FEDERATION OF OBSTETRIC AND GYNAECOLOGICAL SOCIETIES OF INDIA

TOG

Times of Gynaecology™

2022 | Issue 66

Science Integra®

Positive Outcomes

IN Rh-NEGATIVE WOMAN

1st new biological entity with a worldwide patent

AntiD™

Recombinant Anti-Rho (D) Immunoglobulin 300 mcg

Positive for Negative

Prevents sensitisation†

from BSV that launched 1st innovator biological product

† NHS. Prevention – Rhesus disease. Information available at https://www.nhs.uk/conditions/rhesus-disease/prevention/#:~:text=Rhesus%20disease%20can%20largely%20be,an%20immune%20response%20to%20it. Last accessed on 10th March 2021.

INFORMATION FOR PATIENTS:

What does this package leaflet enclose?
This leaflet gives you the details of the medicine that will be given to you. The details will be regarding the contents of the medicine, how to use it, and what side affects you should be careful about.

What is Anti D?
Recombinant Anti Rho-D Immunoglobulin contains– Anti Rho-D Immunoglobulin as active ingredient.

Which case this medicine should be used?
Recombinant Anti Rho-D Immunoglobulin is indicated to prevent Rho-D negative women from forming antibodies to fetal rhesus positive red blood cells that may pass into the maternal blood during childbirth, abortion or certain other sensitizing events.

Which information you must know before taking Recombinant Anti Rho-D Immunoglobulin?
You should not take Recombinant Anti Rho-D Immunoglobulin if any of the following apply to you.
! History of allergic symptoms or hypersensitivity to human immunoglobulin.

Care should be taken:
Recombinant Anti Rho-D Immunoglobulin if used use after delivery, should be given intramuscularly only in the mother. Recombinant Anti Rho-D Immunoglobulin should not be given to the newborn.
The mother should be observed for at least 20 minutes after administration. **Children:** This medicine in not for children.

With other medicinal products/ food or beverages:
Recombinant Anti Rho-D Immunoglobulin has not been studied for interactions with other medicines. It is given in hospital after your delivery. No food interactions have been known. Tell your doctor if you are taking any other medications.

Pregnancy and Lactation:
Recombinant Anti Rho-D Immunoglobulin does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient. No studies have been done during lactation.
Sports or Effects on ability to drive and use machine The effect on sports or ability to drive is not known. The effects of excipients are not known. But they may cause allergic reactions in certain individuals. If any unusual signs or symptoms occur, then immediately inform your doctor.

How to take Recombinant Anti Rho-D Immunoglobulin? Instruction for good use:
Recombinant Anti Rho-D Immunoglobulin should always be given to mothers with blood group Rh negative means who do not have Rh antibodies, in their blood and who have just delivered infants with blood group Rh positive means who have Rh antibodies. You will receive the medicine if you are Rh negative blood group and pregnant to protect you from sensitization to Rh antibodies. Recombinant Anti Rho-D Immunoglobulin should not be given to the infant and to Rho-D positive individuals.

If you have taken more Recombinant Anti Rho-D Immunoglobulin
Recombinant Anti Rho-D Immunoglobulin as it is given by your doctor hence very rare chance of getting more drug. There is no report of overdose received by the marketing company.

If you forget taking Recombinant Anti Rho-D Immunoglobulin.
Recombinant Anti Rho-D Immunoglobulin should be given within 72 hours of delivery. It is given by your doctor during the pregnancy or after delivery. The effectiveness of dose after 3 days of delivery is not known.

If you stop taking Recombinant Anti Rho-D Immunoglobulin.
Recombinant Anti Rho-D Immunoglobulin is given only once as soon as possible after the delivery or during the pregnancy based on physician decision.

What are the possible side effects?
There are no known side effects. However local pain, fever, flushing, headache and chills may occur on administration. Side effects of excipients are not known. They may cause allergic reactions depending on individual. If any unusual signs or symptoms occur, then immediately inform your doctor.

How to store Recombinant Anti Rho-D Immunoglobulin?
Recombinant Anti Rho-D Immunoglobulin should be stored under refrigeration at 2°C to 8°C and should not be freeze. Keep out of sight of children. Do not use after the time limitation indicated on the package box. The expiry date refers to the last day of the indicated month.

Shelf life of the Recombinant Anti Rho-D Immunoglobulin is 24 months.

Medicinal product after opening should be used immediately and unused liquid should be discarded.

If the package is damaged or seal opened, then do not use the medication. The medicine should be discarded by your doctor as per hospital or clinic procedure. It should not be thrown in sewage or domestic dirt.

For Patient Counseling Information (or Patient Information) Refer Full Prescribing information.

To report Suspected Adverse Reactions, contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com/adverse.html.

Glycine I.P. 30 mg, Sodium Chloride I.P. 5.84 mg, Water for Injection I.P. q.s. to 1.0 ml.

The Anti Rho-D immunoglobulin content is expressed as mcg per dose. It can also be expressed as International Units (IU) per dose. The conversion factor is 1 mcg = 5 IU.

PHARMACEUTICAL FORM:
Recombinant Anti Rho -D immunoglobulin preparation is a clear, colorless, and sterile solution.

DESCRIPTION:
Recombinant Anti Rho -D immunoglobulin preparation is a clear sterile solution containing recombinant antibodies reactive to Rh D positive red cells. Recombinant Anti Rho- D Immunoglobulin is produced by recombinant technology using genetically engineered Chinese Hamster Ovary (CHO) cells; purified using protein affinity chromatography and used in preventing Rh immunization.
Recombinant Anti Rho -D immunoglobulin preparation contains IgG anti-D (anti-Rh) for use in preventing Rh immunization. These are antibodies that bind and cause destruction of foetal Rh D positive red blood cells that have passed from the foetal circulation to the maternal circulation. Therefore, in a Rh-negative mother it can prevent sensitization of the maternal immune system to Rh D antigens, which can cause rhesus disease in the current or in subsequent pregnancies.

PHARMACOLOGICAL PROPERTIES:
Description & Pharmacotherapeutic group. ATC code: J06BB01 anti-D (rh) immunoglobulin.

Mechanism of Action:
Recombinant Anti Rho-D Immunoglobulin is protein with a molecular weight of 150 kD and is stabilized with excipients to ensure the stability till the end of shelf life of 24 months from the date of manufacturing.

Recombinant Anti Rho-D Immunoglobulin act by suppressing the immune response of Rh-negative individual to Rh positive red blood cells and hence prevents allomimunization. Passive administration of r – anti D causes rapid non – inflammatory clearance of passive anti D coated red blood cells, which stops the inflammatory destruction of fetal red blood cells, evoking a natural immune response. Additionally, suppression of the immune response lead to the down regulation of maternal immature dendritic cells or anti D specific B cells before the anti D response develops.

Pharmacodynamic properties:
Recombinant Anti Rho-D Immunoglobulin coated red cells are rapidly cleared from the maternal blood. Recombinant Anti Rho-D Immunoglobulin is known to mediate Antibody- Dependent Cell Mediated Cytotoxicity (ADCC). Mononuclear phagocytic system is also thought to be responsible for clearance of anti-D-sensitized erythrocytes. There is more evidence building up in recent years that ADCC may not be the primary mode of red cell clearance in vivo. Antibody mediated B-cell inhibition is emerging as the possible mechanism for red cell clearance.

Inhibition of B cells by crosslinking heterologous receptors (co-inhibition):
! FcγIIb inhibitory activity requires bridging to specific co-targets.
! Inhibition many activate pathways in both healthy and diseased B cells.
! Could result in potent suppression of B-cell responses without destroying B cells.

Pharmacokinetic properties:
The PK parameters of Recombinant Anti Rho-D Immunoglobulin are expected to be like a biologically similar preparation of monoclonal anti-D.
Pharmacokinetic parameters of monoclonal anti-D are as follows: Median Tmax (h) - 168, Mean Cmax (ng/mL) 42.83, Mean AUC0t (ng.h/mL) 3024.17, AUC0∞ (ng.h/mL)

Preclinical Safety Data:
Toxicity studies were done on animals – rats, mice, rabbits, and dogs. Single dose toxicity, acute toxicity and repeat dose toxicity studies have been performed. All safety and toxicity studies show no adverse effect in animals.

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Acute toxicity studies of r – anti D were conducted on Swiss Albino mice using single dose of 2400 mcg/kg body weight, administered either intramuscularly or subcutaneously. Similar studies were performed using Wistar rats. These rodents were observed for clinical signs of toxicity, body weight and mortality, for a period of 14 days. Treated rodents did not reveal treatment attributed behavior alterations, clinical signs, gross pathological abnormalities, preterminal deaths and adverse effects on body weight gain. In conclusion, r – anti D is safe substance for given dose level of 2400 mcg/kg body weight in treated rodents when administered intramuscularly or subcutaneously.

