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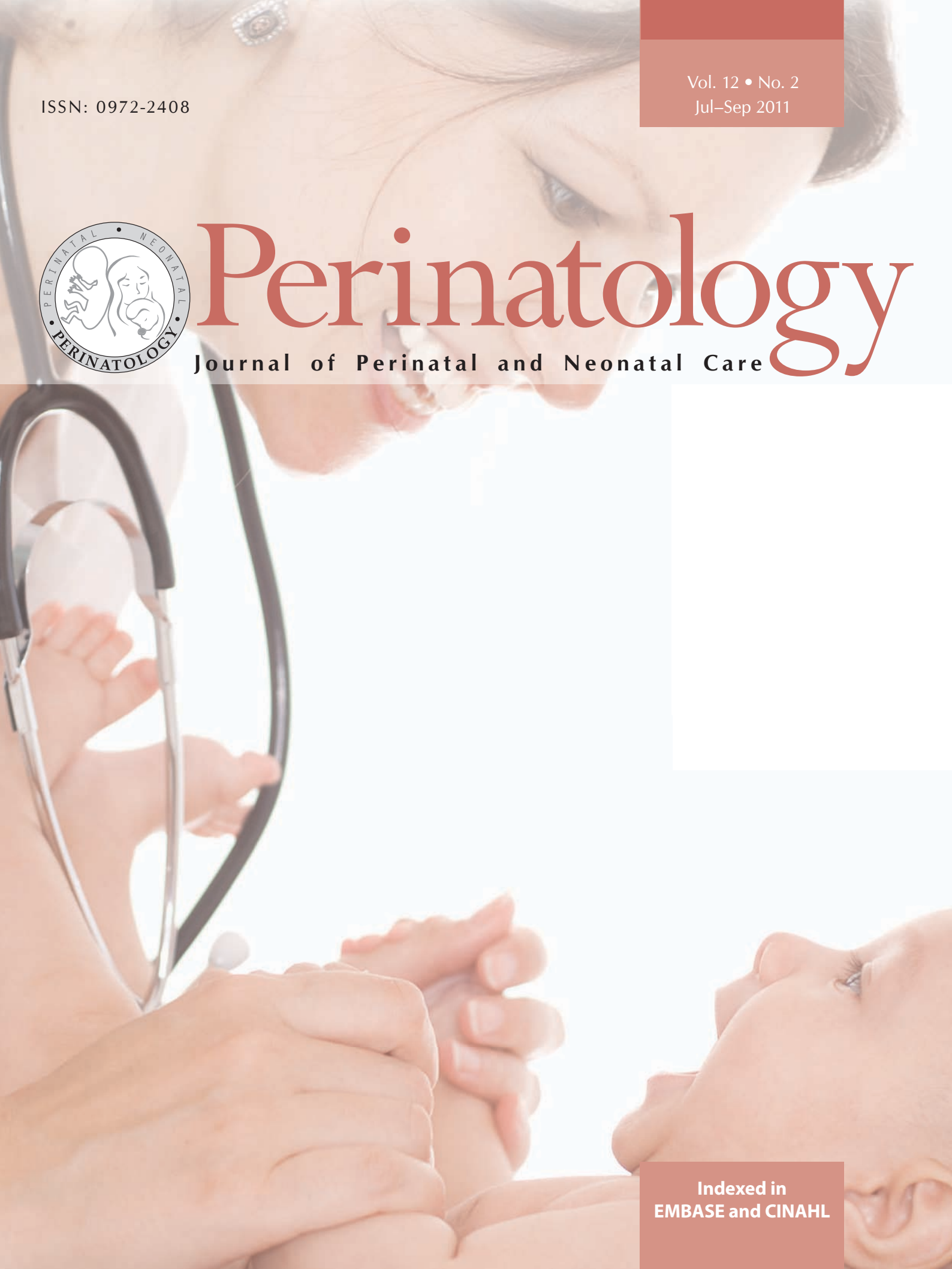
Perinatology

Journal of Perinatal and Neonatal Care



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General Information

The Journal

Perinatology (ISSN 0972-2408), one of the few journals dedicated to the emerging multidisciplinary field of perinatal medicine, is published and distributed quarterly (in the months of January, April, July, and October every year) at The Himalaya Drug Company. The journal publishes original research articles, review articles, brief reports on clinical and laboratory observations, case reports, and clinical studies. The journal is indexed in EMBASE, the Excerpta Medica database, CINAHL® database, and Cumulative Index to Nursing and Allied Health Literature® print index.

