensive research with aspirin being the potential therapy. However, there have been a lot of speculations on the population, dose and timing of aspirin administration to get the optimal maternal and neonatal outcome

**This trial, is a landmark trial** that can affect change in practice from the currently existing concepts. In this trial, the women at high risk were identified by means of combined screening with maternal demographic characteristics and historical factors, biophysical and biochemical markers. This model has shown to be superior to the other methods in various studies[2-5].

Another important outcome of this trial is the earlier gestational age range at the onset of treatment (11 to

14 weeks of gestation) with aspirin. A recent meta-analysis suggested that aspirin confers greater benefit if it is started at or before 16 weeks of gestation and that prevention is confined to preterm preeclampsia[6,7]. Currently, prophylactic aspirin is given in a low dose of 81mg per day. However recently, robust evidence suggests dose-dependant benefit of therapy[8]. The dose of 150 mg of aspirin per day in this trial has been proven to effective without any untoward side effects.

**In conclusion,** in women identified by first trimester combined screening to be at high risk for preterm preeclampsia, the administration of aspirin at a dose of 150 mg / day from 11 to 14 weeks till 36 weeks significantly reduces the incidence of preterm preeclampsia. There is no significant difference in the neonatal outcome, or adverse effects of aspirin.

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# Next Generation Sequencing for the Next Generation Obstetrician: Changing paradigms in prenatal diagnosis and reproductive medicine

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## Introduction

Recent years have witnessed rapid advancements in genetic technologies and bioinformatics, which have changed the diagnostic and management paradigms across all medical specialities. The obstetric practice has also witnessed the arrival of novel and complex genetic tests based on Next generation sequencing(NGS) technology for interrogating the genetic makeup of the unborn baby. While new research studies are being published and guidelines regarding the use of this technology in clinical practice are still evolving, it is imperative to review the literature evidence on this exciting new advancement and how it can act as a game changer in the realm of prenatal diagnosis and other reproductive case scenarios.

## Background

### Current Approach to Prenatal Diagnosis

Prenatal diagnosis is the detection of a fetal abnormality prior to birth using non-invasive or invasive means. Traditionally the goal of prenatal diagnosis has focussed on i) detection of fetal structural abnormality, this being performed using various imaging modalities, the primary being ultrasonography and ii) the diagnosis of chromosomal abnormalities in the fetus. Diagnosis of chromosomal abnormalities has been performed using fetal karyotyping on amniotic fluid or chorionic villus samples obtained by invasive means in second and first trimester of pregnancy respectively. As invasive testing is associated with a risk of pregnancy loss, hence decision for such a testing has been guided by various screening results, like ultrasonography indicators, maternal serum biomarkers, history of a previous child with aneuploidy, parental chromosomal rearrangements or advanced maternal age. As chromosomal diseases are associated with intellectual handicap in the postnatal period, their detection in a fetus has wide reaching implications for pregnancy management beyond guidance towards postnatal surgical repair in case of an isolated structural abnormality. Literature review indicates that 10-30% of prenatally detected structural abnormalities result from an underlying chromosomal disorder, hence a structural defect in the fetus is an important indication for invasive sampling and fetal karyotyping. The year 2005 saw the use of chromosomal microarray for detection of submicroscopic chromosomal abnormalities also k.a. copy number defects in fetuses with ultrasonic abnormalities and normal karyotype. Microarray was found to have an additional diagnostic yield of 6-10% in such fetuses, thereby enabling decision making regarding pregnancy management. Subsequently, many studies on prenatal as well as stillbirth cohorts, led to establishment of microarray as the first tier test to interrogate genetic aberrations undetectable by karyotype in these clinical settings. However, a combination of karyotype and microarray can identify underlying etiology in only upto 40% cases with ultrasonic abnormalities and are unable to provide a definitive answer in a significant proportion.[1] In such a scenario, majority of patients with fetal ultrasonographic abnormalities are counselled regarding prognosis and management on basis of incomplete and uncertain knowledge of the postnatal phenotype, which may have additional morbidities like intellectual handicap and other functional defects undetectable on prenatal imaging.

### Next Generation Sequencing and Genetic diseases in the fetus

Next generation sequencing is a novel technology which enables reading the sequencing of the entire human genome in a single experiment. The human genome is 3 billion base pairs long, and till the advent of NGS, it was possible to read it in only small segments of 500-5000 base pairs using Sanger sequencing. Sequencing or reading of the DNA sequence enables diagnosis of a specific type of genetic disorders known as Single gene/ Monogenic or Mendelian disorders. Figure 1 depicts the three main categories of genetic disorders and the tests employed to diagnose them. If we look at the postnatal cohort of birth defects, we find that at 25-35% of these are due to genetic etiologies, of which chromosomal abnormalities contribute 10-15%, copy number defects 3-5% and single gene disorders 10-15%. As compared to the multifactorial etiologies, where the prognosis depends on the nature of birth defects perse, in case of a genetic etiology, there are other significant morbidities, the most significant being intellectual handicap. An example is a congenital heart defect, on one hand this can be an isolated defect of multifactorial origin where surgical repair will determine the outcome; whereas

on the other hand, it could be a part of a chromosomal disorder like Down syndrome, or a copy number defect like Di George syndrome or a single gene disorder like Noonan syndrome, all of which are associated with intellectual disability. Similarly, a prenatally detected malformation could be part of a genetic disease, and the technologies of karyotype and microarray enable only diagnosis of the first two categories. Next generation sequencing was utilized the first time for diagnosis of a single gene disease in a fetus with multiple anomalies in the year 2014. Following this, there have been numerous studies reported in literature of NGS based diagnosis for fetal abnormalities. Most of the NGS based testing has been in the form of Exome sequencing, which involves sequencing of only the coding region of the DNA, this constituting 1-2% of the whole genome, but harbouring 80-90% of the disease causing mutations. Figure 2 provides an overview of the technology.

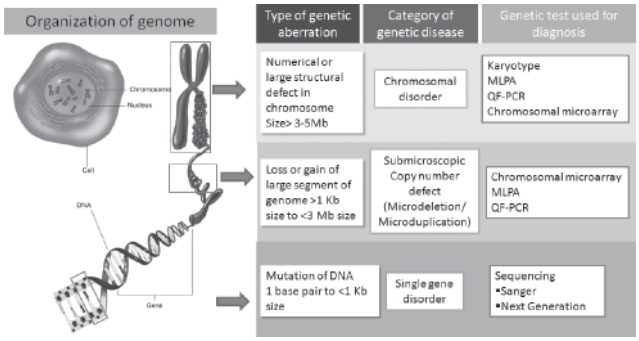


**Fig 1: Genetic Tests for different Genetic diseases**

## Review of Published Literature Reports

The year 2017-2018 witnessed the publication of at least 40 studies of fetal exome sequencing including case reports, three of them from India. Although case reports predominate, there are few larger series which provide more accurate estimates of the diagnostic yield and a brief overview of the same is provided in the following paragraphs.

In the October 2017 issue of Genetics in Medicine, the official publication of the American College of Medical Genetics & Genomics, Yates et al. report a cohort of 84 deceased fetuses with ultrasound abnormalities which underwent exome sequencing [2]. The predominant anomalies were central nervous system defects, hydrops fetalis, cardiac defects and genitourinary abnormalities. Multiple anomalies were present in 52/84 of these fetuses and 68/84 cases were normal on karyotype and/ or chromosomal microarray studies. The phenotyping of these cases was performed using the standard databases like Human Phenotype Ontology, Online Mendelian Inheritance in Man and others, and the variants identified after exome sequencing were interpreted using ACMG variant classification recommendations. The study reported identification of a pathogenic variant in 17/84(20%) cases, a possibly pathogenic variant

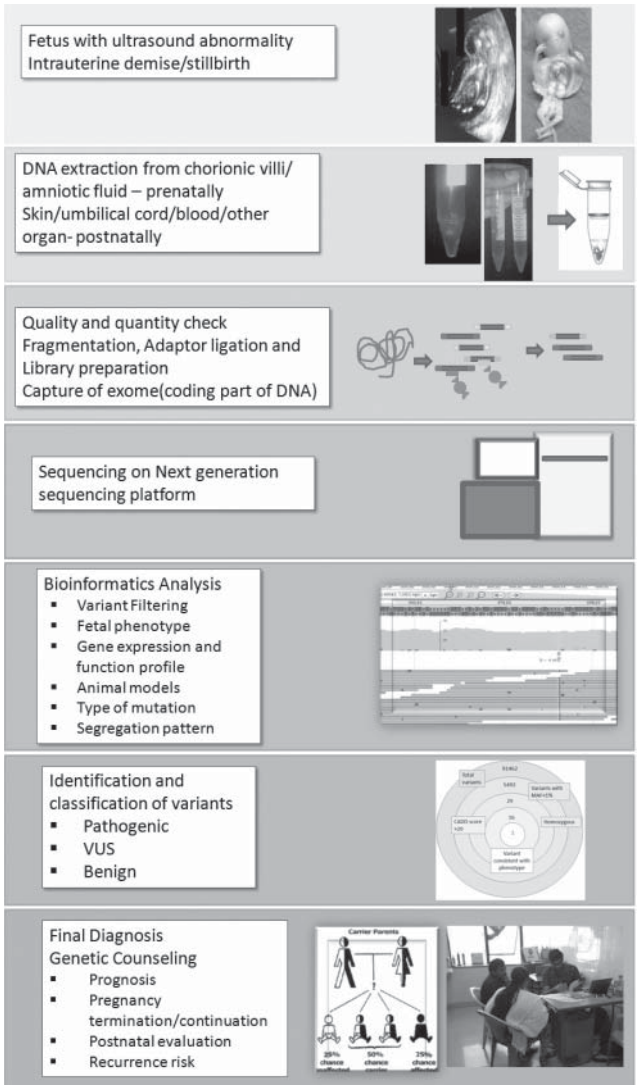


**Fig 2: An Overview of the Technology**

in 38/84(45%) and a novel candidate gene in 7(95) cases. Diagnostic rates were higher(24% vs 14%) in Trios ( sequencing of parents and fetus done together) compared to Solo (only fetal exome sequencing) as this enabled identification of de-novo variants in autosomal dominant & X-linked disorders and confirming familial segregation in autosomal recessive conditions. The authors concluded by saying that exome sequencing in a wide spectrum of fetal abnormalities helps in providing a specific genetic diagnosis in at least 20%, thereby enabling accurate prognostication and management of pregnancy as well as recurrence risk counseling in the family. Additional research benefits involve the identification of prenatal phenotypes of already known single gene disorders and identification of novel genetic etiologies of fetal developmental abnormalities.

Shamseldin et al reported a cohort of 44 deceased fetuses that underwent postmortem evaluation in the online July issue of the same journal [3]. This cohort had structurally normal fetuses also, including those with

unexplained intrauterine demise. This study was based in Saudi Arabia, a country known for higher rates of consanguinity, hence majority of these families (86%), had recurrent abnormalities, suggestive of autosomal recessive inheritance. Exome sequencing was done Solo or as a Duo (only parental sequencing when fetal DNA was not available). These authors reported a pathogenic or likely pathogenic variants in 22/44(50%) cases and novel candidate genes in an additional 14 cases. The authors suggested the role of a molecular autopsy using exome sequencing in addition to conventional autopsy in cases with fetal demise/termination or in lieu of the latter if it is not possible.

In another study of a smaller cohort of 15 fetsues by Vora et al. a diagnostic yield of 47% was reported [4]. A large study by Fu et al. from China included 196 fetuses with structural abnormalities and normal karyotypes and chromosomal microarray[5]. 47/196(24%) were found to have phenotype related pathogenic variants on exome sequencing. Diagnostic yield was higher in cases with multiple malformations (30%), skeletal abnormalities(30%) and cases where trio exomes were done (26%). Fetuses with central nervous system defects, genitourinary abnormalities, or craniofacial abnormalities had a 23% prevalence of a pathogenic variant. The cohort had predominance of autosomal dominant diseases. This same study also provides a relative contribution of 18.2% for karyotype and 8.2% for chromosomal microarray in a larger cohort of fetuses with similar abnormalities, indicating an overall higher contribution of Monogenic disorders as a group relative to the other two categories of genetic diseases[5]. Many other studies including those prior to 2017 also indicate an overall diagnostic yield of 10-57% in fetal cohorts[1].

Studies from India have been scarce, however many groups are working on evaluating the utility of exome sequencing in fetal cohorts. A report by Singh et al revealed a homozygous variant in *TRIM36* as cause of autosomal recessive anencepahly in an Indian family[6]. Our group has also reported two separate cases of fetuses undergoing autopsy, which were found to have complex phenotypes indicative of a single gene disorder. In one fetus, exome sequencing revealed a blended/dual Mendelian phenotype of Marfan and Beals syndrome due to pathogenic mutations in *FBN1* and *FBN2* genes[7]. In the other family, recurrent corpus callosum agenesis was found to be due to homozygous variants in *EPG5* gene[8]. Our preliminary analysis indicates a high diagnostic yield for exome sequencing with 11/14(79%) cases in our fetal cohort revealing a pathogenic variant. An important limitation in use of exome sequencing for prenatal testing arises due to the difficulty in bioinformatics analysis in view of the incomplete phenotype. This accounts for the wide variability in the diagnostic yields in different studies and our analysis also reveals that in at least 3 cases, the exome results would have come as negative had the autopsy phenotype not been available.