Repeat dose toxicity study was performed in Wistar rats at selected doses of 15, 50, and 150 mcg/kg administered intramuscularly over a period of 14 days. Repeat dose administration did not show any clinical signs and mortality in any of the treated animals. The body weight gain, hematological paarmeters and clinical biochemistry parameters in all the treatment groups were comparable with control group animals. Gross pathology and histopathology did not reveal any significant changes related to treatment at 150 mcg/kg body weight/day when compared with control group animals. It was concluded, No Observed Adverse Effect Level (NOAEL) for Recombinant Anti Rho-D Immunoglobulin is 150 mcg/kg body weight in rats.

Similar results were observed in repeat dose toxicity study conducted on New Zealand White Rabbits at a dose of 15, 50, 150 mcg/kg administered intramuscularly over a period of 14 days.

Repeated dose toxicity study on Beagle Dogs at a dose of 1500 and 2000 mcg/dog/day for 14 consecutive days had no effect on general health of the animal. There were no toxicity signs, changes in body weight, feed consumption, haematology and clinical chemistry parameters. It was concluded that No Observed Adverse Effect Level (NOAEL) for Recombinant Anti Rho-D Immunoglobulin is 2000 mcg/dog/day.

The allergenicity study in Guinea pigs to estimate sensitizing potential of r-anti D was conducted. There was no skin reaction observed at topical challenge exposure site. The reaction score found was 0 - 8 % i.e., grading-1, hence r-anti D Immunoglobulin was classified as a weak sensitizer.

Carcinogenicity and genotoxicity:
IgG is a normal constituent in human plasma and has not been reported to be associated with any embryo-foetal toxicity or oncogenic/ carcinogenic potential. No study was done for evaluating carcinogenicity or genotoxicity.

CLINICAL PARTICULARS:
Therapeutic indications (Approved)
Recombinant Anti Rho-D Immunoglobulin is indicated to prevent Rh negative women from forming antibodies to foetal rhesus positive red blood cells, that may pass into the maternal blood during child birth, abortion or certain other sensitizing events.

Posology and method of administration:
! Recombinant Anti Rho-D Immunoglobulin should always be given to rhesus negative mothers with no anti-D antibodies in their serum and who have just delivered rhesus positive infants. A dose of 300 mcg should be given intramuscularly as soon as possible within 72 hours after delivery.
! It is recommended that in cases of abortion or termination of pregnancy, the Rh-negative women should be given 150 mcg of Recombinant Anti Rho-D Immunoglobulin within 72 hours, if the pregnancy is of 12 weeks duration or less. In cases of miscarriage in an advanced stage of pregnancy, 300 mcg should be administered within 72 hours.
! Other sensitizing events during pregnancy in Rh negative women at a risk of transplacental haemorrhage and not known to have been sensitized should begiven 150 mcg or 300 mcg of Recombinant Anti Rho-D Immunoglobulin

Method of administration:
! Route of administration - Intramuscular administration.
The administration of Recombinant Anti Rho-D Immunoglobulin should be performed under the supervision of a physician.

Contraindications:
Recombinant Anti Rho-D Immunoglobulin is contraindicated in:
! Pregnant woman with positive ICT (Indirect Coombs' test)
! Pregnant woman is Rh– D positive
! Should not be given to an infant.

Drug to Drug interactions:
No drug-to-drug interactions studies were conducted with Recombinant Anti Rho-D Immunoglobulin.

Special warnings and precautions for use:
- Recombinant Anti Rho-D Immunoglobulin is for intramuscular use only, do not inject intravenously.
- The product is intended for maternal administration.
- Do not inject the new-born infant.
- Administer with caution to patients who have had prior severe systemic allergic reactions to human immunoglobulin.

Specific Population Use:
Pregnancy and Lactation: Recombinant Anti Rho-D Immunoglobulin does not harm the fetus or affect future pregnancies or the reproduction capacity of the maternal recipient. This medicinal product is intended for use in other sensitizing events during pregnancy. No studies have been done during lactation.

Effects on ability to drive and use machine:
No data available.

Geriatric use:
It is not indicated in Geriatric use.

Renal & Hepatic impairment:
No study done on renal and hepatic impairment condition.

Undesirable effects/ Adverse Reactions (Common, Uncommon, Rare):
! Injection site reactions include swelling, induration, redness and mild pain or warmth.
! Fever, flushing, headache, and chills may rarely occur.
! Adverse events noted in the clinical study were pyrexia, abdominal pain, pruritus, hypertension, hypotension, abnormal White Blood Cell counts.
! Clinical experience adverse events seen during Phase III clinical study

In Anti D phase 3 study following adverse events were observed:

Adverse reaction System Organ Class Preferred Term	Recombinant Anti Rho-D Immunoglobulin(n= 144)	Rhogam (n=71)
Any	4	4
General disorders and administration site conditions Pyrexia		
Gastrointestinal disorders, Abdominal pain	2	0
Skin and subcutaneous tissue disorders Pruritus	0	1
Vascular disorders, Hypertension	0	1
Hypotension	0	2
Investigations White blood cell counts abnormal	1	0

Post marketing experience adverse events:
No data available of post marketing experience.

Overdose:
Overdosage can lead to any adverse events as listed above. No antidote for this drug. The stoppage of drug administration shall ameliorate the symptoms gradually.

CLINICAL STUDIES:
A prospective, randomized clinical trial to confirm safety and efficacy of recombinant anti-D immunoglobulin in prevention of isoimmunization in comparison with polyclonal anti-D immunoglobulin r-anti D was conducted in total of 215 subjects; 144 subjects were randomized to receive the recombinant anti D (Test group) and 71 subjects were randomized to receive polyclonal anti D (RhogamR) (Reference group).
Each eligible subject received a single intramuscular injection either the Test or Reference anti-D IgG within 72 hours of delivery. Insignificant p value for Indirect Coombs Test (ICT) for Day 90 (p=0.30) and Day 180 (p=0.49) was observed between Test and Reference in prevention of Rh iso-immunization in Rh (D) negative pregnant women delivering Rh (D) positive infant. Four subjects from each group experienced 1 adverse event. All the adverse events were mild in severity. No subject receiving Test developed antibodies to r-anti D post administration of drug. This study observed equal efficacy between Test and Reference as sensitization (as evaluated by positive ICT at Day 90 or 180) was not noted in any subject in both the groups. The safety profile was same in both groups with mild severity.

PHARMACEUTICAL PARTICULARS:
! Shelf life - 24 months from date of manufacturing.
! Special precautions for Storage, Handling & Disposal - Store at 2°C to 8°C. Do not freeze.
! Nature and contents of container - A glass vial or PFS containing clear, colourless and sterile liquid having Recombinant Anti Rho-D Immunoglobulin activity of 300 mcg.

MARKETED BY: Bharat Serums and Vaccines Limited, 17th Floor, Hoechst House, Nariman Point, Mumbai – 400 021, India.

MANUFACTURED BY: Bharat Serums and Vaccines Limited, Plot No. K-27, Anand Nagar, Jambivili Village, Additional MIDC, Ambernath (East) - 421506, Tal: Ambernath City, Dist.: Thane-Zone5, Maharashtra, India.

DATE OF CREATION OF THE TEXT: 01st March 2021. VERSION: 1.1.

TOG Times of Gynaecology™
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Reach us at: production@scienceintegra.com to submit your articles and cases

President's Message

From the desk of Dr. S. Shantha Kumari – President, FOGSI 2021

As we get into the swing of work for another year, we must think in unison as "FOGSI for All". There are many Gynecologists in India who do not belong to FOGSI, including many members of other associations too. We are currently reaching out to those non-members through direct mail and solicitations and hope to demonstrate to them the value of supporting FOGSI's growth. We believe our vision for the future.. "FOGSI For All", presented here and which will be showcased in other venues, will draw more Obstetricians into the circle of those working both in and for the cause of Women.

FOGSI owes its existence to defending the rights of our doctors and also the women whom we treat. I propose we continue in that vein and expand our role in defending the rights of these Doctors and Women. We will focus on Dheera and the fight against Violence on Women and Doctors.

In looking ahead to my year as President of FOGSI, besides being humbled by the opportunity to serve my colleagues, I want to build on the expertise and unique gifts individual presidents have given to our academy.

In recent years, we have been guided by leaders in the field of Crticial Care Research, Infertility, Surgeons and Professors with unique perspectives from the trenches of general medical practice, and leaders in clinical trials, ethics, and public affairs. TOG, continues to be a valuable and expanding resource for our members and a critical tool in attracting leaders and clinicians from outside our academy, closer to the field of gynecology and our "big tent."

I wish you all a good Scientific feast through this platform and many others that will be introduced soon. Happy reading and do contribute your papers here as well.

"Live as if you were to die tomorrow. Learn as if you were to live forever."
— Mahatma Gandhi

Best wishes!

Dr. S. Shantha Kumari

MD, DNB, FICOG, FRCPI (Ireland),
President FOGSI 2021
Professor Obgyn, Chairperson ICOG 2018
Vice President FOGSI 2013
ICOG Governing Council Member
IAGE Managing Committee Member

Editorial Message

Dear FOGSIans,

To take over the steering wheel from an experienced skipper is a challenge for the new one. What course should be taken in order to go towards old and new destinations? The journal stands on an old foundation of publishing a broad range of articles covering fundamental aspects of obstetrics and gynecology as well as subspeciality topics. We plan to extend on this and introduce new items to enhance readability of the journal. The issues will start by an Editors' Message highlighting contributions and news of specific interest. More wide-ranging medical news will be added in due course, both from interiors of India and globally.