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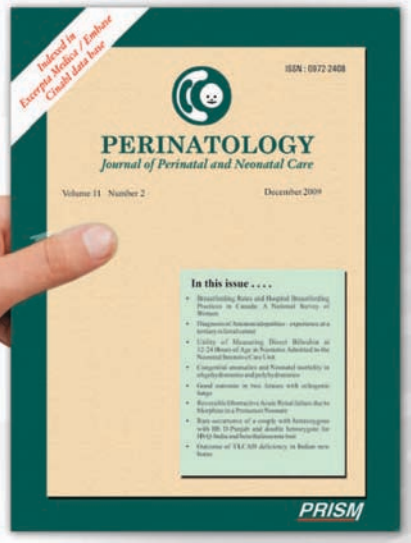
Contents



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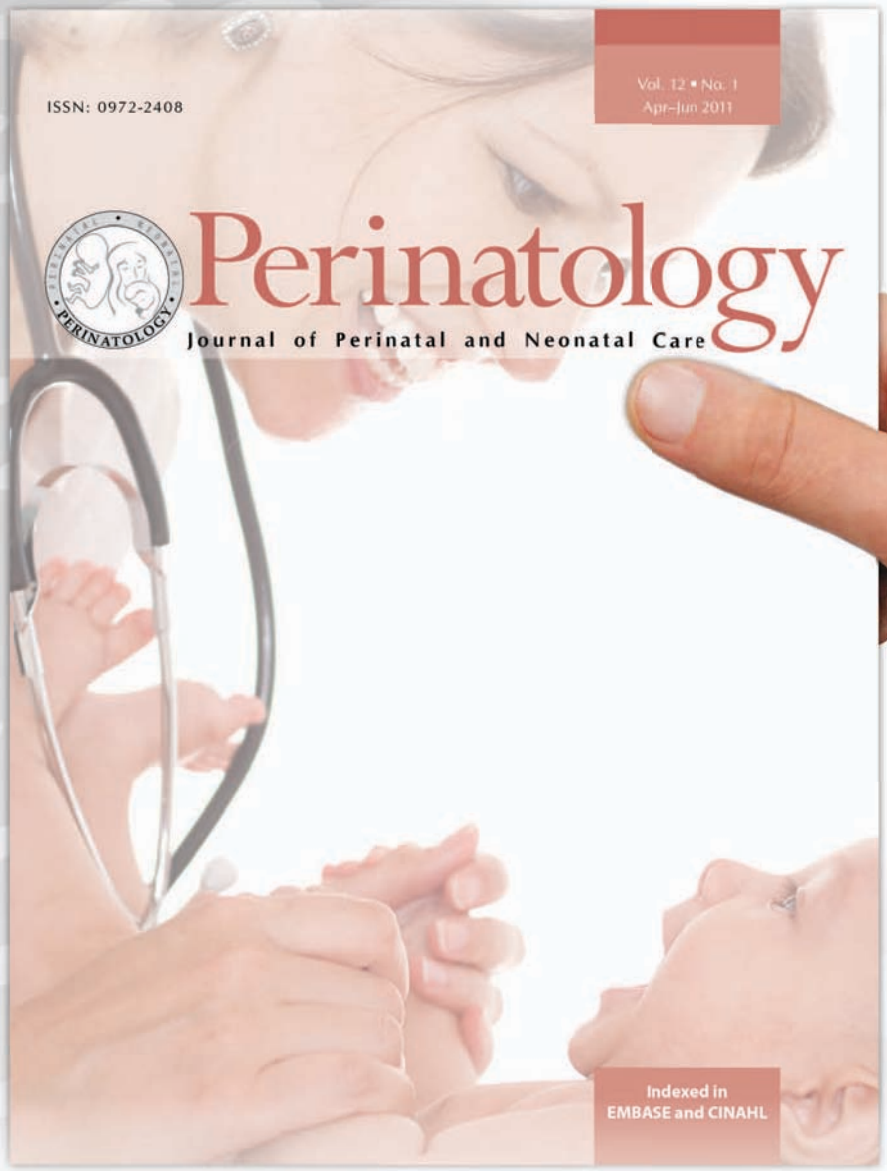

Now in a new look...

Perinatology

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Editorial

Dear friends,

On behalf of the editorial board and publishers, I am glad to present the second issue of Volume 12. You may have noticed that the first issue, which is published under the new publisher—The Himalaya Drug Company, has a new look, and an improved layout and style. I look forward to your feedback, suggestions, and comments which will help us in our endeavor to achieve higher standards.