Besides incomplete phenotypic information, other problems with routine use of this technology for prenatal diagnosis at present are the cost and turn-around times. With rapid advancements in technology, both these aspects are evolving and becoming favourable. At present, the cost for a targeted exome sequencing ranges from Rs 20-40,000 and the turnaround time from 3-6 weeks. As compared to chromosomal microarray which has a cost of Rs 12-30,000/ and a much lower diagnostic yield and similar turnaround times, exome sequencing appears to be developing as a more useful testing modality for prenatal diagnosis in pregnancies with structural fetal defects or other specific phenotypes.

Another major limitation of this new technology is inherent in its nature of being a genome wide approach. The sequencing of the whole coding region of the genome typically yields some 80-90000 variants in different genes. Only 1-2 of these are likely to be related to the fetal phenotype. In such a scenario, bioinformatics analysis by a laboratory geneticist well versed with NGS data analysis pipelines in conjunction with a clinical geneticist with expertise in fetal dysmorphology is imperative to identify the correct pathogenic variant. In many instances, despite this, the identified variant cannot be correctly identified as pathogenic or benign, and is labelled a Variant of unknown significance(VUS). This raises dilemmas in the prenatal period for prognostication and counseling of the couple. Also, in many instances, pathogenic variants unrelated to fetal phenotypes(secondary findings) or other findings like non-paternity, carrier status for recessive diseases, etc. (incidental findings) may be revealed, which raise ethical concerns regarding disclosure vs non-disclosure and counseling[1,9].

## Professional Societies' Guidelines

Considering all these complex technical and counseling issues involved in this emerging technology, ACOG committee in 2016 December had indicated that NGS based testing in the prenatal setting should be limited to Clinical trials and if performed otherwise should be in consultation with a clinical geneticist[10]. Following the publication of several studies in 2017, ***International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) have released a Joint Position of Statement on use of genome wide sequencing for fetal diagnosis in January 2018[11].*** The statement indicates that "Routine use of prenatal sequencing as a diagnostic test cannot currently be supported due to insufficient validation data and knowledge about its benefits and pitfalls. Currently, it is ideally done in the setting of a research protocol. Alternatively, sequencing may be performed outside a

research setting on a case-by-case basis when a genetic disorder is suspected for which a confirmatory genetic diagnosis can be obtained more quickly and accurately by sequencing. Such cases should be managed after consultation with and under the expert guidance of genetic professionals working in multidisciplinary teams with expertise in the clinical diagnostic application of sequencing, including interpretation of genomic sequencing results and how they translate to the prenatal setting, as well as expertise in prenatal imaging and counseling." The statement also indicates the need for pre and post- test genetic counseling and informed consent prior to use of this technique[11].

### Other uses of Next generation sequencing in Reproductive Medicine

Non-invasive prenatal testing from maternal plasma is an NGS based test which is clinically available and recommended as a high performance screening test for fetal aneuploidies. Other potential uses of NGS based testing are in the setting of hypogonadism/infertility, genitourinary malformations, unexplained recurrent pregnancy losses or neonatal deaths, carrier testing for autosomal recessive conditions, and many others. A multi-disciplinary team involving the OBG practitioner and the clinical geneticist is imperative to enable optimum utilization of this novel technology in practice.

## Conclusion

Next generation sequencing is a novel and powerful technology that is emerging as a modality to interrogate fetal genetic abnormalities and is likely to change the paradigms of prenatal diagnostic testing in the years to come.

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**Disclosure:** Part of Figure 1 has been adapted from the National Institutes of Health Website(URL: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0025047)

## Calendar of Monthly Clinical Meetings 2017-2018

| Months | Name of the Institute |
|---|---|
| 23rd April 2018 | Apollo Hospital, Sarita Vihar |
| May 2018 | DDU Hospital |

# WHO Recommendations: Intrapartum care for a positive childbirth experience (2018)

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Childbirth is a physiological process that can be accomplished without complications for the majority of women and babies. The majority of approximately 140 million births that occur globally are low risk. Nevertheless, the time of birth is critical to the survival of women and their babies, as the risk of morbidity and mortality could increase considerably if complications arise.

With increasing institutional deliveries over the last two decades, there has been substantial increase in the application of a range of labour practices to initiate, accelerate, terminate, regulate or monitor the physiological process of labour, with the aim of improving maternal and neonatal. This increasing medicalization of childbirth processes tends to undermine the woman's own capability to give birth and negatively impacts her childbirth experience. In addition, the increasing use of labour interventions in the absence of clear indications continues to widen the health equity gap between high- and low-resource settings.

Considering the lacunae in existing practices of intrapartum care, World Health organization issued new guidelines in 2018 "WHO recommendations: Intrapartum care for a positive childbirth experience" which advances a woman-centered and human-rights-based-approach to labor and childbirth. Consistent with the recent ANC guideline, the document highlights every woman's right to a "positive childbirth experience," or one that "fulfils or exceeds a woman's prior personal and sociocultural beliefs and expectations, including giving birth to a healthy baby in a clinically and psychologically safe environment with continuity of practical and emotional support from a birth companion(s) and kind, technically competent clinical staff." Furthermore, the guideline seeks to identify the most common practices used throughout labor to establish norms of good practice for uncomplicated labor and childbirth—while clarifying that "the concept of 'normality' in labor and childbirth is not universal or standardized." It is based on the premise that most women want a physiological labour and birth, and to have a sense of personal achievement and control through involvement in decision-making, even when medical interventions are needed or wanted.

This up-to-date, comprehensive and consolidated guideline on essential intrapartum care brings together new and existing World Health Organization (WHO) recommendations that, when delivered as a package, will ensure good-quality and evidence-based care irrespective of the setting or level of health care. The recommendations presented in this guideline are neither country nor region specific and acknowledge the variations that exist globally as to the level of available health services within and between countries. It introduces a global model of intrapartum care which takes into account the complexity and diverse nature of prevailing models of care and contemporary practice.

The new WHO guideline includes **evidence from 17 Cochrane Reviews** and has 56 evidence-based recommendations on what care is needed throughout labour and immediately after for the woman and her baby. Out of these recommendations, 26 are newly developed recommendations and 30 are recommendations integrated from existing WHO guidelines. Recommendations are presented according to the intrapartum care context to which they are relevant namely, care throughout labour and birth, care during the first stage of labour, care during the second stage of labour, care during the third stage of labour, immediate care of the newborn, and immediate care of the woman after birth. Each recommendation is classified into categories of Recommended, Not Recommended, recommended only in specific contexts or only in the context of rigorous research.

## Recommendations

### Care throughout Labour and Birth

Every women in labour should receive ***Respectful Maternity Care*** maintaining their dignty, privacy and confidentiality. There should not be any harm or mistreatment. They should be enabled to make informed choices. It also recommends Interventions aiming to ensure a respectful and dignified working environment for those providing care. Staff should be respectful, encouraging and supportive to the emotional needs of the women. There should be effective communication. Privacy should be maintained. ***A companion of choice is recommended for all women throughout labour and childbirth.*** The companion in this context can be any person chosen by the woman to provide her with continuous support during labour and childbirth. This may be someone from the woman's family or

social network, such as her spouse/partner, a female friend or relative, a community member (such as a female community leader, health worker or traditional birth attendant) or a doula (i.e. a woman who has been trained in labour support but is not part of the health care facility's professional staff). Evidence for this recommendation was derived from a Cochrane systematic review of 26 trials involving 15 858 women.[1] The quantitative evidence on the effectiveness of labour companionship suggests that labour companionship can reduce caesarean section by 25%, instrumental vaginal birth by 10% and the use of pain relief by 10%. There is also evidence of short labour duration, less post partum depression and positive birth experience.

## First Stage of Labour

### Latent & Active Stage

*The transition from latent to active first stage of labour has been defined to occur at* ***5 cm of cervical dilatation****.* Evidence on the definitions of onset of latent and active phases of the first stage of labour was derived from three systematic reviews.[2,3,4] It is also recommended that *Women should be informed that a standard duration of the latent first stage has not been established and can vary widely from one woman to another. However, the duration of active first stage (from 5 cm until full cervical dilatation) usually does not extend beyond* ***12 hours in first labours****, and usually does not extend beyond* ***10 hours in subsequent labours****.* Evidence was derived from a systematic review of 37 studies evaluating the duration of spontaneous labour in women without risk factors for complications.[3] The GDG emphasized that the decision to intervene when the first stage of labour appears to be prolonged must not be taken on the basis of duration alone.

### Partograph (Alert Line)

*For pregnant women with spontaneous labour onset, the cervical dilatation rate threshold of* ***1 cm/hour during active first stage (as depicted by the partograph alert line) is inaccurate*** *to identify women at risk of adverse birth outcomes and is therefore not recommended for this purpose.* It is observed that there is insufficient evidence to support the use of the alert line as a classifier to detect women at risk of adverse birth outcomes. In hospital settings the use of the alert line and attempts to maintain cervical dilatation progression of 1 cm/ hour lead to unnecessary interventions due to the perception that labour progress is pathologically slow. Women with suspected slow labour progress should be carefully evaluated to exclude developing complications (e.g. cephalo-pelvic disproportion) and to determine whether their emotional, psychological and physical needs in labour are being met. Considering that preset lines on cervicograph are only one element of the existing WHO partograph, it is still recommended to continue plotting on WHO partographs to monitor the well-being of the woman and her baby and identify risks for adverse birth outcomes. In facilities where referral level facilities are not available, alert line should still be used for triaging women for additional care and referral, but in this plotting should commence from a cervical dilatation of 5 cm, which signifies the onset of active first stage of labour for most women.

*It is recommended not to intervene only for cervical dilatation slower than 1 cm/hour. Also labour may not naturally accelerate until a cervical dilatation threshold of 5 cm is reached. medical interventions to accelerate labour and birth (such as oxytocin augmentation or caesarean section) before 5 cm cervical dilatation (active Phase) is not recommended, provided fetal and maternal conditions are reassuring.* These recommendations aim to prevent iatrogenic adverse maternal and perinatal outcomes by minimizing unnecessary medical interventions, and to improve maternal birth experience. These are based on evidence from a systematic review[4] showing many women experiencing progression slower than 1 cm/ hour for the most part of their labours and yet still achieving vaginal birth with normal birth outcomes.

### Labour room admission

Until further evidence becomes available, a woman presenting to facilities in labour should be admitted and supported appropriately, even when in early labour, unless her preference is to await active labour at home. *Delaying labour ward admission until active first stage is recommended only in the context of rigorous research. R*outine clinical pelvimetry in healthy pregnant women on admission in labour may increase caesarean section without a clear benefit for birth outcomes, so it is not recommended. Also cardiotocography (CTG) on admission in labour is not recommended as it increases the risk of caesarean section without improving birth outcomes. And it also increases other interventions like continuous CTG monitoring and Fetal blood sampling which may negatively impact a woman's childbirth experience. Perineal shaving and enema at admission are also not recommended.

### Monitoring during Labour

*Digital vaginal examination at intervals of* ***four hours*** *is recommended for routine assessment of active first stage of labour* in low-risk women based on consensus reached by the GDG as there is currently no direct evidence on the most appropriate frequency of vaginal examinations to prevent infectious morbidity in the mother and baby.

Continuous cardiotocography is not recommended for assessment of fetal well-being in healthy pregnant women undergoing spontaneous labour. GDG placed its emphasis on evidence that suggests that continuous CTG increases caesarean section and other medical interventions, without being cost effective, and with varying acceptability and feasibility. Continuous CTG increases interventions including cesareans without any

benefit and can restrict other beneficial interventions during labour, such as having a choice of labour and birth positions, and being able to walk around freely, and can be stressful for women.

Countries with high perinatal mortality should consider how the coverage and documentation of intermittent auscultation (IA) could be improved. *Fetal heart rate monitoring is recommended with intermittent auscultation with either Doppler or Fetal Stethoscope, every 15–30 minutes in active first stage of labour, and every 5 minutes in the second stage of labour. Each auscultation should last for at least 1 minute; if the FHR is not always in the normal range (i.e. 110–160 bpm), auscultation should be prolonged to cover at least three uterine contractions.* Fetal heart should be auscultated during a uterine contraction and continue for at least 30 seconds after the contraction. Baseline FHR and the presence or absence of accelerations and decelerations should be recorded.