This will broaden the journals' medical outlook and often take it beyond the traditional scope of obstetrics and gynecology to women's health in a general sense. The editorial team will strengthen its working ties for this purpose. Input from the readers and from leading centers and institutions in our countries will be necessary, as will the role of our international contributors.

In todays googled-world of databases and alert-e.mails, reading becomes universal and less dependent on specific journals many a times. Still it is good to have at least one journal to grasp on a quiet evening or good afternoon at home or during work, feel the pages glide through your hands as you absorb crisp content across therapy areas that you want to be acquainted with, for your own sake and that of your patients. That is the joy of reading a customized article which I know a lot of us really want to exchange for the computer screen.

Dr Nandita Palshetkar
Dr. Krishnakumari
Dr. T Vindhya
Dr. Jayam Kannan
Dr. Aruna Suman
Dr. Kiranmayee
Dr. Fessy Louis

BSV
bringing life to life

For Prevention of Postpartum Hemorrhage due to Uterine Atony

Post Cesarean Section

RECOMMENDED WHO RECOMMENDED

Carbitex™

Carbetocin 100 mcg/ml Injection

Prevents PPH Assures Motherhood

Notable Reduction In[1]

Episodes of PPH	Use of additional uterotonics

WHO recommendations Uterotonics for the prevention of postpartum haemorrhage * Against placebo or no uterotonic

BSV
bringing life to life

For Prevention of
Postpartum Hemorrhage due to Uterine Atony

Post Cesarean Section

RECOMMENDED WHO RECOMMENDED

Rx

Carbitex™

Carbetocin 100 mcg/ml Injection

Prevents PPH Assures Motherhood

Dosage: 100 mcg IV to be given immediately after childbirth[1]

QUALITATIVE AND QUANTITATIVE COMPOSITION: Each 1 ml of solution for injection in ampoule contains: Carbetocin :100 mcg, Excipients: q.s., Water for Injection IP: q.s. to 1 ml **DOSAGE FORM AND STRENGTH:** Solution for Intravenous Injection; 100 mcg/ml **CLINICAL PARTICULARS:** Therapeutic indications: CARBITEX™ is indicated for the prevention of postpartum haemorrhage due to uterine atony. **Posology and method of administration:** Posology: Caesarean section under epidural or spinal anaesthesia: Withdraw 1 ml of CARBITEX™ containing 100 micrograms Carbetocin and administer by intravenous injection, under adequate medical supervision in a hospital. **Method of administration:** For intravenous administration. Carbetocin must only be administered after delivery of the infant, and as soon as possible after delivery, preferably before the delivery of the placenta. For intravenous administration carbetocin must be administered slowly, over 1 minute. Carbetocin is intended for single use only. No further doses of carbetocin should be administered. **Contraindications:** • During pregnancy and labour before delivery of the infant. • Carbetocin must not be used for the induction of labour. • Hypersensitivity to carbetocin or oxytocin. • Hepatic or renal disease. • Serious cardiovascular disorders. • Epilepsy. **Special warnings and precautions for use:** The use of carbetocin at any stage before delivery of the infant is not appropriate because its uterotonic activity persists for several hours. This is in marked contrast to the rapid reduction of effect observed after discontinuation of an oxytocin infusion. In case of persistent vaginal or uterine bleeding after administration of carbetocin the cause must be determined. Consideration should be given to causes such as retained placental fragments, perineal, vaginal and cervix lacerations, inadequate repair of the uterus, or disorders of blood coagulation. Carbetocin is intended for single administration only, intravenous. It must be administered slowly over 1 minute. In case of persisting uterine hypotonia or atonia and the consequent excessive bleeding, additional therapy with another uterotonic should be considered. There are no data on additional doses of carbetocin or on the use of carbetocin following persisting uterine atony after oxytocin. Animal studies have shown carbetocin to possess some antidiuretic activity (vasopressin activity: <0.025 IU/vial) and therefore the possibility of hyponatraemia cannot be excluded, particularly in patients also receiving large volumes of intravenous fluids. The early signs of drowsiness, listlessness and headache should be recognised to prevent convulsions and coma. In general, carbetocin should be used cautiously in the presence of migraine, asthma and cardiovascular disease or any state in which a rapid addition to extracellular water may produce hazard for an already overburdened system. The decision of administering carbetocin can be made by the physician after carefully weighing the potential benefit carbetocin may provide in these particular cases. No data is available on the use of carbetocin in patients with eclampsia. Patients with eclampsia and pre-eclampsia should be carefully monitored. Specific studies have not been undertaken in gestational diabetes mellitus. **Drug Interactions:** Carbetocin has been administered in association with a number of analgesics, spasmolytics and agents used for epidural or spinal anaesthesia, and no drug interactions have been identified. Specific interaction studies have not been undertaken. Since carbetocin is closely related in structure to oxytocin, the occurrence of interactions known to be associated with oxytocin cannot be excluded: Severe hypertension has been reported when oxytocin was given 3 to 4 hours following prophylactic administration of a vasoconstrictor in conjunction with caudal-block anaesthesia. During combination with ergot-alkaloids, such as methylergometrine, oxytocin and carbetocin may enhance the blood pressure enhancing effect of these agents. If oxytocin or methylergometrine are administered after carbetocin there may be a risk of cumulative exposure. Since it has been found that prostaglandins potentiate the effect of oxytocin, it is expected that this can also occur with carbetocin. Therefore, it is not recommended that prostaglandins and carbetocin be used together. If they are concomitantly administered, the patient should be carefully monitored. Some inhalation-anesthetics, such as halothane and cyclopropane may enhance the hypotensive effect and weaken the effect of carbetocin on the uterus. Arrhythmias have been reported for oxytocin during concomitant use. **Use in special population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)** Pregnancy: Carbetocin is contraindicated during pregnancy and must not be used for the induction of labour. Breastfeeding: No significant effects on milk let-down have been reported during clinical trials. Small amounts of carbetocin have been shown to pass from plasma into breast milk of nursing women. The small amounts transferred into colostrum or breast milk after a single injection of carbetocin, and subsequently ingested by the infant are assumed to be degraded by enzymes in the gut. Breast-feeding does not need to be restricted after the use of carbetocin. **Pediatric population:** There is no relevant use of carbetocin in children below 12 years of age. **Geriatric patients:** Carbetocin is not recommended to use in geriatric patients. **Effects on ability to drive and use machines:** No studies on the effects on the ability to drive and use machines have been performed. **Undesirable effects:** The adverse events observed with carbetocin during the clinical trials were of the same type and frequency as the adverse events observed with oxytocin. Intravenous administration* - Tabulated summary of adverse reactions:

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 and < 1/10	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Anaemia	
Nervous system disorders	Headache, Tremor	Dizziness	
Cardiac disorders			Tachycardia, bradycardia***, arrhythmia*** myocardial ischaemia*** and QT prolongation***
Vascular disorders	Hypotension, flushing		
Respiratory, thoracic and mediastinal disorders		Chest pain, dyspnoea	
Gastrointestinal disorders	Nausea, abdominal pain	Metallic taste, vomiting	
Skin and subcutaneous tissue disorders	Pruritus		
Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions	Feeling of warmth	Chills, pain	

* Based on studies in caesarean section. *** Reported with oxytocin. (closely related in structure to carbetocin)

Shelf life: 24 Months. **Packaging information:** 5 ampoules of 1ml are packed in a carton with leaflet. **Storage and handling instructions:** Store at refrigerated temperature 2-8°C. Do not freeze. Protect from light. Once the ampoule has been opened, the product should be used immediately.

To report Suspected Adverse Reactions, contact Bharat Serums and Vaccines at pv@bharatserums.com or visit the website www.bharatserums.com/adverse/

Manufactured in India by: **Precise chemipharma Pvt. Ltd.**, At-N.H.No.8, Near Grid, At Post-Kabilpore - 396424, Dist. Navsari, Gujarat.

Marketed in India by: BSV **BHARAT SERUMS AND VACCINES LIMITED,** 17th Floor, Hoechst House, Nariman Point, Mumbai - 400021.