In the current Union budget, there have been some disappointing features in relation to health care, such as the increase in duty on medicines. However, the overall fund allocation for health sector has been increased by 20% when compared to the previous year. The allocation for National Rural Health Mission (NRHM) has also been increased with a view of reaching every common man. In addition to the funds allocated, we need motivation among all the people who will be a part of health care sector. Let us re-dedicate ourselves to work hard and have an efficient, friendly, and affordable health care infrastructure.

In this issue, there is an array of articles related to perinatal health care in addition to the many regular features. I hope you will find them interesting and informative.

Dr Ranjan Kumar Pejaver
Editor in chief

Perinatology
Journal of Perinatal and Neonatal Care
Vol. 12 • No. 2 • Jul–Sep 2011

World Breast-feeding Week 2011

World Breast-feeding Week (WBW) will be held from August 1–7, 2011. The theme of WBW this year is "Talk to Me! Breast-feeding—a 3D Experience."

Objectives

- **Support:** Identify people in your network to work with and design programs or events for WBW. Remember, it is a team effort!
- **Promote:** Take advantage of the theme of this year and find creative ways to publicize your events. Try linking with universities and health centers that reach wider audiences.
- **Protect:** Sustain the momentum from your WBW celebrations—interview your participants about their experience, gather simple statistics on breast-feeding in your community, and use these results to lobby for a breast-feeding friendly environment.

WBW Celebration Awards

The Breast-feeding Promotion Network of India (BPNI) is happy to announce awards for WBW 2011 in the following categories.

- Individuals—10 prizes for best activities
- Organizations—10 prizes for best activities

The award consists of a memento and a certificate from BPNI. If the activities you plan to undertake are informed, in advance, to BPNI office, they could promote your organization by publicizing the activities on the BPNI Website.

The decision of the BPNI National WBW Coordination Committee with regard to the awards will be considered final. The prizes will be announced on November 15, 2011 and the list of the award winners will be published on the BPNI website.

Breast-feeding Promotion Network of India (BPNI)
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PERINATOLOGY • Vol. 12 • No. 2 • Jul–Sep 2011

Rapid versus Slow Intravenous Iron Sucrose Administration in an Indian Rural Pregnant Population with Iron Deficiency Anemia

Hema Divakar,* Gautham MS, Manyonda IT

Abstract

Background and Objectives: The iron folic acid (IFA) program launched in India around 30 years ago, to provide free iron and folate supplements to pregnant women for eradicating iron deficiency anemia (IDA), has evidently failed as the prevalence of IDA during pregnancy still remains to be >50%. Intravenous administration of iron sucrose circumvents many of the obstacles that have contributed to the failure of IFA program, but requires careful and rigorous evaluation in a low resource setting such as India. This study was conducted to compare the efficacy, safety, and cost of two methods of administering intravenous iron sucrose—the conventional slow intravenous infusion and the rapid bolus push technique.

Patients and Methods: The study included 152 pregnant women at 20 to 24 weeks of gestation with iron deficiency anemia (Hb <11g/dL) attending two rural antenatal clinics in India between November 2008 and February 2009. The patients were randomly divided into two groups to receive 400 mg intravenous iron sucrose either by the conventional slow infusion technique (Group A: n = 75) or by the rapid bolus push technique over 2 to 5 minutes (Group B: n = 77). Iron was administered in two equal doses of 200 mg each at an interval of 2 to 4 days. Any adverse reactions were recorded after the first injection. Posttreatment Hb was estimated at 4 weeks. Data were analyzed using SPSS version 11. Per unit additional costs incurred were calculated for each method.

Results: The two groups were comparable with regard to patient demographics and pretreatment hemoglobin. A statistically significant ($P<.05$) increase in the mean Hb level compared to baseline was observed in both the groups. However, there were

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no differences in the mean increase in the Hb levels between the two groups. Minor adverse reactions were reported in 5 (6.7%) women in group A and 15 (19.5%) women in group B ($P<.05$). No major adverse events necessitating hospitalization were reported in either group. Cost analysis revealed that the bolus push technique was seven times cheaper than the slow infusion technique (INR 30 versus INR 200).

Conclusions: The bolus push technique may represent a cost-effective approach to the mass treatment of iron deficiency anemia during pregnancy in low-resource settings.