**Pain Relief:**

**For** pain relief (if requested) *epidural analgesia with lowest possible effective concentration of local anaesthetic* is recommended. *Parenteral opioids such as fentanyl*, diamorphine and pethidine are also effective choices but have some undesirable side-effects, such as drowsiness, nausea and vomiting. Pethidine is not the preferred opioid option as as shorter-acting opioids tend to have fewer undesirable side-effects. *Relaxation techniques*, including progressive muscle relaxation, breathing, music, mindfulness and other techniques and *Manual techniques*, such as massage or application of warm packs are also recommended for labour pain relief depending on woman's preferences.

**Interventions to prevent delay**

Early amniotomy alone or in combination with oxytocin augmentation, active management of first stage of labour, intravenous fluids – all interventions to shorten labour duration, are found to be unnecessary interventions and thus not recommended.

## Second Stage of labour

Onset of the second stage of labour in clinical practice is often not precisely known. Though duration of second stage is variable, *standard duration considered is **3 hours in first labour** and **2 hours in subsequent ones**.* A decision about curtailing the second stage of labour should be based on surveillance of the maternal and fetal condition, and on the progress of labour. Interventions to expedite childbirth are to be considered once has extended beyond standard durations as chances of spontaneous delivery within a reasonable time decreases.

*Encouraging the adoption of **a birth position of the individual woman's choice**, including upright positions, is recommended*. There is no difference in most birth outcomes according to birth positions even if epidural analgesia is used. Having a choice of birth positions during the second stage of labour might positively impact maternal birth experience and improve equity. The health care professional should ensure that the well-being of the baby can be adequately monitored in the woman's chosen position.

Women should be should be encouraged and supported *to follow their own urge to push during the expulsive phase of the second stage.*

For women with epidural analgesia in the second stage of labour, *delaying pushing for one to two hours after full dilatation or until the woman regains the sensory urge to bear down is recommended* in the context where resources are available for longer stay in second stage and perinatal hypoxia can be adequately assessed and managed.

*Techniques to reduce perineal trauma and facilitate spontaneous birth* (including perineal massage, warm compresses and a "hands on" guarding of the perineum) are recommended during second stage based on available options and woman's preferences.

***Practices of routine use of episiotomy and manual fundal pressure are not recommended***. Fundal pressure can be potentially harmful for both the mother and the baby.

## Third stage of labour

*The use of uterotonics for the prevention of postpartum haemorrhage (PPH) during the third stage of labour is recommended for all births and **Oxytocin (10 IU, IM/IV)** is the recommended uterotonic drug.* In settings where oxytocin is unavailable, the use of other injectable uterotonics (if appropriate, ergometrine/methylergometrine, or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol (600 μg) is recommended.

Delayed umbilical cord clamping (not earlier than 1 minute after birth) is recommended for improved maternal and infant health and nutrition outcomes. Controlled Cord Traction is recommended in settings where skilled birth attendants are available. Sustained uterine massage is not recommended as an intervention to prevent postpartum haemorrhage (PPH) in women who have received prophylactic oxytocin. The GDG considered that Active Management of Third Stage package has a primary intervention: the use of a uterotonic.[5] In the context of oxytocin use, CCT may add a small benefit, while uterine massage may add no benefit for the prevention of PPH. Early cord clamping is generally contraindicated.

## Newborn Care

Newborns without complications should be kept in skin-to-skin contact ***(SSC) with their mothersduring***

***the first hour after birth*** to prevent hypothermia and promote breastfeeding. All newborns who are able to breastfeed, *should be put to the breast as soon as possible after birth when they are clinically stable, and the mother and baby are ready*. Newborns should be given *1 mg of vitamin K intramuscularly* after birth (after first hour). *Bathing should be delayed until 24 hours after birth.* Baby should be adequately clothed and the mother and baby should not be separated and should stay in the same room 24 hours a day.

## Care of the woman after birth

***Postpartum abdominal uterine tonus assessment*** for early identification of uterine atony is recommended. Routine antibiotics even in deliveries with episitomy are not recommended.

All postpartum women should have regular assessment of vaginal bleeding, uterine contraction, fundal height, temperature and heart rate (pulse) routinely during the ***first 24 hours*** starting from the first hour after birth. Blood pressure should be measured shortly after birth. If normal, the second blood pressure measurement should be taken within six hours. Urine void should be documented within six hours. After an uncomplicated vaginal birth in a health care facility, healthy mothers and newborns should receive care in the facility for at least 24 hours after birth.

The aim of this guideline is to improve the quality of essential intrapartum care with the ultimate goal of improving maternal, fetal and newborn outcomes. To optimize the potential of the new model and ensure that all women receive evidence based, equitable and good-quality intrapartum care in health care facilities, these recommendations should be implemented as a package of care in all facility-based settings, by kind, competent and motivated health care professionals who have access to the essential physical resources. Health systems should aim to implement this model of care to empower all women to access the type of individualized care that they want and need, and to provide a sound foundation for such care, in accordance with a human rights-based approach.

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# Announcement

21st Practical Course and CME organized by Department of Obstetrics and Gynecology, MAMC to be held at Maulana Azad Medical College Auditorium from 7th to 9th September, 2018. For details contact Dr Deepti Goswami, 9968604348 / Dr Sangeeta Bhasin 9873617591

# Events Held in March 2018

- Health Camp under aegis of AOGD on 08th March 2018 at community centre, Ghazipur Village, Delhi, under the able guidance of Dr Richa Sharma, Dept of Obs & Gynae & Dr Anita Gupta, Dept. of Community Medicine, UCMS & GTBH



- FOGsd under the dynamic leadership of Dr Anita Sabharwal celebrated Women's Day & conducted a CME on 08th March 2018 on Gynecological Cancer


- Awareness Programme for Adolescent Girls under aegis of AOGD on 20th March 2018 at Sanskar Ashram, Delhi, under the leadership of Dr Richa Sharma, Dept of Obs & Gynae UCMS & GTBH



- AOGD Monthly Clinical Meeting & GBM on Friday, 23rd March 2018 at UCMS & GTB Hospital, New Delhi


- Handover of AOGD Ofiice & Felicitation of New Office Bearers




- Handover of AOGD Office & Felicitation of New AOGD sub – committee Chairpersons




# DR DASH'S 'HANDS ON' COURSE ON

## BASIC AND ADVANCED GYNAE LAPAROSCOPIC & HYSTEROSCOPIC SURGERY

**Course Highlights:**

- Focused hands on training on creating pneumoperitoneum, port placement
- Orientation and hands on to basic and advanced laparoscopic and hysteroscopic surgeries
- Hands on Pelvi-trainer

**Proposed Schedule:**
26th-31st March & 21st-26th May, 2018

**8:00 am to 12:00 pm**

- Live surgery 2-3 cases every day
- Diagnostic laparoscopy and hysteroscopy
- Hysteroscopic polypectomy & septal resection
- Total laparoscopic hysterectomy
- Laparoscopic myomectomy
- Laparoscopic adhesiolysis (depending upon availability of cases)

**8:00 am to 12:00 pm**

- Interactive lectures on laparoscopic instruments & energy sources
- Video sessions discussing critical steps of surgery, managing bleeders, dealing with complications

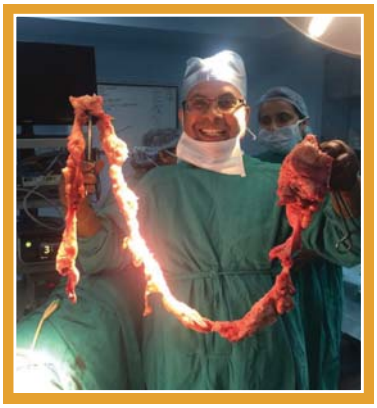
**3:00 pm to 5:00 pm**

- Pelvic trainer exercises including hand-eye coordination
- Laparoscopic suturing & knot tying

**Registration fee: INR 29,000/-**
**Secretariat / Correspondence:**

**REJOICE FERTILITY & GYNAE ENDOSCOPY CLINIC**
**A-28, South Extension Part-II, New Delhi-110049**
**Ph- 011-26261352, 9212397781**
**Website: www.gynelaparoscopy.in, Email- bishulee@gmail.com**

**FACULTIES:**
**Dr B B Dash, Dr Sonia Chawla**



**Organised By:** Rejoice Clinic and Sukhmani Hospital, New Delhi

# Embryo Transfer: Myths & Facts

**Sunita Arora[1], Hrishikesh Pai[2], Nandita Palshetkar[2]**
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[2]Director, Bloom IVF Centres

Embryo transfer is one of the most critical steps in process of In Vitro Fertilization. After excluding confounding factors like embryo quality, good technique and clinical expertise is a decisive factor in the success rate of Embryo transfer.

The present article incorporates the **ASRM guidelines 2017** for recommendation regarding the various issues and controversies for Embryo Transfer. These guidelines were based on systematic review of literature. The present article discusses the role of patient preparation, acupuncture, relaxants, Sedation, Prophylactic antibiotics, role of transabdominal USG during embryo transfer, presence of endocervical mucus and its correlation with pregnancy and live birth rates. Type of catheter, positioning of catheter, blood on catheter tip, retained embryos, bed rest after embryo transfer are also discussed.

**Acupuncture:** This has been the focus of significant interest and research and an important tradition in Chinese medicine. A number of randomized control trials have been published with varying results. But Systematic reviews and meta analyses failed to show any significant improvement in clinical pregnancy rate with acupuncture.[1]

**Conclusion:** There is fair evidence that acupuncture performed at the time of embryo transfer does not improve live birth rates in IVF (Grade B)

**Analgesic use and Embryo Transfer**: No relevant studies were found.

***Conclusion:*** There is insufficient evidence to recommend for or against analgesics to improve IVF-Embryo transfer outcomes. (Grade C)

**Anaesthesia:** Two large cohort studies found no added benefit of embryo transfer under anaesthesia

***Conclusion*:** There is no clear benefit, rather there are inherent risks associated with anesthesia, routine anesthesia is not recommended to improve IVF-Embryo transfer outcomes. (Grade C)

## Massage Therapy

Single retrospective observational study analysis which studied effects of massage therapy in cryopreserved cycles and demonstrated improved pregnancy rates and live birth rates with massage therapy in cryopreserved cycles.[2]

***Conclusion**:* There is insufficient evidence to recommend for or against massage therapy to improve IVF-Embryo transfer outcomes.

## Trans-cutaneous Electrical Acupoint Stimulation

Only one RCT is available which studied the effect of transcutaneous electrical acupoint stimulation (TEAS) on embryo transfer.[3] Live birth rates and clinical pregnancy rates increased significantly in patients who received TEAS on day of Embryo Transfer. The clinical pregnancy rate was 29.3% with mock TEAS vs 42.7% with single TEAS. Live birth rate was 21.2% with mock TEAS vs 37.3% with single TEAS.

***Conclusion:*** There is fair evidence based on only one RCT that TEAS improves IVF-Embryo transfer outcomes. (Grade B)

However, due to lack of any other study, a recommendation for or against TEAS to improve IVF-ET outcomes cannot be made.

## Use of Prophylactic Antibiotics

Only one RCT which found that the antibiotics significantly reduced catheter contamination rates, but the clinical pregnancy rates were no different.

***Conclusion*:** There is fair evidence based on single RCT that an antibiotic regimen which includes amoxicillin and clavulanic acid given on the day before and the day of embryo transfer does not improve pregnancy rates. (Grade B)

## Physician preparation, use of latex free gloves:

One RCT conducted on 712 women didn't found any difference in the IVF pregnancy rates with use of powdered gloves as compared to unpowdered gloves use.

**Conclusion:** There is fair evidence based on one single center RCT that powdered gloves worn during embryo transfer do not have an adverse effect on pregnancy rates (Group B)

No specific type of glove is recommended for embryo transfer.

## Routine use of abdominal ultrasound for guidance during embryo transfer

Ten RCTs and various cohort studies concluded that transabdominal ultrasound guided embryo transfer was found to improve implantation rates and pregnancy rates.[4,5] One study found that Transvaginal guidance improved patient comfort relative to transabdominal scan.

**Conclusion**: There is good evidence based on 10 RCTS to recommend transabdominal ultrasound guidance during embryo transfer to improve clinical pregnancy rates and live birth rate (Grade A)

## Role of removing mucus from endocervical canal prior to embryo transfer

studies have found better clinical outcome if mucus is removed with swab or catheter aspiration before ET.[6]

**Conclusion:** There is fair evidence based on one RCT and one prospective cohort study that there is benefit of removing cervical mucus at the time of embryo transfer to improve clinical pregnancy and live birth rates.(Grade B)

## Does the type of catheter used for embryo transfer affect pregnancy and live birth rates.

A meta analysis by ASRM practice committee showed that pregnancy rates were higher with use of soft catheters for ET as compared to firm ones.

10 RCTs and 1 cohort studies showed no difference in IVF outcomes when they compared different types of soft catheters.

***Conclusions:*** There is good evidence to recommend the use of soft embryo transfer catheter to improve IVF-embryo transfer pregnancy rates (Grade A) Data on live birth rates and specific types of soft catheters are limited.