Overdose: Overdosage of carbetocin may produce uterine hyperactivity whether or not due to hypersensitivity to this agent. Hyperstimulation with strong (hypertonic) or prolonged (tetanic) contractions resulting from oxytocin overdose can lead to uterine rupture or postpartum haemorrhage. Overdosage of oxytocin may lead to hyponatraemia and water intoxication in severe cases, especially when associated with excessive concomitant fluid intake. As carbetocin is an analogue of oxytocin, the possibility of a similar event cannot be excluded. Treatment of overdosage of carbetocin consists of symptomatic and supportive therapy. When signs or symptoms of overdosage occur oxygen should be given to the mother. In cases of water intoxication, it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur. **PHARMACOLOGICAL PROPERTIES Mechanism of Action:** Like oxytocin, carbetocin selectively binds to oxytocin receptors in the smooth muscle of the uterus, stimulates rhythmic contractions of the uterus, increases the frequency of existing contractions, and raises the tone of the uterus musculature. **Pharmacodynamics:** On the postpartum uterus, carbetocin is capable of increasing the rate and force of spontaneous uterine contractions. The onset of uterine contraction following carbetocin is rapid after intravenous or intramuscular administration, with a firm contraction being obtained within 2 minutes. A single 100 micrograms intravenous or intramuscular dose of carbetocin administered after the delivery of the infant is sufficient to maintain adequate uterine contraction that prevents uterine atony and excessive bleeding comparable with an oxytocin infusion lasting for several hours. **Pharmacokinetics:** The pharmacokinetics of carbetocin have been investigated in healthy female subjects. Carbetocin shows biphasic elimination after intravenous administration with linear pharmacokinetics in the dose range of 400 to 800 micrograms. The median terminal elimination half-life is 33 minutes after intravenous administration. Renal clearance of the unchanged form is low, with <1% of the injected dose excreted unchanged by the kidney.

For the use of registered medical practitioner or hospital only.

1. WHO recommendations Uterotonics for the prevention of postpartum haemorrhage

Recombinant anti–D in preventing maternal alloimmunization: A novel alternative to mono or polyclonal anti-D

Drug in Focus

Dr Priyankur Roy
MS, FIRM, FAGE, DRM,
Dip. Gynae-Endoscopy (Germany),
PGDHHM, PGDMLS, FIAOG

Maternal Alloimmunization: An epidemiological aspect

Maternal alloimmunization is the primary cause of hemolytic disease of the fetus and newborn (HDFN), leading to 50,000 fetal deaths annually, predominantly in low– and middle–income countries.[1] Fetal maternal hemorrhage during pregnancy or parturition leads to maternal alloimmunization. Based on the prevalence of blood group antigens within the population, the possibility of alloimmunization varies; the estimated frequency of rhesus antibody-D [Rh(D)] negativity is reported to be around 3%–8% among the African and Indian people, and 0.1%–3% among the Asian population.[2]

Benefits of administering anti–D immunoglobulin prophylaxis

Researchers found that passive immunization of Rh(D)–negative mothers with anti–D (anti–Rh(D) immunoglobulin [IgG]) soon after parturition could protect women from sensitization against Rh(D)–positive red blood cells.[3] Thus, anti–D IgG prophylaxis is part of routine obstetrical care for Rh(D)–negative women at risk, which led to a dramatic fall in the number of Rh affected babies. Also, it is an immunological success story in the conquest of HDFN across the world.[1] Evidences showed that the incidence of Rh sensitization reduced from 14% to 1% in Rh(D)–negative women delivering Rh(D)–positive newborns due to the administration of anti–D IgG prophylaxis after delivery of Rh(D)–positive newborns. Also, administration of anti–D IgG prophylaxis in the antenatal period reduced the incidence of Rh sensitization from 1.8% to 0.07%.[1] Therefore, guideline for prophylactic use of Rh(D) immunoglobulin in pregnancy care recommended administration of anti–D IgG prophylaxis in every non-sensitized Rh(D) –negative woman at 28 weeks of gestation during each pregnancy, immediately after delivery of every Rh(D)–positive child, or in any event such as abortion, miscarriage where the Rh(D)–negative mother is exposed to the Rh(D) antigen.[3]

Recommendations from the guideline[4]

Strong recommendation according to the guideline for prophylactic use of Rh(D) immunoglobulin in pregnancy care[4]
All pregnant women should undergo screening to identify ABO/Rh blood type and antibodies in their early pregnancy period.
Non-invasive prenatal testing (NIPT) must be conducted from 11^{+0} weeks of pregnancy for better accuracy in all Rh(D)–negative mothers.
Targeted antenatal Rh(D) immunoprophylaxis Rh(D)–negative mothers with no preformed anti–D antibodies.
Antenatal Rh(D) IgG must be administered in Rh(D)–negative mothers with no preformed anti-D antibodies to prevent Rh(D) alloimmunization.
Postnatal Rh(D) immunoprophylaxis should be continued in all Rh(D)–negative mothers with no preformed anti–D antibodies and Rh(D)–positive newborn (predicted by NIPT for fetal RhD)
Rh(D) immunoprophylaxis dose is not increased in Rh(D)–negative mothers with high body mass index.

Shortcomings of conventional mono and polyclonal anti-D immunoglobulin

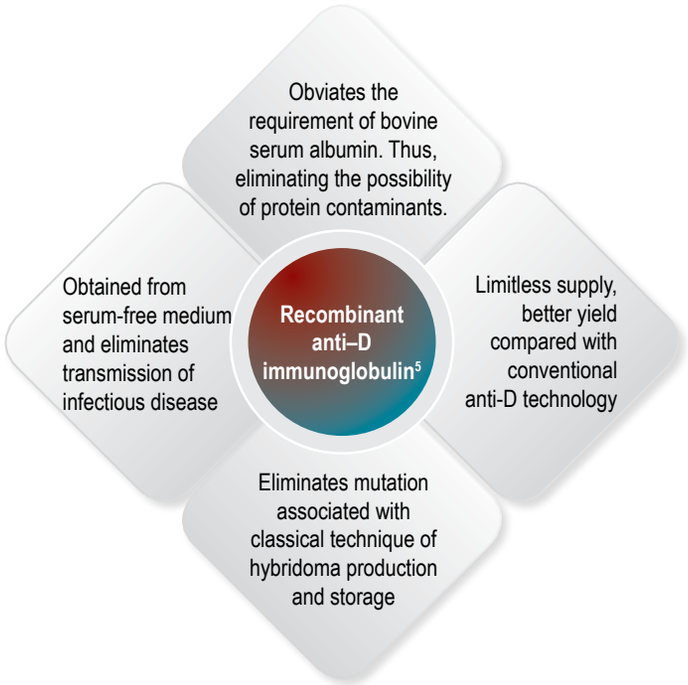
Conventional anti-D IgG prophylaxis[5]

- Polyclonal anti–D IgG prophylaxis: Fractionation of immunoglobulin from pooled plasma of donor (Rh[D]) –negative men who were deliberately immunized with Rh[D]–positive red blood cells).
- Monoclonal anti–D immunoglobulin: Produced by hybridoma technology.

Limitations[5]

- Shortage of volunteer Rh(D) –negative human donor
- Limited capacity of production (low yield)
- Risk of transmission of viral/prion diseases
- Hybridoma technology is time-consuming and laborious.
- Low availability of growth supplements such as fetal bovine serum (FBS)
- FBS might contain protein contaminants

Recombinant anti–D immunoglobulin: A novel successor of hybridoma-derived antibodies



Efficacy and safety of recombinant anti–D IgG when used in post-partum immune-prophylaxis

- A randomized controlled trial was conducted on Rh(D)–negative pregnant women who were not given antenatal anti–D and had delivered Rh(D)–positive babies and showed negative indirect Coombs tests (ICTs) at baseline. Researchers compared properties such as safety, efficacy, and immunogenicity of recombinant anti–D IgG with conventional polyclonal anti-D IgG prophylaxis in the trial. The subjects were randomized in a 2:1 ratio to recombinant anti–D group (n=144 women) and polyclonal anti-D group (n=71 women). The recombinant anti–D group was administered with 300 mcg of recombinant anti–D IgG, and the polyclonal anti-D group was administered with 300 mcg of conventional polyclonal anti-D IgG; the drugs were administered in both groups intramuscularly within 72 hours of delivery. Researchers conducted ICT at 72 hours, 90 and 180 days after injection of anti–D IgG; and bridging enzyme-linked immunosorbent assay (ELISA) was performed to quantify antibodies against recombinant anti–D IgG at 90 and 180 days.[5]

Finding showed that[5]:

» The baseline characteristics such as type of delivery, gestational age, and demographic of the recombinant anti–D group were comparable with the polyclonal anti-D group.

» At 180 days, researchers reported that 86.71% of subjects in the recombinant anti–D group and 91.04% in the polyclonal anti-D group had a negative ICT result. Moreover, Fisher's exact test calculation depicted that the p-value for ICT results at 90 days was p=0.30 and 180 days was p=0.49;

the results were not statistically significant owing to a comparable efficacy among recombinant anti–D and polyclonal anti-D group.

» Subjects in both groups (n=4) subjects in each group; < 1% in each group) experienced mild adverse events such as pyrexia, abdominal pain, itching, hypertension owing to a similar safety profile of recombinant anti–D IgG to polyclonal anti-D IgG.

» The ELISA test confirmed that no subjects developed antibodies against recombinant anti–D proving that recombinant anti–D IgG is non-immunogenic.

- Researchers conducted a randomized study on 46 healthy Rh(D)–negative pregnant women to investigate the safety and pharmacokinetics of recombinant anti–D. The subjects were administered with placebo or recombinant anti–D (dose: 30–3000 µg) intravenously (i.v.), and 12 among these subjects were administered with recombinant anti–D intramuscularly (i.m.); the subjects were observed for 6 months after administration.[6] Researchers found that[6]:

  » During the trial, 14 treatment-emergent adverse events (AEs) were reported in nine subjects. However, the AEs related to the treatment were mild or moderate and were observed evenly among subjects in the recombinant anti–D and placebo groups.