## Positioning of catheter at time of embryo transfer and effect on implantation, pregnancy and live birth rates

Different RCTs studied embryo placement distance from fundus and outcomes. Statistically significant higher implantation rates were found with embryo placement 1.5, 2.0 cm from fundus compared with 1cm. It found statistically significant higher implantation rates for placements farther than fundus.[7] Few studies found no difference in implantation rates and pregnancy rates. Placement of outer catheter is also compared in different studies. Overall pregnancy rates were better[8] for whom outer sheath did not cross internal Os (57.3%) as compared to patients where outer catheter crossed internal os (43.1%)

**Conclusions:** There is a fair evidence that embryo transfer placement affects implantation and pregnancy rates (Grade B). There is fair evidence based on several RCTs that placement of catheter tip in upper or middle area of uterine cavity ,greater than 1 cm from fundus, optimizes pregnancy rates (Grade B)

## Time interval between embryo placement and withdrawl of catheter

There are studies which compared immediate withdrawal, withdrawl in 30 seconds, withdrawl at 60 seconds and did not find any significant difference.

***Conclusions:*** There is fair evidence to recommend immediate withdrawl of embryo transfer catheter after embryo expulsion(Grade B)

## Presence of blood on catheter tip and (once it is withdrawn) and correlation with pregnancy and live birth rates.

Total of 17 RCTs were evaluated. None of the studies demonstrated significant difference in outcomes if catheter tip was blood stained. A large cohort study from Australian data base also demonstrated no significant difference on clinical pregnancy rates based on catheter tip contamination.[9] While other cohort studies reported decreased clinical pregnancy rates with presence of blood on catheter.

***Conclusions*** There is insufficient evidence to state that presence of blood or mucus on the catheter, once it is withdrawn, is associated with implantation or pregnancy rates(Grade C).

## Correlation between injection speed at embryo transfer and live birth rates

Few studies suggested that injection velocity of embryos could impact impact implantation rate and risk of ectopic pregnancy, but there are no RCTs

**Conclusions** Due to paucity of data there is insufficient evidence to recommend any specific injection speed at the time of embryo transfer(Grade C)

## Correlation between retained embryos in transfer catheter and immediate re-transfer and pregnancy outcomes

Incidence of retained embryos varies between 5% -10% in different studies. In various cohort and one RCT studies, clinical outcome of implantation, clinical pregnancy and spontaneous abortion rates were statistically not different between 2 groups (no retained embryos Vs retransfer after retained embryos).

***Conclusions:*** There is fair evidence based on RCTs to suggest that retained embryos in transfer catheter and immediate retransfer do not affect implantation, clinical pregnancy and spontaneous abortion rates(Grade B)

## Does bed rest or ambulation after IVF-embryo transfer affect pregnancy rates and live birth rates

14 studies included in systematic review[10] and none of these studies demonstrated a benefit of bed rest of any duration. Additional RCTs also didn't show any benefit.

**Conclusions** There is good evidence not to recommend bed rest after embryo transfer (Grade A)

# Recommendations

The following interventions are supported by the

literature for improving pregnancy rates:

- Abdominal ultrasound guidance for embryo transfer
- Removal of cervical mucus
- Use of soft embryo transfer catheters
- Placement of embryo transfer tip in the upper or middle (central) area of the uterine cavity, greater than 1 cm from the fundus, for embryo expulsion
- Immediate ambulation once the embryo transfer procedure is completed

The following interventions have been shown not to be beneficial for improving pregnancy rates:

- Acupuncture
- Analgesics, massage, general anesthesia, whole systems–traditional Chinese medicine
- Prophylactic antibiotics to improve embryo transfer outcomes
- Waiting after expulsion of embryos for any specific period of time before withdrawing the embryo transfer catheter

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## Answer Key to Quiz in March Issue

**Q1. A)** T, **B)** F, **C)** F, **D)** T, **E)** T, **F)** F

**Q2. A)** 6 weeks, **B)** UTI, carcinoma, calculus, **C)** Hunner's ulcer **D)** Sodium pentosan polysulphate, **E)** Carnett's sign

**Q3. A)** F, **B)** F, **C)** T, **D)** T, **E)** F

**Q4.** A, **Q5.** A, **Q6.** March 8, **Q7.** Ultrasound

**Q8.** Laparoscopic approach & detorsion of ovary/ adnexa

**Q9. ERAS-** enhanced recovery after surgical protocols
**ISSVD-** International society of the study of vulvovaginal diseases
**ESSIC-** European society for the study of interstitial cystitis

**Q 10.** A

# Cascade Testing: Testing women for known genetic mutations associated with cancer

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A relatively new concept, cascade testing, also referred to as cascade screening is genetic counselling and testing of blood relatives of individuals known to have specific genetic mutations. Here the concerned individuals being tested are those who do not have the disease. Usually they are the ones who are referred from a health facility with a report of their blood relative being affected by a particular genetic mutation and the cancer thereafter for further counselling and testing and thus assessment of their cancer risk. If there is a positive family history or diagnosis of cancer but the affected individual has not undergone genetic testing, then the person being referred for the same will not be considered for cascade testing.

Eligibility for genetic testing should be known to the treating physician so that the available resources are used to the fullest and maximum women are benefitted. Obstetricians and gynaecologists are usually the first contact of these women and may play an important role in identifying high risk women with hereditary cancer syndromes. Certain genetic mutations like BRCA1 and 2 as well as mutations in DNA mismatch repair genes like MLH1, MSH2 etc in hereditary breast ovarian cancer syndromes and Lynch syndrome respectively are being increasingly identified in women and thus comes the role of cascade testing. Women with germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, associated with Hereditary Breast & Ovarian Cancer syndrome, have up to an 85% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian, tubal, and peritoneal cancers. Similarly, women with mutations in the DNA mismatch repair genes, MLH1, MSH2, MSH6, or PMS2, associated with the Lynch/ Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, have up to a 40-60% lifetime risk of both endometrial and colorectal cancers as well as a 9-12% lifetime risk of ovarian cancer. Mutations in other genes including TP53, PTEN, and STK11 are responsible for hereditary syndromes associated with gynecologic, breast, and other cancers. Evaluation of the likelihood of a patient having one of these gynecologic cancer predisposition syndromes enables physicians to provide individualized assessments of cancer risk, as well as the opportunity to provide tailored screening and prevention strategies such as surveillance, chemoprevention, and prophylactic surgery that may reduce the morbidity and mortality associated with these syndromes. CDC has listed ***Hereditary Breast -Ovarian Cancer Syndrome*** and ***Lynch Syndrome*** as high priority syndromes for cascade testing. The treating personnel should be aware of the educational programs for the patients, their families and also for the health care providers, should help increase access to genetic counselling and testing and participate in cancer registries for to and fro information.

## Protocol

Letter of documentation of a relative having a specific mutation
↓
Pre test genetic counselling either by a trained gynecologist or a genetic counsellor or an oncologist about the risks, limitations and benefits
↓
Counsel about the possible outcomes of the test
↓
If decision for testing is agreed upon order the specific test
↓
Post test counselling with the result.
↓
Recommend testing and preventive services.

Disclosure to the family is an ethical issue and women should be counselled and encouraged to do the same.

## Advantages

1. Cost effective because testing for a particular gene mutation is less expensive than whole gene sequencing.
2. Increased access to screening allows relatives of tested patients who lack a particular mutation to exit further screening protocols and avoid undue interventions.

## Barriers to Cascade Testing

1. Genetic testing is not always completed for the index patient.
2. The index patient may or may not be able to divulge the necessary details to the family due to emotional and physical constraints
3. The index patient may be estranged from the family.
4. The lack of insurance could be a potential barrier in seeking further screening and follow up treatments

## Conclusion

The health care provider should be aware of the importance of cascade testing and more importantly whom to offer and the appropriate timing of the same. Cascade screening can go a long way in decreasing the cancer related morbidity and mortality.

## Suggested Reading


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# PORTEC 3 Trial: A critical review

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## Abstract

### Background

Although women with endometrial cancer generally have a favourable prognosis, those with high-risk disease features are at increased risk of recurrence. The PORTEC-3 trial was initiated to investigate the benefit of adjuvant chemotherapy during and after radiotherapy (chemoradiotherapy) versus pelvic radiotherapy alone for women with high-risk endometrial cancer.

### Methods

PORTEC-3 was an open-label, international, randomised, phase 3 trial involving 103 centres in six clinical trials collaborating in the Gynaecological Cancer Intergroup. Eligible women had high-risk endometrial cancer with FIGO 2009 stage I, endometrioid-type grade 3 with deep myometrial invasion or lymph-vascular space invasion (or both), endometrioid-type stage II or III, or stage I to III with serous or clear cell histology. Women were randomly assigned (1:1) to receive radiotherapy alone (48·6 Gy in 1·8 Gy fractions given on 5 days per week) or radiotherapy and chemotherapy (consisting of two cycles of cisplatin 50 mg/m2 given during radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m2) using a biased-coin minimization procedure with stratification for participating centre, lymphadenectomy, stage of cancer, and histological type. The co-primary endpoints were overall survival and failure-free survival. We used the Kaplan-Meier method, log-rank test, and Cox regression analysis for final analysis by intention to treat and adjusted for stratification factors. The study was closed on Dec 20, 2013, after achieving complete accrual; follow-up is ongoing. PORTEC-3 is registered with ISRCTN, number ISRCTN14387080, and ClinicalTrials.gov, number NCT00411138.

### Results

686 women were enrolled between Nov 23, 2006, and Dec 20, 2013. 660 eligible patients were included in the final analysis, of whom 330 were assigned to chemoradiotherapy and 330 were assigned to radiotherapy. Median follow-up was 60·2 months (IQR 48·1-73·1). 5-year overall survival was 81·8% (95% CI 77·5-86·2) with chemoradiotherapy versus 76·7% (72·1-81·6) with radiotherapy (adjusted hazard ratio [HR] 0·76, 95% CI 0·54-1·06; p=0·11); 5-year failure-free survival was 75·5% (95% CI 70·3-79·9) versus 68·6% (63·1-73·4; HR 0·71, 95% CI 0·53-0·95; p=0·022). Grade 3 or worse adverse events during treatment occurred in 198 (60%) of 330 who received chemoradiotherapy versus 41 (12%) of 330 patients who received radiotherapy (p<0·0001). Neuropathy (grade 2 or worse) persisted significantly more often after chemoradiotherapy than after radiotherapy (20 [8%] women vs one [1%] at 3 years; p<0·0001). Most deaths were due to endometrial cancer; in four patients (two in each group), the cause of death was uncertain. One death in the radiotherapy group was due to either disease progression or late treatment complications; three deaths (two in the chemoradiotherapy group and one in the radiotherapy group) were due to either intercurrent disease or late treatment-related toxicity.

### Interpretation

Adjuvant chemotherapy given during and after radiotherapy for high-risk endometrial cancer did not improve 5-year overall survival, although it did increase failure-free survival. Women with high-risk endometrial cancer should be individually counselled about this combined treatment. Continued follow-up is needed to evaluate long-term survival.

## Introduction

Endometrial cancer is one of the most common cancers of women in western world. Majority of women with endometrial cancer presents with early stage and has a favorable prognosis with 5-year OS of 88%[1]. However, a subset of women with early stage endometrial cancer has significantly decreased survival with 5-year OS of about 65%[1]. This group comprises women with high risk features of higher grade and/or stage, deep myometrial invasion, lympho-vascular space invasion, and non-endometrioid histologies such as serous and clear cell carcinoma. Despite adequate surgical debulking, these women are characterized by higher incidence of local as well as distant recurrences and are therefore, targets for further adjuvant treatment.

## Adjuvant Radiation Therapy for Early Stage Endometrial Cancer

PORTEC-1 Trial[1] was one of the four randomized trials that established the role of radiotherapy (RT) in women with intermediate risk early stage endometrial carcinoma, showing that pelvic external beam RT (EBRT) provides significant improvement in local-regional recurrence (LRR), without showing any advantage in survival outcomes.

In 2004, a similar prospective study on women with early-stage EC with intermediate-risk disease (GOG#99)[2] was published. Four hundred forty-eight patients with stage

IB, IC, or II (occult) disease were randomized to EBRT (50.4 Gy) versus no additional therapy (NAT), following hysterectomy, bilateral salpingo-oophorectomy (BSO), and lymph node dissection (LND). The primary outcome was a recurrence-free interval; Overall survival (OS) was a secondary endpoint. EBRT reduced the 24-month cumulative incidence of recurrence (CIR) from 12% to 3% (p-0.007). A greater reduction was seen (CIR of 13% vs. 27%) within HIR group. However, as in PORTEC-1, the difference in OS was not statistically significant.

In both PORTEC-1 and GOG#99, the majority (75%) of the LRRs were located in the vagina (mainly vaginal vault) [1,2]. The success of salvage therapy was higher after vaginal relapse compared with pelvic and distant recurrence. In PORTEC-1, the 3-year survival after salvaging vaginal recurrence was 73% compared with pelvic (8%) and distant relapse (14%). Thus, in view of high salvage rates for pelvic recurrences, it was thought if EBRT can be safely substituted with vaginal brachytherapy to improve QoL.

Therefore, the subsequent randomized PORTEC-2 trial (2010)[3] for International Federation of Gynecology and Obstetrics (FIGO) 1988 Stage I--IIA EC patients with HIR factors confirmed that EBRT could safely be substituted by vaginal brachytherapy (VBT), with less toxicity and better quality of life.

Although LLRs were well taken care of by radiation therapy in all randomized trials (PORTEC 1, GOG 99 and PORTEC 2), many patients with high-risk disease still have distant metastatic relapses with poor survival outcomes. Therefore, subsequently a systemic treatment with adjuvant chemotherapy was proposed as a solution, with or without radiotherapy.

## Adjuvant Chemotherapy for Early Stage Endometrial Cancer

Four randomized trials evaluated the use of chemotherapy in early-stage disease. An Italian study[4] randomized 345 patients to chemotherapy or RT. No progression free survival (PFS) or OS difference was seen between the two arms. Most patients had stage III disease, and chemotherapy delayed distant metastases and radiotherapy delayed pelvic recurrence, but without differences in overall survival or progression-free survival.

Similarly, after randomizing 475 patients to chemotherapy or RT, the Japanese GOG[5] concluded that chemotherapy had no PFS or OS benefit over RT. In their ad hoc analysis, they found that chemotherapy significantly improved PFS and overall survival in a "high-to-intermediate-risk group" (stage IC in patients over 70 years or with grade 3 or stage II or IIIA with positive cytology) (PFS was 84% vs. 66%, p5.024; and OS was 90% vs. 74%, p5.006). Because of increased pelvic relapse with the use of adjuvant chemotherapy alone, the combination of chemotherapy and radiotherapy merited exploration.

## Adjuvant Chemo-radiotherapy for High Risk Endometrial Cancer

In a phase 2 trial (RTOG 9708)[6] among women with high-risk endometrial cancer, the combination of external beam radiotherapy with two concurrent cycles of cisplatin, followed by four adjuvant cycles of cisplatin and paclitaxel, was tested, resulting in 4-year overall survival of 85% and disease-free survival of 81%. In a Finnish trial[7], 156 patients were randomized to RT with or without chemotherapy and it was concluded that there was no OS benefit despite sequential chemo-radiotherapy tended to increase PFS by 7 months (p=0.134) and to postpone death by 14 months (p=0.148).

Thereafter, 2 trials (NSGO-EC-9501/EORTC-55991 and MaNGOILIADE-III)[8] randomized 540 patients to RT with or without chemotherapy and showed that RT with chemotherapy significantly improved 5-year PFS compared with RT alone (82% vs. 75%). OS approached statistical significance with HR-0.69. However, it should be noted that LND was optional (only 26% had LND and 46% with unknown status), and the concept of HR disease was not pre-defined in the inclusion criteria but was left to the discretion of the participating departments.

Since, the combination of radiotherapy and chemotherapy seemed more effective than either treatment alone, and because data for toxicity and quality of life were lacking, the randomized PORTEC-3 trial[9] was initiated to evaluate the benefit of chemo-radiotherapy versus radiotherapy alone for women with early stage high-risk endometrial cancer in terms of overall survival and failure-free survival improvement (FFS), as well as toxicity and effects on health-related quality of life.

With the endpoints of 5-year OS and failure-free survival (FFS), the final analysis revealed that adjuvant CT did not significantly improve the 5-year OS (82% CTRT vs. 77% RT, p=0.1). However, addition of chemotherapy did improve 5-year FFS (75.5% Vs 68.6%, p=0.022).(Fig: 1)

Women with stage III endometrial cancer have shown maximum benefit in FFS where there was shown to be an 11% improvement in those who received adjuvant CT vs. RT alone. The improvement was clinically relevant as having exceeded the 10% improvement used to design the study. (Fig: 2)

This trial also contained an extensive quality of life analysis, that correlated the more severe toxicities experienced by those who received adjuvant CT with lower quality of life during and 6 months after the treatment period.

## Discussion

Identifying novel and effective therapy regimens in women with early stage endometrial cancer has been difficult. The rationale for systemic therapy exists and is supported by preliminary evidence from earlier trials suggesting DFS benefit with sequential radiation and

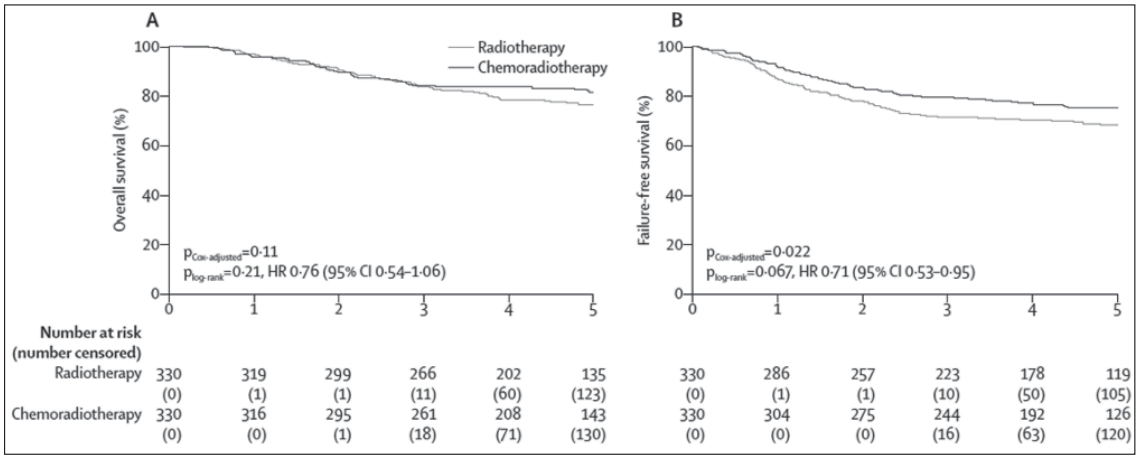


**Fig 1: Kaplan-Meier survival curves for overall survival (A) and failure-free survival (B) in all patients**

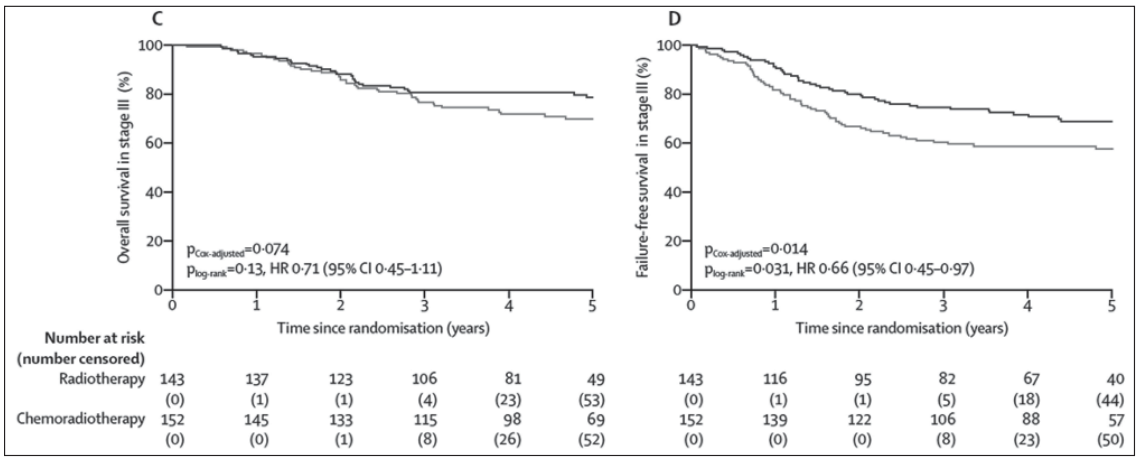


**Fig 2:**

chemotherapy. Thus, the author should be applauded for the trial design and completion for the large prospective trial.

A total of 660 women (after exclusion of 26 women) were randomized to radio therapy and radio-chemotherapy arms. Since, it was an intention to treat (ITT) analysis, all 7 women (2 in radiation arm and 5 in radio-chemotherapy arm) who received out of the protocol treatment were also included in the final analysis.

Because the number of deaths in the PORTEC-3 trial was lower than expected at the time of trial design, the required number of overall survival events was not reached till the pre-specified time of follow-up. Hence, a time-based final analysis rather than event-based was done at median follow up of 5 years with 42 extra months of follow up after recruitment of last patient. This may reflect that population under trial was a low risk population cancer related deaths and for recurrence (pelvic and/or distant).

Patient characteristics were well balanced between both the treatment arms. However, the trial contains heterogeneous patient population (as commonly seen in adjuvant therapy trials in endometrial cancer), with women both in early as well as advanced stage and also women with both type I and type II histologies, thus, potentially diluting the therapeutic effect.

In addition, lymph node dissection was not performed in nearly half of the patients, possibly impacting the stage interpretation. Since the maximum benefit of combining chemotherapy and radiation has been shown in stage III women (as per subset analysis), the number remain underestimated that again may undermined the therapeutic benefit.

Treatment-related toxicity was worse in the chemo radiotherapy group, with 60% of patients experiencing grade 3 or worse adverse events compared with 12% in those receiving radiotherapy alone. These differences disappeared by 12 months, but grade 2 toxicity remained higher in the chemotherapy group at 5 years, mostly due to neuropathy. Considered together, the significant improvement in failure-free survival seen in patients with stage III disease seems to justify the accompanying toxicity.

On multivariate analysis, only being older than 70 years was associated with treatment effect and providers should council the elderly women about this beneficial effect of chemo-radiotherapy. This is an important consideration as more than 50% of elderly are less likely

to receive adjuvant chemotherapy or radiotherapy after surgery than their younger counterparts.

Lastly, women with measurable residual disease were excluded from enrollment on trial and this population could have been benefitted most from a combined approach.

## Conclusion

Combined adjuvant chemotherapy and radiotherapy cannot be recommended as a new standard of care for patients with stage I–II endometrial cancer because no survival differences were found and pelvic control was high with radiotherapy alone. Patients with stage III cancer had the greatest benefit with chemo radiotherapy because of their higher risk of disease recurrence; for these patients, combined treatment should be considered to maximise failure-free survival. Nevertheless, the benefits and risks should be discussed for each individual patient.

Further studies may benefit from molecular classification of endometrial cancer, in an effort to better risk stratification of patients, to identify relevant prognostic factors and to develop more effective treatment paradigms. Continued assessment of toxicity, QoL and cost will be paramount to define optimal adjuvant therapy.

## What Future Trials will Offer

Two more trials (GOG-249 and GOG-258)[10] have not yet been fully published, but have been presented as abstracts at conferences. The results of the GOG-249 trial, which compared pelvic radiotherapy with a combination of three cycles of carboplatin-paclitaxel chemotherapy and vaginal brachytherapy in stage I–II patients with high (intermediate) risk factors reported overlapping progression free survival and overall survival curves, and significantly more pelvic and para-aortic recurrences in the chemotherapy group. The GOG-258 trial compared chemo radiotherapy (the same schedule as used in the PORTEC-3 trial) with six cycles of Carboplatin–paclitaxel chemotherapy alone. No differences in overall or recurrence-free survival were reported, but significantly more vaginal and pelvic or para-aortic recurrences were reported in the chemotherapy group.

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Lancet Oncol. 2018 Mar;19(3):295-309

# Breaking News!! Role of Minimally Invasive Surgery in Cervical Cancer

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## Introduction

The use of laparoscopy for gynecologic cancers has increased in all disease sites in recent years, but only for endometrial cancer has a randomized trial been published demonstrating the non-inferiority of a Minimally invasive surgery (MIS) approach for cancer outcomes. The LAP 2 trial demonstrated non-inferiority of laparoscopy vs laparotomy for surgical staging in uterine cancer, and long-term follow up found no difference in overall survival, with low recurrence rates in both groups.[1,2] The management of early stage cervical cancer often includes surgery in the form of radical hysterectomy, radical trachelectomy, or radical parametrectomy. Surgical techniques have evolved to include minimal invasive approaches, and more recently, to include robotic assisted techniques. However, randomized data for RH for cervical cancer are not published until recently a revelation was made in the Society of Gynecologic Oncology (SGO) meet in 2018 in New Orleans, New Orleans, Louisiana, United States of America, where the following two abstracts of a randomized trial of role of MIS in RH were presented, that have incited a huge debate amongst gyne oncologists nationally and internationally.

## Abstracts[3]

### 1. Phase III randomized trial of laparoscopic or robotic versus abdominal radical hysterectomy in patients with early- stage cervical cancer: LACC Trial

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**Objective:** Minimally invasive radical hysterectomy is routinely performed in the management of patients with early-stage cervical cancer. The goal of this study was to investigate whether disease-free survival (DFS) among patients who underwent laparoscopic or robotic (MIS) was non-inferior compared to standard-of-care open (TARH) radical hysterectomy.