  » No human antibodies against recombinant anti–D IgG were reported in 6 months after its administration.

  » The mean serum exposure to recombinant anti–D IgG increased from 4.4 at 30 µg i.v. to 22,557 ng/ml.day at 3000 µg i.v. Also, the terminal elimination half-life ranged from 18–22 days, and absolute bioavailability was 73%-80% after IM administration.

Recombinant anti–D IgG was well-tolerated and safe intravenously and intramuscularly in Rh(D)–negative pregnant women. Also, the pharmacokinetic profile of recombinant anti–D IgG is similar to conventional polyclonal anti-D IgG. Thus, recombinant anti–D IgG is an effective and safe alternative to conventional polyclonal anti-D.[6]

Summary

- The conventional polyclonal anti-D IgG is accompanied by the risk of transmission of infectious disease and low production yield, whereas monoclonal anti–D IgG exhibited certain inherent limitations of hybridoma technology. These shortcomings led to research for an alternative method.
- Recombinant anti–D IgG eliminates infectious disease transmission and prevents classical hybridoma production technology problems.
- The efficacy and safety of recombinant anti–D was similar to the conventional polyclonal anti-D. Also, recombinant anti–D were non-immunogenic. Thus, recombinant anti–D IgG is well-tolerated, safe, effective, and suitable alternative to current anti–D IgG to prevent maternal alloimmunization.

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Association of Folate and Vitamin B12 with gestational diabetes mellitus: Mechanisms and fetal implications

Scientific Review

Dr. Elizabeth Jacob
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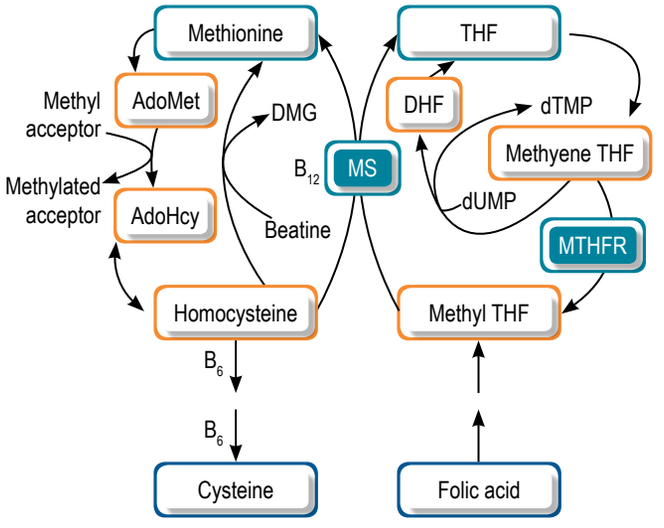
Impact of gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a common disorder during pregnancy that affects 12.9% of pregnant women worldwide. During pregnancy, the disease is characterized by new-onset of impaired glucose tolerance and insulin resistance, which can result in various adverse maternal and neonatal outcomes. Women with GDM are at an increased risk of preeclampsia, cesarean section, and post-partum diabetes mellitus, while neonates are at higher risk of obesity and diabetes mellitus later in life. Thus, identification and modification of potential risks factors for GDM can significantly impact both maternal and neonatal health.[1] Various studies have identified a relationship between maternal B vitamin imbalance, with high folate (Vitamin B9) and low vitamin B12 levels, and an increased risk of developing GDM.[2]

Role of folate and vitamin B12 during pregnancy

Folate and vitamin B12 are two essential nutrients for early pregnancy that are metabolically interlinked in one-carbon metabolism. Both are required for DNA methylation and production of nucleotides which are needed for increased cellular replication and fetal growth. Folate is one-carbon unit donor for the re-methylation of homocysteine to methionine and then to S-adenosylmethionine. Folate along with vitamin B12 as cofactor is necessary to maintain normal homocysteine levels, as high homocysteine levels are known to cause various pregnancy complications due to its pro-inflammatory effect (Figure 1). As a result, both these nutrients (folate and vitamin B12) are closely intertwined in this

FIGURE 1 Interrelation between folate, vitamin B12 and homocysteine metabolism[3]



AdoHcy: Adenosylhomocysteine; AdoMet: Adenosylmethionine; DHF: Dihydrofolate; DMG: Dimethylglycine; MS: Methionine synthase; MTHFR: Methylenetetrahydrofolate reductase; THF: Tetrahydrofolate

important metabolic function and deficiency of either of them can potentially result in pregnancy-related complications.[1,3]

Folate and/or B12 deficiency cause macrocytic anemia, neurological manifestations like cognitive decline and psychological disorders, and severe developmental delay in infants. Folate deficiency has long been linked to the development of neural tube defects (NTD) and congenital heart defects in the fetus.[2]

Folate, Vitamin B12, and Gestational Diabetes Mellitus: A link

The relationship between folate and vitamin B12 status and GDM is gaining interest in obstetrics. In the last twelve years, several studies have linked high folate in combination with low vitamin B12 status in mothers to an increased risk of GDM, as well as insulin resistance (IR) in offspring. A study including pregnant women found that mothers with vitamin B12 deficiency and high folate concentrations have the highest risk of GDM, with an odds ratio (OR) of 3.08 compared to high folate alone (OR=1.98) mothers, and that high vitamin B12 concentrations reduce the risk of GDM (OR=0.30).[2]

When a high folate/low vitamin B12 status was combined with a higher maternal age and pre-pregnancy BMI, Li et al., showed an even greater increase in GDM risk, indicating that nutrient imbalances and maternal factors can act synergistically to increase GDM risk.[2] Lai JS et al., also assessed the cross-sectional associations of plasma folate, vitamins B6, B12, and homocysteine concentrations with GDM and glycemia at 26 weeks' gestation in 913 pregnant women. The study demonstrated that higher maternal folate with low vitamin B12 levels were associated with higher GDM risk.[4]

The methyl-trap resulting in elevated homocysteine levels and impaired methylation reactions, as well as alterations in mitochondrial metabolism may be the contributory factors.[2]

Methyl-trap and gestational diabetes mellitus

In the presence of normal/high folate, vitamin B12 deficiency inhibits the intracellular conversion of 5-methyltetrahydrofolate to tetrahydrofolate and homocysteine to methionine, resulting in a functional folate deficiency, and a reduction in de novo purine and thymidine generation. The resultant impaired DNA synthesis could play a role in the development of IR.[2]

High folate levels in low vitamin B12 conditions can also oxidize the cobalt of vitamin B12, resulting in the formation of cob(II)alamin from the active methylcobalamin and cob(I)alamin forms of the enzyme. This prevents vitamin B12 from accepting the methyl group from 5-methyltetrahydrofolate as this reaction requires a highly reduced enzymatic. This could enhance the methyl-trap mechanism and the development of a functional folate deficiency and the exacerbating IR.[2]

Excessive folic acid consumption and gestational diabetes mellitus

High dose of folic acid supplementation in pregnant women can result in the appearance of un-metabolized folic acid in plasma. The presence of un-metabolized folic acid is linked to altered natural killer (NK) cell cytoactivity and this immune dysregulation has been associated in GDM pathology, through altering cell infiltration and signaling pathways.[2]

Association of elevated homocysteine and low methionine with gestational diabetes mellitus

A vitamin B12 deficiency, in addition to a functional folate deficiency, reduces the conversion of homocysteine to methionine. This can lead to two issues:

1. **Low methionine levels:** Because methionine is an essential amino acid, its deficiency can

decrease protein synthesis and lean tissue deposition. As increased adipose tissue volume impairs insulin sensitivity, a decrease in lean tissue mass can promote IR.[2]

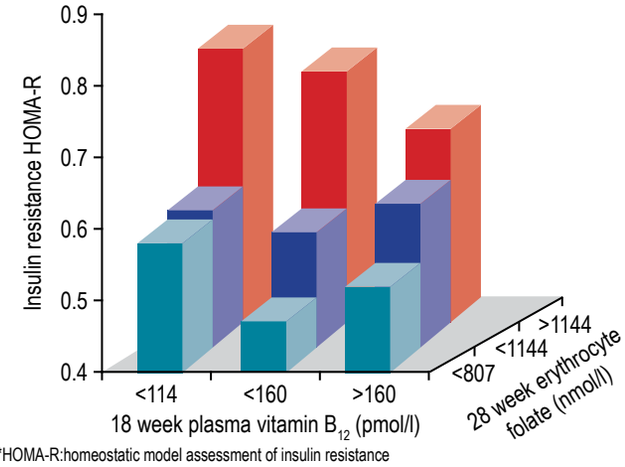
Methionine deficiency causes DNA hypomethylation and altered methylation has been linked to the pathogenesis of type 2 diabetes mellitus (T2DM). A similar mechanism may be involved in GDM.[2]

2. **High homocysteine levels:** Hyperhomocysteinemia (elevated homocysteine concentrations in plasma) have been associated with various diseases, including cardiovascular disease, dementia, osteoporosis, preeclampsia, and spontaneous pregnancy loss. Some of the pathogenetic consequences of high homocysteine include oxidative stress mediated apoptosis, endothelial and DNA damage. While several studies have also linked elevated homocysteine levels to the development of T2DM via IR and endothelial dysfunction, it is unclear whether this relationship is applicable to GDM risk. Some studies have demonstrated that women with GDM have significantly increased homocysteine concentrations as compared to non-GDM pregnant women.[2]

Maternal folate/vitamin B12 status and fetal implications

Yajnik et al., conducted a study to examine the association between maternal vitamin B12, folate, and total homocysteine (tHcy) status during pregnancy, children adiposity and insulin resistance at 6 years (n=674). The study showed that higher maternal folate concentrations at 28 weeks gestation, and lower maternal vitamin B12 concentrations at 18 weeks of gestation were associated with higher homeostatic model assessment of insulin resistance in children. The children of mothers with lowest vitamin B12 and highest folate concentrations were the most insulin resistant (Figure 2).[5]

FIGURE 2 Insulin resistance in children at 6 years in association with maternal vitamin B12 (18 weeks) and erythrocyte folate (28 weeks)



*HOMA-R:homeostatic model assessment of insulin resistance

Conclusion

Both folate and vitamin B12 are essential factors for nuclei acid synthesis, methyl group generation and conversion of homocysteine to methionine. Hence, balance of these factors needs to be looked into with further studies to understand the potential implications for maternal, fetal and neonatal health.

A systematic review and meta-analysis conducted also showed that no association was observed between serum folate and risk of GDM in majority of studies. Further, conflicting results were also observed between the risk of GDM with vitamin B12 deficiency.[1]

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Decorin: A novel biomarker to determine the quality of oocytes for ART

Infertility Corner

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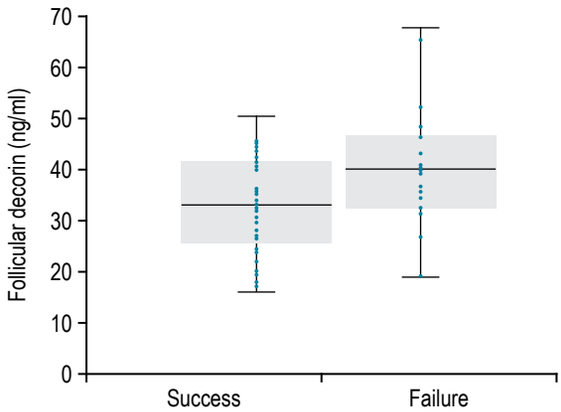
Decorin is a bioactive substance that belongs to leucine-rich proteoglycan family. In ovaries, decorin is present in the follicular fluid of ovulatory follicles, connective tissues, follicular thecal compartments, and corpus luteum. Decorin is reported to play a role in follicle growth, ovulation, and retaining the corpus luteum by regulating the growth factors. Granulosa cells (GCs) of pre-antral and antral follicles does not contain decorin, but the knowledge on its origin and expression in GCs of mature follicles is limited.

Considering the role of decorin in the development and maturity of oocytes, Sawada Y et al conducted a retrospective cohort study (130 oocytes of 88 patients, aged 27 to 50 years) to investigate if decorin is a useful biomarker for outcomes of assisted reproductive technology (ART). In this study, researchers have speculated that GCs of mature follicles might produce decorin. This assumption was supported by the immunocytochemistry and western blotting analysis that revealed the absence of decorin in the GCs of mature follicles.

Follicular decorin levels and fertilization outcomes

- Results showed that decorin levels in the follicular fluid (median value, 39.26 ng/ml) were approximately 8 times higher than that in the serum.
- Based on the receiver-operating characteristic curve, a cut-off level of 34.5 ng/ml was set for decorin.
- Fertilization rates of the oocytes of follicles with follicular decorin levels lower than 34.5 ng/ml was good when compared to that of oocytes with follicular decorin levels higher than 34.5 ng/ml (p=0.052).
- Oocytes fertilized by the intra cytoplasmic sperm injection (ICSI) had significantly lower levels of follicular decorin when compared to the oocytes that were not fertilized (p=0.043) (Figure 1).

FIGURE 1 Follicular decorin (median values) in the case of successful and failure fertilization using ICSI



- The sensitivity, 0.72, specificity, 0.58, positive predictive value, 0.86, and negative predictive value, 0.37, of follicular decorin signifies its possibility as a biomarker to predict the fertilization outcomes in ART.
- Therefore, with examination of the follicular decorin levels in the corresponding follicles during ICSI cycles, it is possible to predict the fertilization potential of oocytes.

Reference

Sawada Y, Sato T, Saito C, et al. Clinical utility of decorin in follicular fluid as a biomarker of oocyte potential. Reprod Biol. 2017. doi: 10.1016/j.repbio.2017.12.001.

Single vitrified-warmed ET with IVF: An effective fertility treatment strategy for hypogonadotropic hypogonadism

Infertility Corner

Women with hypogonadotropic hypogonadism (HH) have deficient secretion of gonadotropins from the pituitary gland which leads to diminished ovarian function.

Vitrification methods have shown high survival rates of embryos after warming and comparable pregnancy outcomes with that of fresh embryos transfer (ET). In women with HH, IVF with multiple fresh ET has shown acceptable clinical pregnancy outcomes but with a high multiple pregnancy rate. Single frozen-warmed ET with freeze all policy having low incidence of complications and is increasingly being used as an IVF treatment strategy. This also avoids the ET under non physiological conditions.

In a recent retrospective study, researchers analyzed the clinical outcomes of combined freeze-all embryos and single vitrified-warmed ET in infertile women with HH (n=79), during hormone replacement cycle. These women underwent 117 oocyte retrieval cycles. No competent embryo for freezing was obtained after oocyte retrieval and IVF in two cycles, and 135 vitrified-warmed ET cycles (n=77) were classified into 26 cleavage ET cycles and 109 blastocyst transfer cycles.

The results of the study revealed that:

Pregnancy outcomes after single vitrified-warmed blastocyst transfer

The rates of clinical pregnancy, live birth, and miscarriage in 26 single cleavage ET cycles and single vitrified-warmed blastocyst transfer are given in Table 1. The crude and expected cumulative live birth rate with 95% confidence intervals (CI) after the single vitrified-warmed ET procedures is given in Table 2.

Table 1. Pregnancy outcomes in infertile women with hypogonadotropic hypogonadism

	Cleavage embryo	Blasto-cyst	Total
No. of embryo transfer cycles	26	109	135
Clinical pregnancy (/embryo transfer)	9 (34.6 %)	71 (65.1 %)	80 (59.3%)
Ongoing pregnancy (/embryo transfer)	9 (34.6 %)	63 (57.8 %)	72 (53.3 %)
Live birth (/embryo transfer)	7 (26.9 %)	55 (50.5 %)	62 (45.9 %)
Miscarriage (/pregnancy)	2 (22.2 %)	16 (22.5%)	18 (22.5 %)
Multiple pregnancy (/embryo transfer)	0 (0)	0 (0)	0 (0)

Table 2. Cumulative live birth rate after single vitrified-warmed blastocyst transfer in women with hypogonadotropic hypogonadism

	Treatment cycle number		
	1	2	3
Crude cumulative live birth rate (%)	55.7	72.2	73.4
Low 95% CI (%)	44.6	61.3	62.6
High 95% CI (%)	66.2	80.9	82.0
Expected cumulative live birth rate (%)†	55.7	79.7	83.1
Low 95% CI (%)	44.6	67.7	70.1
High 95% CI (%)	67.2	88.0	91.1

†Expected cumulative live birth rate was estimated by taking into account the effect of censoring (Kaplan–Meier method). CI, confidence interval.

Conclusion

In women with HH, IVF with single vitrified-warmed ET in adjusted endocrine milieu during the HR cycle showed an improved live birth rate with a reduced risk of multiple conceptions. Therefore, IVF with single vitrified-warmed ET can be used as an effective fertility treatment for women with HH.

Single vitrified-warmed ET during IVF is an effective fertility treatment for women with HH. It improves the live birth rate and decreases the incidence of complications.

Reference

Kuroda K, Ezoe K et al. Infertility treatment strategy involving combined freeze-all embryos and single vitrified-warmed embryo transfer during hormonal replacement cycle for in vitro fertilization of women with hypogonadotropic hypogonadism. J Obstet Gynaecol Res. 2018;44(5):922–28.