**Method:** This was a prospective randomized, international, multicenter, non-inferiority phase III trial, confirmed stage IA1 (lymphvascular invasion) to IB1 tumor. Histologic subtypes were squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. Randomization (1:1). Aimed to recruit 740 patients (370 per arm) to have over 90% power to declare non-inferiority in DFS at 4.5 years, with a margin of 7.2% (90% in TARH to 82.8% in MIS).

**Results:** At closure, 312 patients were randomized to TARH; 319 patients to MIS (83% laparoscopy and 16% robotic surgery). The majority (92% in both) were stage IB1. Treatment arms were well balanced on baseline characteristics, including age (mean 46 years in both) and BMI (median 26 vs 27 kg/$m^2$). In the TARH group, 88% received their randomized treatment versus 91% in the MIS group. Conversion rate to laparotomy was 3%. Table 1 shows the similarity of treatment groups on histopathology and adjuvant therapy. At the time of analysis, the information available at 4.5 years was 60%, with over 80% power for the primary endpoint and median follow-up of 2.5 years. The non-inferiority boundary of −7.2% for DFS at 4.5 years was breached (TARH 97% versus MIS 86%, difference −10.6%, 95% CI −16.4% to −4.7%, $P$ = 0.87). MIS was found to have over a 3-fold increase in DFS events (7/312 vs 27/319, HR = 3.74, 95% CI 1.63–8.58, $P$ = 0.002), which was consistent when adjusted for age, BMI, stage of disease, LVSI, lymph node involvement, and ECOG status. MIS was also associated with a decrease in overall survival (3/312 vs 19/319, HR = 6.00, 95% CI 1.48–20.3, $P$ = 0.004). There were no differences in rates of intraoperative complications by treatment received (11% in both, $P$ = 0.76).

**Conclusion:** In this prospective randomized trial, laparoscopic or robotic radical hysterectomy was associated with higher recurrence rates and worse overall survival when compared with the open approach in women with early-stage cervical cancer.

## 2. Comparative effectiveness of minimally-invasive staging surgery in women with early-stage cervical cancer

**Melamed[1], L. Chen[2], N.L. Keating[3], M.G. Del Carmen[4], J.D. Wright[5] and J. A. Rauh-Hain[6].**

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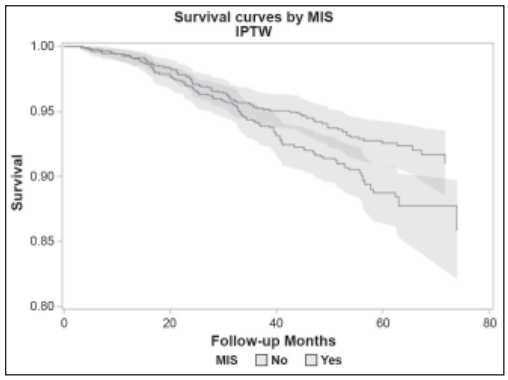
**Objective:** Despite the absence of randomized controlled trials, minimally invasive (MIS) radical hysterectomy (RH) is a widely accepted treatment for early-stage cervical cancer (CeCa). The aim of this study was to examine the association between use of MIS and survival among women undergoing RH for CeCa in a large U.S. population.

**Method:** We utilized the National Cancer Data Base to identify women diagnosed with stage 1A2–1B1 CeCa who underwent RH between 2010 and 2012. We used propensity score inverse probability treatment weighting (IPTW) to compare women who underwent RH by MIS or laparotomy but were otherwise balanced on covariates. Survival analyses utilized IPTW Kaplan-Meier and Cox proportional hazard models. To assess whether these findings were due to causal effects, we conducted an interrupted time series to evaluate whether adoption of MIS led to a change in survival.

**Results:** We identified 1,166 (52.5%) women who underwent an RH via laparotomy, and 1,055 had MIS (47.5%). In the MIS group, 833 (79%) had robotic surgery. Patients who received MIS were more often white, were privately insured, were from zip codes with higher income and educational levels, were treated in academic centers, had smaller, lower grade tumors, and more often had adenocarcinomas. All covariates were well-balanced in the propensity-matched cohorts. There was no difference between the groups in rates of parametrial invasion (12% vs 9%, $P$ = 0.09), positive margins (5% vs 5%, $P$ = 0.47), or lymph node involvement (11% vs 9%, $P$ = 0.15). The median follow-up was 51 months for MIS and 53 for laparotomy. Women who had MIS had 48% higher hazard of death from any cause compared to those who had laparotomy (HR = 1.48, 95% CI 1.10–1.98). In an interrupted time series, before adoption of MIS (2000–2006) there was a non-significant trend toward improved survival over time (annual percentage change 0.4, 95% CI 0.1–0.8). Adoption of MIS was associated with a significant change of trend ($P$ = 0.02), with 4-year survival declining by 1.0% per year (95% CI 0.3–1.6) after 2006. See Figures 1A and 1B.

**Conclusion:** Despite minimal evidence of the benefits of MIS, a significant number of women with CeCa undergo MIS RH. Compared with laparotomy, MIS is associated with lower survival for women with early-stage CeCa.



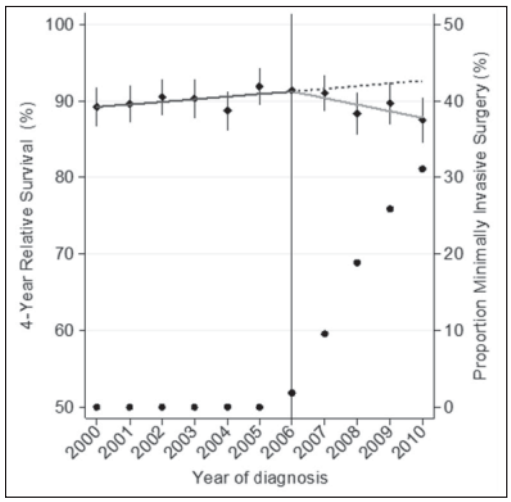




**Fig. 1a.** Kaplan–Meier survival curves for the propensity-matched IPTW groups. Women who underwent MIS RH had inferior overall survival compared with those who underwent laparotomy (plog rank = 0.02). The probability of death within 4-years of diagnosis was 8.4% among MIS compared with 4.7% among those who had laparotomy.

**Fig. 1b.** Interrupted time series evaluating the effect of adoption of MIS RH on 4-year relative survival among women with CeCa. The 4-year survival among women receiving RH for CeCa (diamonds) and 95% CI (whiskers) are plotted annually 2000- 2010. The proportion of RH undertaken using a MIS approach (circles) is plotted on the right axis. In the years before the adoption of MIS there was a nonsignificant trend toward improved survival (annual percent change [APC] 0.4; 95%CI -0.1 to +0.8). Adoption of MIS was associated with a significant change of temporal trend (p=0.02), with 4-year survival declining by 1.0% (95%CI 0.3-1.6) per year annually after 2006.

## Comment

Despite any randomized data available, surgeons adapted MIS for radical hysterectomy (RH) for early stage cervical cancer and some retrospective and cohort studies did establish equivalent long term and short term outcomes. In a retrospective study by Dilver E et al, data of 383 women who underwent upfront management of cervical cancer with RH over the 14-year period between 2000 and 2013, with a mean follow-up of 5.1 ± 4.2 years

was analysed.[4] Pelvic nodes were retrieved more in the MIS group and perioperative transfusion, hospital stay, perioperative complications, estimated blood loss (EBL) was more in the laparotomy group. The need for any chemotherapy after RH was not different between the 2 groups (16.7% for MIS vs 21.3% for XL; p = .32), nor was the need for any radiation therapy (19.8% for MIS vs 24.5% for XL; p = .86). There was no difference in the rate of recurrence of cervical cancer by mode of RH (5.0% for MIS group vs 6.4% for XL; p = .86) and no difference in overall survival, with 95% of both cohorts alive at 5 years (median not reached; log-rank p = .29). They concluded that while awaiting the results of the ongoing LACC trial, the present study and others support the continued use of MIS RH for the treatment of early-stage cervical cancer, which is associated with improved short-term clinical outcomes without compromising long-term cancer care.

Another systematic review and metaanalysis evaluated 26 studies to compare surgical safety and clinical effectiveness of robotic hysterectomy versus laparoscopic hysterectomy and laparotomy for cervical cancer.[5]

No significant differences were found in survival outcomes. The length of stay (LOS) was shorter and transfusion rate was lower with robotic hysterectomy compared to Open or laparoscopic hysterectomy. EBL was significantly reduced with robotic compared to laparotomy. Compared to laparotomy, overall complications, urinary infection, wound infection, and fever were significantly less frequent with robotic hysterectomy. The overall, peri-operative, and post-operative complications were similar in other comparisons. They concluded that compared to laparoscopy, the current evidence is not enough to clearly determine the clinical safety and effectiveness of robotic hysterectomy. Further rigorous prospective studies with long-term follow-up that overcome the many limitations of the current evidence are needed.

It is difficult to explain the reasons behind decreased survival and increased recurrence after MIS in the LACC trial. Some hypothetical answers are related to specimen retrieval, vaginal cuff formation, mesothelial ischemia but definite answers await the whole publication of the trial.

To conclude, as we all wait for the publication of the LACC trial, surgeons should tailor their techniques for maximum patient advantage. Given the current prevalence of MIS RH, it is important to ensure that patient outcomes, including survival, cancer recurrence, and need for adjuvant therapy, are not compromised with newer surgical techniques.

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# Important Day of the Month:
# World Health Day

**World Health Day** is a global health awareness day celebrated every year on 7th April, under the sponsorship of the World Health Organization(WHO), as well as other related organisations.

In 1948, the Assembly decided to celebrate 7th April of each year, WHO founder's day with effect from 1950, as the World Health Day. WHO organizes international, regional and local events on the Day related to a particular theme. World Health Day is acknowledged by various governments and non-governmental organizations with interests in public health issues, who also organize activities and highlight their support in media reports, such as the Global Health Council.

**World Health Day's 2018** message is simple: ***giving people access to healthcare without the prospect of financial hardship. This is regardless of where they're from; they could be in Africa, Asia, South America or the United States***. What matters to the World Health Organisation (WHO), the group behind it, is that there's "**Health for All**". It's also the impetus behind the current organization-wide drive to support countries in **moving towards Universal Health Coverage (UHC)**.

It has its reasons, too. The WHO asserts, following countless studies, that countries which invest in universal healthcare will make a "sound investment in their human capital"; indeed, access to a very bottom line of care and financial protection will not only truly improve someone's health and life expectancy, but also "protects countries from epidemics, reduces poverty and the risk of hunger, creates jobs, drives economic growth and enhances gender equality".

In their 70th anniversary year, WHO called on world leaders to live up to the pledges they made when they agreed the Sustainable Development Goals in 2015, and commit to concrete steps to advance the health of all people. This means ensuring that everyone, everywhere can access essential quality health services without facing financial hardship.

The Organization will maintain a high-profile focus on UHC via a series of events through 2018, starting on World Health Day on 7 April with global and local conversations about ways to achieve health for all.

## What World Health Day can do?

Some countries have already made significant progress towards universal health coverage. But half the world's population is still unable to obtain the health services they need. If countries are to achieve the SDG target, one billion more people need to benefit from UHC by 2023.

Throughout 2018, WHO will aim to **inspire**, **motivate** and **guide** UHC stakeholders to make commitments towards UHC:

- **Inspire**—by highlighting policy-makers' power to transform the health of their nation, framing the challenge as exciting and ambitious, and inviting them to be part of the change.
- **Motivate**—by sharing examples of how countries are already progressing towards UHC and encourage others to find their own path.
- **Guide**—by providing tools for structured policy dialogue on how to advance UHC domestically or supporting such efforts in other countries (e.g. expanding service coverage, improving quality of services, reducing out-of-pocket payments).

## World Health Day messages

- Universal health coverage is about ensuring all people can get quality health services, where and when they need them, without suffering financial hardship.
- No one should have to choose between good health and other life necessities.
- UHC is key to people's and nations' health and well-being.
- UHC is feasible. Some countries have made great progress. Their challenge is to maintain coverage to meet people's expectations.
- All countries will approach UHC in different ways: there is no one size fits all. But every country can do something to advance UHC.
- Making health services truly universal requires a shift from designing health systems around diseases and institutions towards health services designed around and for people.
- Everyone can play a part in the path to UHC, by taking part in a UHC conversation.

WHO use the anniversary of their founding day not only as an opportunity to celebrate the organization and its work but also as an opportunity to highlight a current global health priority.

"Body, Mind and Soul"

# Surya Namaskar

**Rashmi**

Asstt Professor, Deptt of Obstetrics & Gynaecology, University College of Medical Sciences & GTB Hospital, Delhi

***"The rhythm of the body, the melody of the mind & the harmony of the soul create the symphony of life,"*** reads BKS Iyengar's quote on Yoga.

The literal meaning of the Sanskrit word yoga is 'to add', 'to join', 'to unite', or 'to attach,' and that union is of one's consciousness with the higher forces or universal consciousness. One of the most important sequence of asanas in Yoga practice is Surya Namaskar, *Surya Namaskar (*Sun salutation) literally means to bow down to the sun. *Surya Namaskar* is one of the best yogic practices to energize the body and start the day with an intention of gratitude towards the source of life on earth – which is the Sun. Surya Namaskar includes a set of 12 fixed, cyclic postures synchronized with one's breath, which detoxifies and stimulates almost every organ of the human body. Apart from the body, *Surya Namaskar* also has a rejuvenating effect on a person's mind and soul. It is a **complete exercise for your mind, body and soul.** The complete set of "asanas" combined with proper deep and rhythmic breathing can provide significant physical and mental benefits.

## Beneficial Effects

### *Physical Benefits*

Practicing Surya Namaskar regularly can keep your physical body in good shape. ***Surya Namaskar*** practice engages the ***core, stretches the hamstrings, and loosens the shoulders***. Regular practice improves ***blood circulation*** throughout the entire body, ***massages the internal organs***, and promotes overall health. When practiced at a fast pace, it provides an ***excellent cardiovascular workout*** and aids weight loss. When practiced at a slower pace, the routine is ***calming and grounding***. The physical benefits of Surya Namaskar practice are:

- It benefits joints, ligaments and the skeletal system by improving posture, flexibility and balance
- Boosts blood circulation. Promotes glow in the skin and hair growth.
- Benefits the Endocrine system and enables the various endocrinal glands to function properly. These include the thyroid, parathyroid and pituitary glands as well as the adrenal gland, testes and ovaries
- Helps people suffering from insomnia
- It is good for the heart and stimulates the cardiovascular system. It is a form of cardiovascular exercise.
- Tones up the digestive system by the alternate stretching and compression of abdominal organs. It activates digestion and gets rid of constipation and dyspepsia
- It stimulates the lymphatic system and supports respiratory system health, as well
- Influences the pineal gland and hypothalamus to prevent pineal degeneration and calcification
- One of the best techniques to keep sugar under control in Diabetes
- It gives vitality and strength. It also reduces the feeling of restlessness and anxiety
- Surya Namaskar relieves stress, improves concentration and gives inner peace

*Surya Namaskar* is generally done at the beginning of any further *yoga asana* practices/poses. It acts as a good **warm-up** exercise to perform more advanced *asanas*.

The deep breathing while performing Surya namaskar increases *prana* into our system and ***makes us feel more alive.***

### *Effects on Mind*

The main purpose of *Surya Namaskar* is to feel gratitude for the sun. When we feel thankful for the things we already have, it has a very positive impact on our emotions. When we practice gratitude we attract more of the positive things and experiences in our life to be thankful for. Deep and calming breathing practices in sun salutations and other *yogic* practices ***help us to remove any negative emotional blockages from our mind and body***. All this has very positive effect on the mind.

### *Spiritual benefits*

When practiced in the morning, it is a spiritually uplifting exercise and promotes a keen awareness of the interconnectedness of your body, mind and breath. One will find connecting to a ***deeper level of intuition, greater internal wisdom and a sense of higher knowledge***.

## How to perform Surya Namaskar?

The 12 asanas are performed rhythmically in a sequence and need to be synchronized with breathing. Surya Namaskar is best done early in the morning on empty stomach. Warming up exercises should be done before starting Surya Namaskar. Each round of Sun Salutation consists of two sets, and each set is composed of ***12 yoga poses/ asanas***. It is recommended to do at least 12 rounds of Sura Namskar daily, though in the beginning one can start with 2-3 rounds and then gradually increae it. Steps of 12 asanas (Fig 1) are described below:

1. **Pranamasana (Prayer pose)**: Stand erect at the edge of your mat with feet together. Expand your chest and relax your shoulders. Now bring both your arms in front of the chest and join them in a prayer position. This posture induces a state of relaxation and calmness.
2. **Hastauttanasana (Raised Arms pose)**: Inhale, lift the joint hands up and back pushing the pelvis forwards so that the biceps are close to your ears and the back is arched, stretching the whole body. This posture stretches the chest, abdomen and spine and lifts the prana (energy) upwards to the upper parts of the body.
3. **Hasta Padasana (Hand to Foot pose)**: Exhale and bend forwards from the waist, keeping the spine erect. Now place both the hands on the floor beside the feet. This helps massage the abdominal organs like liver, kidneys, pancreas, uterus, ovaries and cause a good flow of blood to the brain.
4. **Ashwa Sanchalanasana (Equestrian pose)**: Inhale, push the left leg back as far as possible and drop it to the ground. The right knee is bent in between both the hands. Lift the spine, open the chest and look up.
5. **Parvatasana (Mountain pose)**: Exhale and bring your left leg back to the right, parallel to the ground and simultaneously push your hips up, keeping the arms and legs straight. Lower your head between the arms forming a mountain-like pose and try touching the heel to the floor. This pose helps strengthen the arms , calves, legs and nerves. Take a deep breath while in the posture.
6. **Ashtanga Namaskara (Salute With Eight Parts/ Points)**: Exhale and gently drop both knees to the ground, slowly slide the body down. Bring the chest and chin to the ground. All toes, knees, chest, hands and chin should touch the floor. The butts should be up. Hold your breath. This posture develops the chest and strengthens arms.
7. **Bhujangasana (Cobra pose)**: On inhalation, lower the hips while pushing the chest forward and upward, elbows are bent so that the spine is arched and head is facing up. This posture helps relieve tension in the back muscles and spinal nerves.
8. **Parvatasana (Mountain pose)**: Exhale and resume to posture 5.
9. **Ashwa Sanchalanasana (Equestrian posture)**: Inhale and bring the right leg in front between the hands. Left leg remains back like posture 4.
10. **Padahastasana (Hand to Foot pose)**: Exhale, bring the left foot forward, join both the legs and resume posture 3.
11. **Hastauttanasana (Raised Arm pose)**: Inhale, raise the arms up and resume posture 2.
12. **Pranamasana (Salutation pose)**: Straighten the body, join arms in front of the chest and resume posture 1.

**Fig 1: 12 Steps of Surya Namaskar**

To conclude, surya namaskar is a complete work out for body, mind and soul. It helps on all the 5--dimensions of our body. strengthens body, creates awareness of mind , helps in strengthening bones and joints and helps in transformation spiritually by working on so many energy centers. Over time, Surya Namaskar helps one achieve a sense of well-being and purpose. A beautiful quote by Paramahansa Yogananda says "***Yoga is a simple process of reversing the ordinary outward flow of energy and consciousness so that the mind becomes a dynamic center of direct perception no longer dependent upon the fallible senses but capable of actually experiencing Truth.***"

# Journal Scan

**Bindiya Gupta**
Assistant Professor, Department of Obstetrics & Gynecology, University College of Medical Sciences & GTB Hospital, Delhi

**1. J Clin Oncol. 2018 Feb 12:JCO2017759985**

## Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: A randomized controlled trial

**Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri Chopra S, Kerkar R, Engineer R, Tongaonkar H, Ghosh J, Gulia S, Kumar N, Shylasree TS, Gawade R, Kembhavi Y, Gaikar M, Menon S, Thakur M, Shrivastava S, Badwe R**

### Purpose

We compared the efficacy and toxicity of neoadjuvant chemotherapy followed by radical surgery versus standard cisplatin-based chemoradiation in patients with locally advanced squamous cervical cancer.

### Patients and Methods

This was a single-center, phase III, randomized controlled trial (ClinicalTrials.gov identifier: NCT00193739). Eligible patients were between 18 and 65 years old and had stage IB2, IIA, or IIB squamous cervical cancer. They were randomly assigned, after stratification by stage, to receive either three cycles of neoadjuvant chemotherapy using paclitaxel and carboplatin once every 3 weeks followed by radical hysterectomy or standard radiotherapy with concomitant cisplatin once every week for 5 weeks. Patients in the neoadjuvant group received postoperative adjuvant radiation or concomitant chemotherapy and radiotherapy, if indicated. The primary end point was disease-free survival (DFS), defined as survival without relapse or death related to cancer, and secondary end points included overall survival and toxicity.

### Results

Between September 2003 and February 2015, 635 patients were randomly assigned, of whom 633 (316 patients in the neoadjuvant chemotherapy plus surgery group and 317 patients in the concomitant chemoradiation group) were included in the final analysis, with a median follow-up time of 58.5 months. The 5-year DFS in the neoadjuvant chemotherapy plus surgery group was 69.3% compared with 76.7% in the concomitant chemoradiation group (hazard ratio, 1.38; 95% CI, 1.02 to 1.87; P = .038), whereas the corresponding 5-year OS rates were 75.4% and 74.7%, respectively (hazard ratio, 1.025; 95% CI, 0.752 to 1.398; P = .87). The delayed toxicities at 24 months or later after treatment completion in the neoadjuvant chemotherapy plus surgery group versus the concomitant chemoradiation group were rectal (2.2% v 3.5%, respectively), bladder (1.6% v 3.5%, respectively), and vaginal (12.0% v 25.6%, respectively).

### Conclusion

Cisplatin-based concomitant chemoradiation resulted in superior DFS compared with neoadjuvant chemotherapy followed by radical surgery in locally advanced cervical cancer.

**2. J Obstet Gynaecol. 2017 Oct;37(7):877-882.**

## Prediction of preeclampsia in primigravida in late first trimester using serum placental growth factor alone and by combination model

**Agarwal R, Chaudhary S, Kar R, Radhakrishnan G, Tandon A**

We investigated a placental growth factor alone and combined clinical (mean arterial pressure, MAP), biophysical (uterine artery pulsability index, PI) and biochemical (placental growth factor, PLGF) model for predicting preeclampsia in late first trimester. The inclusion criteria was primigravida (<40 years) attending their first hospital visit with singleton pregnancy at 11-14 weeks of gestation. Of the enrolled and followed 291 subjects, 35 (12%) later developed PE (5.8%)/GH (6.2%). An equal number of randomised women with normotensive non-proteinuric course were considered as reference group. For preeclampsia, PLGF alone had detection rate of 40% and 51% with 5% and 10% FPR, respectively. On addition of MAP, the AUC improved to 0.937 for PE. Further, addition of mean PI slightly improved AUC to 0.965. This signifies that a model with all three markers had better prediction of preeclampsia rather than PLGF alone. Impact statement In view of high morbidity and mortality due to hypertensive disorders in pregnancy, there has been extensive research for

developing markers to detect/screen the condition in early pregnancy. Several such markers have been tested in their individual capacities and in combination during early pregnancy. Most of these studies have originated from high income countries and focussed mainly on the second trimester of pregnancy. We investigated a placental growth factor alone and combined clinical (mean arterial pressure, MAP), biophysical (uterine artery pulsability index, PI) and biochemical (placental growth factor, PLGF) model for predicting preeclampsia in the first trimester in primigravida (<40 years). A nested case control model was used for our study. For preeclampsia, PLGF alone had detection rate of 40% and 51% with 5% and 10% FPR, respectively. On addition of MAP, the AUC improved to 0.937 for PE. Further, addition of mean PI slightly improved AUC to 0.965. The present study has been done in an Indian subcontinent setting (where maternal mortality related to preeclampsia are even higher) where very limited studies are available for the role of either PLGF or in combinations for prediction of preeclampsia. Our research pointed shows better predictability for PE when a combination of markers is used especially in low-risk nulligravida. These are easy, cheap and non-invasive measurements that can be taken in all women at their first routine antenatal visit.

**3. International Journal of Gynecology and Obstetrics-India (April-May 2017);3(1):1-6**

## Effect of vitamin D supplementation in pregnancy on maternal and neonatal outcome: A double-blind randomized controlled trial

**Pankila Mittal, Himsweta Srivastava, Shalini Rajaram, Neerja Goel, SV Madhu, MMA Faridi, Vishnu Bhartiya**


### Purpose

Antenatal vitamin D status has been associated with the risk of adverse pregnancy outcome. Currently, there is insufficient evidence regarding the benefits of vitamin D supplementation during pregnancy. The prevalence of vitamin D deficiency in pregnant women is high, hence it could be a modifiable risk factor with important public health implications. The study was aimed to assess the effect of antenatal vitamin D supplementation on maternal and neonatal outcome.

### Materials and Methods

A double-blind randomized controlled trial was conducted. Total 484 primigravidas aged 18 to 30 years at 16 to 24 weeks of gestation were randomized by computer-generated sequences to two groups. Study group received vitamin D in dose of 60,000 IU cholecalciferol/week for 6 weeks followed by 60,000 IU per month till term. Control group received placebo for same duration. DiaSorin assay was used for estimation of 25(OH) D levels.