Human Reproduction and Embryology

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Impact of paternal smoking during preconception: A risk for spontaneous miscarriage

Fossé N.D et.al. Paternal smoking in the preconception period is associated with an increased risk of spontaneous miscarriage in a dose-dependent manner: A systematic review and meta-analysis. Abstract number: P-718

Lifestyle disorders such as cigarette smoking, alcohol consumption, and obesity, apart from affecting general health, also significantly impact reproductive health. Risk factors for maternal-related miscarriage are known, but paternal risk factors are scanty. Biological evidence stipulates that paternal smoking, obesity, and excessive alcohol consumption can also lead to miscarriage. A meta-analysis and systematic review were conducted using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Researchers investigated the risk of spontaneous miscarriage due to smoking, alcohol intake, and body mass index. The paternal smoking was categorized into 1–10 cigarettes per day, 11–19 cigarettes per day, ≥20 cigarettes per day, and 'any smoking' (regardless of the quantity of smoking). Further, the study involved only cases where the mother is a non-smoker, or adjusted risk estimates were provided for maternal smoking. Paternal smoking of >10 cigarettes per day in the preconception period was found to be associated with an increased risk of spontaneous miscarriage after adjustment for maternal smoking status; {adjusted odds ratio [AOR] for total pregnancy loss is 1.01, [95% confidence Interval (CI) 0.97–1.06]} in the smoking 1–10 cigarettes per day category; AOR for total pregnancy loss is 1.12, [95% CI 1.08–1.16] in smoking 11–20 cigarettes per day category and AOR for total pregnancy loss is 1.23, [95% CI 1.17–1.29] for smoking >20 cigarettes per day). Results show a significant association between spontaneous miscarriage and paternal smoking. Therefore, paternal smoking during the preconception period can increase the risk of spontaneous miscarriage.

Abnormal vaginal and endometrial microbiome in women with chronic endometritis

Lozano FM. Characterization of vaginal and endometrial microbiome in patients with chronic endometritis (CE). Abstract number: O-143

Chronic endometritis (CE) is an inflammatory condition of the endometrial lining having a characteristic vaginal and endometrial microbiome. An observational cohort study was conducted to compare the endometrial and vaginal microbiome of women with and without chronic endometritis. The study involved 60 patients with endometritis prepared for assisted reproductive technologies (ART). The vaginal and endometrial samples was taken from both patients with and without endometritis before embryo transfer for Preimplantation Genetic Testing of aneuploidy (PGT-A). Results show that patients with and without endometritis had a difference in the vaginal and endometrial microbiome. Patients with endometritis had higher alpha diversity in vaginal samples (p=0.15 for the Shannon index), and significant differences were also reported in endometrial samples (p=0.01 for the Shannon index). No significant difference was observed in beta diversity between the groups with and without endometritis. So, endometrial and vaginal samples diagnosed with endometritis showed a significant difference in both alpha diversity (p=0.06 for the Shannon index and p=0.08 for the Simpson index) and beta diversity (p<0.001). Women with endometritis had a higher abundance of microbiome other than *Lactobacillus* spp., identified as *Ralstonia* and *Gardnerella, in* the endometrial sample, and the genera *Streptococcus* and *Ureaplasma* in the vaginal sample. Patients with chronic endometritis have characteristic vaginal and endometrial microbiota, and species differ in patients with or without chronic endometritis. Thus, abnormal vaginal microbiota and chronic endometritis are associated.

Cesarean section: Impact on uterine vascularity and its effect on future ART outcomes

Moliner B. Uterine vascularity in women with previous caesarean section and its potential role in implantation failure: A retrospective cohort study. Abstract number: P-286

Uterus vascularization and contractility are distorted after cesarean section (CS). A previous history of CS reduces the live birth rate in assisted reproductive treatment compared with vaginal delivery. A retrospective study investigated the effect of CS on uterine vascularization and its consecutive effect on embryo transfer. Researchers examined 196 patients undergoing embryo transfer, and 12 of these patients had previously undergone CS. After defining the endometrial volume, all patients underwent an investigation of vascularization parameters like vascularization index (VI) and vascularization flow index (VFI). Further, uterine contractility was also assessed by 4D ultrasound. Results showed that both the CS and control groups had similar baseline characteristics. However, the 3D vascularization parameters of the CS group were significantly lower than those of women with previous vaginal delivery (control group). VI observed in CS group was 0.8% as compared to control group (2.3%; p=0.038), VFI was 0.2% in CS group and 2.3% in control group (p=0.038). Also, uterine contractility was lower in the CS group (0.8 contractions per minute) than in the control group (1.1 contractions per minute; p=0.154). Therefore, CS caused a decrease in uterine vascularization parameters owing to a reduction in uterine irrigation, negatively impacting assisted reproductive treatment.

What's New in Gynecology ?

Association of placental iron with maternal iron status in women at risk of gestational IDA

Barad A, Guillet R, Pressman EK, et al. Placental iron content is lower than previously estimated and is associated with maternal iron status in women at greater risk for gestational iron deficiency and anemia. J Nutr. 2021; nxab416. doi: 10.1093/jn/nxab416

Estimation from limited data presented that the placenta retains 90 mg of iron (Fe) to support placental needs. Researchers conducted a study to characterize placental Fe content, measure placental Fe concentration (p[Fe]), and establish p[Fe] determinants. They collected placentae from singleton-carrying teens (age ≤18 years, n=132) and women carrying multiples (age: 20–46 years, n=101). The Fe status indicators [hemoglobin, serum ferritin (SF), transferrin receptor (sTfR), serum Fe, total body Fe (TBI)] and regulatory hormones (erythropoietin (EPO), hepcidin) of mother and child were measured. Findings showed that in the women carrying multiples, the mean placental Fe content was 23 mg per placenta (95% confidence interval [CI] 15–33) and in teens 40 mg per placenta (95% CI, 31–51; p=0.03). Also, in women carrying multiples, anemic patients showed higher placental Fe concentration (175 µg/g; 95%CI) vs. non-anemic (46 µg/g, 95%CI; p=0.009). Further, the researchers observed that women carrying multiples having low maternal Fe status [low SF (p=0.002) and low TBI (p=0.01)] showed higher p[Fe] and improved Fe status [lower sTfR (p=0.03) and higher TBI (p=0.03)] in teens was associated with higher p[Fe]. Researchers concluded that the placental content of Fe ~50% lower than previously estimated, and p[Fe] (placental concentration) is significantly related to the maternal Fe status.

Moringa oleifera leaf flour biscuits: A novel approach to prevent anemia during pregnancy

Loa M, Hidayanty H, Arifuddin S, et al. Moringa oleifera leaf flour biscuits increase the index of erythrocytes in pregnant women with anemia. Gac Sanit. 2021 35 Suppl 2: S206-S210. doi: 10.1016/j.gaceta.2021.10.022

Anemia is a critical factor leading to serious maternal or fetal complications. *Moringa oleifera* leaves are rich in essential micronutrients that prevents anemia in pregnant women. Researchers studied the impact of consumption of *Moringa oleifera* leaf flour biscuits on the erythrocyte indices; including mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH). They included pregnant women suffering from trimester I and III anemia and divided them into two groups: the biscuit moringa group (n=25) and the control group (n=25). Researchers observed that:

- In the moringa biscuit group, the MCH value increased from 27.55 to 28.00 (mean difference=0.45, p=0.001), and the MCV level increased from 78.57 to 78.93 (mean difference=0.36; p=0.034) owing to a significant increase in both MCH and MCV values before and after consumption of biscuit (p<0.05).
- In control group, the MCH value increased from 26.85 to 26.87 (mean difference=0.02, p=0.584) and the MCV level increased from 77.92 to 77.94 (mean difference=0.02; p=0.881); this showed that the difference in erythrocyte indices before and after treatment were not significant (p>0.05).

Consumption of moringa leaf flour biscuit significantly increased the MCH and MCV value (erythrocyte indices) and showed no significant effect on the MCHC value in pregnant women with anemia. Thus, using moringa leaf (a locally available plant) is beneficial to prevent anemia in pregnant women.

REWIND

HIGH RISK PREGNANCY

Hello friends,

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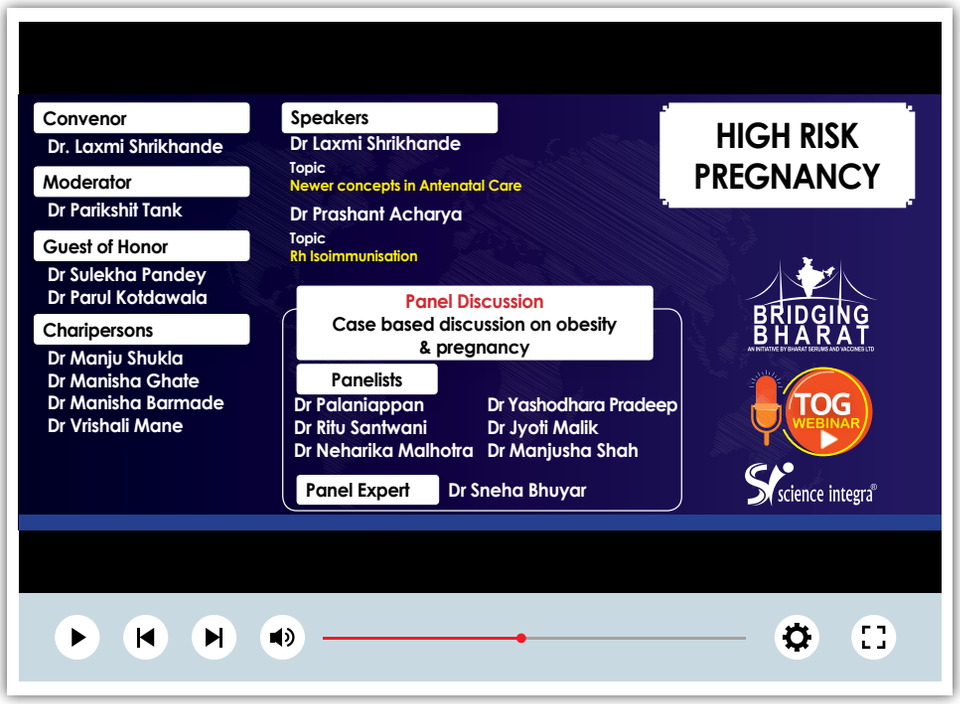

Gynec-o-Pedia

1. Premenstrual syndrome (PMS) has a constellation of possible symptoms. Which of the following would NOT be expected?

A. Abdominal bloating ❑
B. Weight loss ❑
C. Constipation ❑
D. Anxiety ❑
E. Breast tenderness ❑

2. A 46-year-old, non-pregnant, morbidly obese woman presents with irregular periods over the past 6 months. Which of the following represents the most appropriate initial management in this setting?

A. Oral contraceptives ❑
B. Endometrial ablation ❑
C. Office hysteroscopy ❑
D. Dilation and curettage (D&C) ❑
E. Endometrial biopsy ❑

3. A 48-year-old woman presents to the office with a several year histories of low pelvic pain. Which of the following is the LEAST likely cause?

A. Interstitial cystitis ❑
B. Adenomyosis ❑
C. Ectopic pregnancy ❑
D. Herniated disc ❑
E. Inflammatory bowel disease ❑

4. A number of screening tests are performed in all pregnancies at designated gestational ages. Which of the following screening tests is correctly matched with the gestational age?

A. Glucose load test at the first prenatal visit ❑
B. Fetal anatomic survey at 34–36 weeks ❑
C. Chlamydia test at 22–24 weeks ❑
D. Group B β-hemolytic streptococcus (GBS) carrier status at 35–37 weeks ❑
E. Rubella serology at the 6-week postpartum visit ❑

5. A patient who is a chronic hepatitis B carrier delivers vaginally at 39 weeks' gestation. The baby should receive which of the following therapies on the first day of life?

A. Hepatitis B immune globulin (HBIG) ❑
B. Hepatitis B vaccination ❑
C. HBIG and hepatitis B vaccination ❑
D. None of the above ❑

Answers: 1. B; **2.** E; **3.** C; **4.** D; **5.** C

LIVING ARTFULLY

RUBIK'S CUBE

Also known as Magic cube is a 3-dimensional combination puzzle created by Ern Rubik in 1974. This magic cube has various qualities such as permutation-combinations, cycle, and symmetry. Therefore, solving Rubik's cube has an array of benefits.

Improves eye-hand coordination

Aids development of quick reflexes

A good stress-buster and provides relaxation of mind

Improves brains' cognitive skills and thinking capacity

Improves problem-solving skills, focus, attention and makes mind sharp and active.

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IN ANOVULATORY INFERTILITY

HUCOG HP

Highly Purified Chorionic Gonadotrophin (2000. I.U. / 5000 I.U. / 10,000 IU)

The "Trusted HCG Brand in INDIA"

The No. 1 HCG in INDIA**

Unique PFS Packaging

Precise
Accurate dosing[1]

Fast
Faster Delivery[1]

Safe
Sterile[1]

1. Makwana S, Basu B, Makasana Y, et al. Prefilled syringes: An innovation in parenteral packaging. Int J Pharm Investig. 2011;1(4):200–206.

**Awacs Mar 2021

HUCOG HP

Highly Purified Chorionic Gonadotrophin (2000. I.U. / 5000 I.U. / 10,000 IU)

The"Trusted HCG Brand in INDIA"

Composition:

Each ml contains: Chorionic Gonadotrophin highly purified I.H. ..... 2000 I.U. / 5000 I.U. / 10000 I.U.

Water for Injection I.P. ..... q.s.

Excipients & Stabilizers: Disodium Hydrogen Phosphate Dihydrate B.P., Benzyl Alcohol I.P., Sucrose I.P., Poloxamer 188 U.S.P./NF, Methionine B.P., Phosphoric acid I.P.

One IU of Chorionic Gonadotrophin is defined as the activity contained in 1.279 mg of the 2nd International Standard Preparation.

Properties: Chorionic Gonadotrophin (HCG) is a hormonal substance obtained from urine of pregnant women. Its action is predominantly luteinizing.

Indications :

Anovulatory infertility: In the female, HUCOG HP® is used in the treatment of anovulatory infertility. where its administration would form part of recognized treatment regimen involving prior stimulation of follicular maturation and endometrial proliferation e.q. with Menotropin Injection (HUMOG HP).

Hypogonadotrophin hypogonadism and cryptorchidism: In the male, HUCOG HP® stimulates the interstitial cells of the testes and consequently the secretion of androgens and the development of secondary sexual characteristics. With concomitant Menotropin Injection therapy, HUCOG HP® stimulates the induction and maintenance of spermatogenesis.

Dosage and Administration: HUCOG HP® is given by Subcutaneous injection only.

Anovulatory infertility: HUCOG HP® 10000 I.U. is administered in mid-cycle, following treatment with Menotropin Inj. (HUMOG HP) according to a recognised scheme. Details of Menotropin Inj. (HUMOG HP) dosage and monitoring are available on request.

Hypogonadotrophic hypogonadism: HUCOG HP® 2000 I.U. twice weekly concomitant with Menotropin Inj. (HUMOG HP) (1 vial three times a week) if necessary for a minimum period of four months.

Cryptorchidism: Dosing schedule is age dependent and can be modified as per the physicians discretion according to response. Dose of 250 I.U. twice weekly for children less than 1 year of age, 500 I.U. for children between 1 and 5 years of age, and 1000 I.U. for children above 5 years of age.

Contra-Indication and Warnings: Stimulation of ovulation with HUCOG HP® may lead to superovulation and the hyperstimulation syndrome. Oestrogen assays will detect the excessive response so that HUCOG HP® (HCG) may be withheld in that particular treatment cycle. In the male, high dosages of HUCOG HP® may lead to oedema and in such cases dosages should be considerably reduced. If signs of sexual precocity are observed a reduced dosage regimen should be instituted.

Side Effects: Headache, irritability, restlessness, depression, fatigue, edema, gynecomastia, sexual precocity, pain at the site of injection.

Adverse Events: The adverse reactions for use in infertility are: (1) Ovarian hyperstimulation (OHSS), a syndrome of sudden ovarian enlargement, ascites with or without pain, and/or pleural effusion, (2) Rupture of ovarian cysts with resultant hemoperitoneum, (3) Multiple births, and (4) Arterial thromboembolism.

PRECAUTION: HCG should be used in conjunction with human menopausal gonadotropins only by physicians experienced with infertility problems who are familiar with the criteria for patient selection, contraindications, warnings, precautions, and adverse reactions described in the package insert for menotropins.

Interaction with other medicinal products and other forms of interaction: Concomitant use of HUCOG HP® Injection with other agents used to stimulate ovulation (e.g. HMG, clomiphene citrate) may potentiate the follicular response. (See Warnings, Precaution & Overdosage.)

Overdose: The effects of an overdose of HUCOG HP® Injection are unknown, nevertheless one could expect ovarian hyperstimulation syndrome (OHSS) to occur, which is further described as below:

Ovarian Hyperstimulation Syndrome (OHSS) : (See Warnings): OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS is a syndrome that can manifest itself with increasing degrees of severity. It comprises marked ovarian enlargement, high serum sex steroids, and an increase in vascular permeability which can result in an accumulation of fluid in the peritoneal, pleural and, rarely, in the pericardial cavities.

The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea.

Adherence to recommended HUCOG HP® Injection dosage, regimen of administration and careful monitoring of therapy will minimize the incidence of ovarian hyper stimulation and multiple gestations. In ART, aspiration of all follicles prior to ovulation may reduce the occurrence of hyper stimulation. OHSS may be more severe and more protracted if pregnancy occurs. Most often, OHSS occurs after hormonal treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If severe OHSS occurs, gonadotrophin treatment should be stopped if still ongoing, the patient hospitalized and specific therapy for OHSS started. This syndrome occurs with higher incidence in patients with polycystic ovarian disease.

Ovarian response should be carefully monitored to minimize the risk of overstimulation. If the ovaries are abnormally enlarged on last day of gonadotrophin therapy, HCG should not to be administered in this course therapy. This reduces development of OHSS (Ovarian Hyperstimulation Syndrome). Use of ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels can further minimize the risk of overstimulation.

Storage: HUCOG HP® should be stored between 2^0C - 8^0C. Do not freeze. Protect from light. Any unused portion should be discarded.

Presentation: HUCOG HP® is supplied in pre-filled syringes containing sterile having activity of 5000 I.U.
HUCOG HP® is supplied in vials containing sterile having activity of 2000 I.U. / 5000 I.U. / 10000 I.U.

To report the occurrence of any adverse event with this product, please visit https://www.bharatserums.com/adverse.html or write to pv@bharatserums.com

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

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