### Results

The mean 25-hydroxyvitamin D3 (25(OH)D) levels were similar in the vitamin D and placebo group at baseline (7.59 ± 0.60 vs 8.80 ± 0.65 ng/mL; p = 0.17) but was significantly higher in the vitamin D group than placebo group at delivery (25.79 ± 8.04 vs 7.63 ± 4.29 ng/mL, p = 0.00). The incidence of gestational hypertension, preeclampsia, preterm prelabor rupture of membranes, and preterm birth was similar in both the groups. No difference was appreciated in the mode of delivery, mean gestation of delivery, mean birth weight, neonatal intensive care unit (NICU) admission, Apgar at 1 and 5 minutes.

### Conclusion

Antenatal vitamin D3 supplementation significantly raised maternal serum 25(OH)D concentration, but no significant difference was found in maternal and neonatal outcome.

# Proceedings of AOGD Monthly Clinical Meet

**Monthly Clinical Meeting was held at UCMS & GTB Hospital on 23rd March, 2018** from 4:00pm- 5:00pm. Three interesting case reports and a retrospective analysis on Management of Misplaced IUCD was presented.

## 1. Transmigrated & Incarcerated Intrauterine Contraceptive Devices Managed at a Tertiary Care Hospital During 5 Years- A retrospective analysis

**Richa Sharma, Amita Suneja, Kiran Guleria, Abha Sharma, Rashmi Malik, Sruthi Bhaskaren, Archana Chaudhary, Vishnu Bhartiya**

Department of Obstetrics & Gynaecology, UCMS-GTBH, Delhi

**Objectives**: To find the incidence, risk factors and management of Incarcerated and Transmigrated Intrauterine contraceptive devices at a Tertiary care Hospital during past 5 years

**Material and Methods:** A Retrospective Observational study was conducted on women, during past five years ( Jan 2012 to Dec 2016 ) with complaint of absent or snapped strings with failed attempts at removal of IUCD by hook or curette and were posted for Hysteroscopy and Laproscopy/ Laprotomy.

**Results:** Total no. of IUCD insertions were 4557 and 71 (1.6%) women had Incarcerated or Transmigrated IUCD, out of which 63( 88.7%) were embedded and 8 (11.3%) were transmigrated. 35.2% presented with different Gynaecological complains and were not sure of missing String. Missing thread to Hospital reporting interval was more than one month in 28% and more than 6 months in 5.9%. Commonest site of transmigration was omentum, followed by UV fold /bladder. Hysteroscopic removal were 63 (88.7%), although in 19 (30%) women both hysterolaproscopy was done. 4 (5.6%) required Laprotomy and 2 (2.8%) needed cystiscopic removal.

**Conclusion:** A regular follow up, adequate pre & post-insertion counselling and proper training of paramedical staff would help in early recognisition of misplaced IUCD. Any transmigrated, malpositioned or embedded IUCD should be removed.

## 2. Prolonged use of Ormeloxifene (Centchroman) & Uterine Sarcoma: Is there an association?

**Sruthi Bhaskaran, Kiran Guleria, Amita Suneja, Archana Chaudhary, Abha Sharma**

A 35 year old P2L2 presented with heavy and irregular menstrual bleeding for 1 ½ months following amenorrhea of 6 months, lump lower abdomen for 3 months. She was taking "SAHELI" contraceptive continuously for 4 years without supervision. On abdominal examination, uterus was uniformly enlarged to 24 weeks. Ultrasound and CECT suggested multiple degenerated fibroids. Hysteroscopy and guided endometrial biopsy was done and patent discharged after stopping "SAHELI". She followed after 1 month with HPE report of Endometrial stromal sarcoma. Surprisingly, uterine size had reduced to 18 weeks. Staging laparotomy with total hysterectomy with Bilateral salpingo opherectomy and lymph node sampling was done. Final HPE report was Endometrial stromal sarcoma low grade stage 1 b. She received 28 # of radiotherapy and 5 cycles of chemotherapy. Since, the only positive history in this case, was of taking a SERM continuously for a long period and the uterine size reducing on stopping the drug, just for one month, prompted us to think of a possible association.

## 3. Fall Precipitating a Dramatic Gynaecological Emergency

**Gita Radhakrishnan, A.G Radhika, Rachna Agarwal, Alpana Singh, Himsweta Srivastava, Richa Agarwal, Archana Vr.**

Acute non puerperal inversion is an unusual phenomenon encountered by gynaecologists. This is a case report of an acute uterine inversion in a non pregnant woman following trauma. A 30 year old woman had history of fall from stairs followed by something coming out per vaginum with pain abdomen and discharge per vaginum. On examination her vitals were stable with an unremarkable per abdomen examination. On local examination, a 8*7 cm mass was seen protruding through the vagina, with an irregular bosselated hemorrhagic surface. On ultrasonography, there was an echogenic mass in the uterine cavity with indentation of the fundus, with poor visualisation of the uterus and cervix, suggestive of uterine inversion. After stabilisation, antibiotic cover and correction of anemia, hydrostatic reduction was attempted. This failed due to huge edematous fundalfibroid. Hence laparotomy was performed and reduction was attempted by posterior colpotomy and posterior uterine wall bissection. However, decision for hysterectomy was taken for a parous lady due to fundal fibroid, large posterior wall uterine defect and infected uterine cavity. Patient withstood the procedure uneventfully.

Uterine inversion is defined as 'the turning inside out of the fundus into the uterine cavity'. The most common cause of acute inversion of uterus is mismanaged third stage of labour. Non puerperal uterine inversions are rare, with less than 100 case reports. They are of a chronic nature, associated with a pathology of the uterus most commonly a fundal fibroid; endometrial polyps, sarcoma, or other malignancies have to be kept in mind. Diagnosis is based on clinical suspicion and confirmation by imaging. Reduction under anaesthesia, abdominal and vaginal procedures to correct inversion are described. Hysterectomy is resorted only if the above measures fail to achieve correction. Unusual acute presentation of inversion after fall and infected fundal fibroid were the challenges in this case which were overcome by a clinical suspicion on examination and surgical expertise.

## 4. Complex Pelvic Mass: An elusive diagnosis

**Sandhya Jain, Shalini Rajaram, Bindiya Gupta, Anshuja Singla, Shweta Prasad, Bhanupriya**

### Introduction

Lymphomas are of two types: Hodgkin's and Non-Hodgkin's lymphoma. The incidence has been increasing over the last decade. Female genital tract lymphomas are predominantly of non-hodgkin's type and may be present in the retroperitoneum, ovary, uterus, cervix, vagina or vulva. Although rare, retroperitoneal presentation is most common. We present a case of pelvic mass which posed diagnostic dilemma and finally diagnosed to be non-hodgkin's lymphoma.

### Case Report

A 29-year-old lady, P0L0A1 presented with history of pain and lump sensation in lower abdomen for past 5 months and loss of appetite for three months. She had history of genital tuberculosis for which she received antitubercular drugs for 6 months. Abdominopelvic examination revealed a 4x5 cm firm to hard fixed, non-tender mass in left iliac fossa. Tumor markers for ovarian cancer were within normal limits. Her total leucocyte count was notably raised,23,400/ cu mm. USG pelvis showed 8.6 x 8.5 x 6.4 $cm^3$ complex mass with solid and cystic areas in left adnexa, likely ovarian neoplasm. Patient underwent hysterolaparoscopy, which showed 6X5 cm hard fixed retroperitoneal mass. Uterus and B/L tubes and ovaries were normal. MRI pelvis was done which showed well defined lobulated lesion in left adnexa along iliac vessels abutting bladder. USG guided FNAC was done which revealed large number of atypical cells in a background of polymorphonuclear population comprising of histiocytes, neutrophils and eosinophils. A diagnosis of non-hodgkin's lymphoma was made based on further immunohistochemistry. Patient was referred to oncologist for further management as no surgical intervention was required in her case.

Current first-line therapy for non-Hodgkin's lymphoma is chemotherapy, CHOP regime (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) combined with Rituximab for at least 3 cycles and 6 for bulky disease. Five year survival of patients is predicted by 'International Prognostic Index', which includes age of patient, stage of disease, LDH levels, performance status of patient and extranodal involvement.

## The Menstrual God

Oh menstrual God!
You are just like Moon God.
As the moon waxes and wanes in a lunar month
You do the same.
You arouse the feminity in me in your initial days,
When my pinopodes bloom like flower,
You shower my seed with blessings.
Like full moon,
I radiate with glow on my face.
Even if you do not bless me,
In my menstrual blood
I celebrate my womanhood,
My uniqueness.

*– Dr Monika Dayal Sharma*

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**Bank Name & Address:** Syndicate Bank, Sir Gangaram Hospital, Rajinder Nagar, New Delhi-110060,
**IFSC Code:** SYNB0009111

# Royal College of Obstetricians & Gynaecologists
# AICC Northern Zone India

Website: **www.aiccrcognzindia.com**

**Chairperson:** Dr Nirmala Agarwal: (n.menoky@gmail.com /9811888732)

**Vice Chairperson**
Dr Anita Kaul

**Hon. Secretary**
Dr Arbinder Dang

## ANNOUNCING NEXT COURSES / CONFERENCE

1. **AICC-RCOG-North Zone Bi- Annual Comprehensive Colposcopy Course**
**(With Hands-On Module) 27th & 28th May 2018**
(Approved by the International Federation of Colposcopy & Cervical Pathology)
*Venue:* Sant Parmanand Hospital, 18 Sham Nath Marg Civil Lines Delhi 110054
Course Conveners: Dr Saritha Shamsunder (shamsundersaritha@gmail.com /Contact no. 9313826748)
Dr Mamta Dagar (mamtadagar2004@yahoo.co.in/ Contact no. 9811437782)
Dr Sweta Balani (swetagarima@gmail.com/9811395800)
**Course Fee:** Rs 5000/-
Number of Delegates Limited to 50 only for each course

2. **RCOG UK Franchise MRCOG Final Preparation: Part II Written Course**
**Thursday 31st May & Friday 1st, Saturday 2nd June 2018(Total 3 Days)**
**Limited to 40 candidates only (First Come First Serve basis)**
**Course Fee: Rs 35,000**. *Certificate of attendance for this course will be provided by the RCOG UK*
Venue: Sant Parmanand Hospital, 18 Shamnath Marg, Civil Lines Delhi-110054, INDIA
UK Course Organizer & Convener - Dr Sanjeev Sharma
India Conveners and Contacts for details - Dr Sweta Gupta (swetagupta06@yahoo.com/8130140007)
Dr Jharna Behura (jharnabehura@yahoo.co.in/ 9810247593)
**Online payment available on website. www.aiccrcognzindia.com**

3. **Simms Black Travelling Professorship Program to All Postgraduate Students**
***Venue:*** **Guru Teg Bahadur Hospital Delhi - 110095**
***Date:*** **01st August, 2018 (2:00pm - 5:00pm)**
**Prestigious fellowship by RCOG UK. Organized by RCOG NZ**
***Topics:*** 1. Preventing Stillbirths 2. How to reduce litigation in Obstetrics.
3. Expert Panelist for panel discussion on Placenta Accreta/ Hypertensive Disorders in Pregnancy.

4. 32nd AICC RCOG Annual Conference in New Delhi at Hotel Sheraton Saket
*Theme:* Obstetrics & Gynaecology Evidence, Good Practice and Controversies
1st & 2nd November, 2018 Pre Conference Workshops
3rd & 4th November, 2018 Conference
5th & 6th November, 2018 Post Conference Workshops

**REGISTRATION FEE** (Inclusive of Tax)

| | Upto 30th April 2018 | | 1st May 2018 to 30th September 2018 | | 30th September 2018 onwards/spot registration | |
|---|---|---|---|---|---|---|
| | INR | USD | INR | USD | INR | USD |
| Delegates | 10500 | 165 | 11500 | 180 | 12500 | 195 |
| Trainees & Post Graduates | 8000 | 125 | 8800 | 135 | 9600 | 150 |

Registration fee includes: Conference registration fee, Conference kit & bag, Certificate, lunch, morning and evening tea both days. Faculty dinner on Friday, 2nd Nov 2018 at Hotel Sheraton. (Complimentary)
Spot registration subject to availability

| | INR | USD |
|---|---|---|
| Pre Conference Workshops 1st and 2nd November 2018* | 2500 | 40 |
| Special Workshops (Pre Conference = RCOG FOGSI Workshop) ** | 10000 | 156 |
| Special Workshops (Post Conference = Colposcopy Basic & Advanced) ** | 2000+2500 | 31+40 |
| Banquet 3rd November 2018 *** | 3000 | 48 |
| Banquet with 1 Accompanying Person | 5000 | 78 |

* Conference registration mandatory ** Conference registration not mandatory
*** 8:00 PM ONWARDS THEME: "Delhi through the Ages". HOTEL SHERATON. SAKET DELHI
For Accommodation, Hotel Bookings, Travel Enquiry Contact Miss Carolina Fernandez Cox & Kings +919711992043/ carolina.fernandes@coxandkings.com

*Mailing Address:*
**RCOG North Zone Secretariat**
Sant Parmanand Hospital, 18 Alipur Road, Civil Lines Delhi 110054
Tel No - 91-11-23981260 Ext. 314, 9560069925 / 9716801190 • Email: rcognz2017@gmail.com

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