Key Words: Iron deficiency anemia (IDA), iron folic acid (IFA), pregnancy, hemoglobin (Hb), IV iron sucrose

Introduction

Nearly 40 years after the initiation of the iron folic acid (IFA) program to provide free iron/folic acid supplementation to all pregnant women starting from the second trimester till 3 months of lactation, studies show that the prevalence of iron deficiency anemia (IDA) during pregnancy in India is increasing and ranges between 50% and 60%.[1,2] Thus, the IFA program has failed to meet its primary objectives. The reasons include partial coverage of the population, inadequate dosing of the iron supplement, short supplies, defective absorption due to intestinal infestations, diets containing high levels of iron chelators, problems with formulation, inadequate consumption or poor compliance by the beneficiaries, failure to replenish the stocks at the beneficiary level, and lack of effective health education and supervision.[3] In the developed countries, it has been found that intravenous (IV) iron supplementation is effective in the treatment of IDA in various conditions, including pregnancy. There are evidences that compared to oral iron, IV iron sucrose results in a much more rapid resolution of IDA,[4,5] has minimal side effects, and circumvents many of the problems associated with the IFA program such as noncompliance. Unlike intravenous dextran iron, anaphylactic reactions are very rare with iron sucrose.

According to conventional practice, iron sucrose should be administered by a slow intravenous infusion at doses of 50 to 100 mg at one sitting. As a majority of Indian women get afflicted by mild to moderate anemia during pregnancy, they would require multiple infusions to make up for the total dose calculated by the standard formula [2.4 × weight in kg × (target Hb – actual Hb)] and each such infusion increases the cost of treatment significantly. It has been observed that despite educational campaigns and other measures to encourage the uptake of treatments, there is poor response in cases when a treatment requires several hospital visits. Therefore, the challenge is to develop and/or evaluate treatment regimens that are efficacious, safe, and cost-effective and minimize hospital visits.

A prospective randomized trial was conducted to compare the efficacy, safety, and cost of providing intravenous iron sucrose via a bolus push technique over 2 to 5 minutes with the conventional slow intravenous infusion. A maximal permissible dose of 200 mg of IV iron sucrose was administered at one sitting, instead of 50 to 100 mg per dose, in order to minimize the number of visits and maximize compliance.

Patients and Methods

Study subjects

Pregnant women with anemia (Hb <11g/dL) and gestational age of 20 to 24 weeks were included in the study conducted between November 2008 and February

2009 at two rural antenatal clinics in southern India. Women who were taking oral iron supplement, had received a blood transfusion within last 1 year, and those previously investigated and confirmed to be carriers of either thalassemia or sickle cell gene were excluded from the study. Written informed consent was obtained from all participants.

Sample size

In a recent study, a prevalence rate of 69.4% for iron deficiency anemia was reported in rural settings in India (Divakar et al, 2009; submitted). Using this prevalence rate the sample size to assess the two modalities of parenteral iron sucrose therapy was calculated using nMaster software, with a relative precision of 12% and α error at 5% (95% confidence interval). It was calculated that 60 women would be required in each arm.

Study design

Randomized controlled trial.

Methodology

Mebex Plus (Mebendazole and Pyrantel Pamoate from Cipla India Pvt Ltd) was administered at a dose of two tablets to all women for deworming before starting the treatment. Hb estimation was performed using Shali's method.[6,7] Each woman received a total dose of 400 mg intravenous iron sucrose divided into two equal (200 mg) doses administered 2 to 4 days apart, regardless of the pretreatment level of Hb measured before intervention. No specific calculations were conducted to tailor iron sucrose dose to the woman's pretreatment Hb level, unlike conventional therapy. Women were randomized to receive iron sucrose as a slow intravenous infusion in 100 mL saline for 30 minutes (Group A: n = 75), or rapid intravenous bolus push for 2 to 5 minutes, administered through a venous butterfly cannula (Group B: n = 77). No test dose was given, and all women were closely observed for up to 30 minutes for adverse reactions (after the first dose) such as nausea, burning sensation at infusion site, local pain, rashes, and breathlessness during or immediately after the injection. If an adverse reaction occurred and did not resolve in 15 to 20 minutes, one vial of hydrocortisone (100 mg) was given intravenously. Women were advised to contact the unit if they developed any subsequent symptoms. These women were not given any further oral iron supplement. Posttreatment Hb level was measured after 4 weeks of the second dose of iron sucrose.

Cost analysis

The costs involved in the infusion method included costs of 100 mL normal saline (0.9%), intravenous set, cannula, and infusion and bed occupancy charge for 1 hour (30 minutes infusion + 30 minutes observation). The push method considered costs of 10 mL saline (0.9%) and syringe.

Statistical analysis

Data were analyzed using SPSS version 11 (Statistical Package for Social Sciences) software. Paired *t* test was used to estimate the significance of difference between the mean change in Hb levels within each group and between the two groups of women. Student's *t* test was used to test the significance of differences between mean Hb levels of the two groups at baseline and at 4 weeks of treatment. Independent *t* test was used to compare the mean change in Hb percentage between group A and group B.

Results

Characteristics of participants

A total of 152 women participated in the study. The women were divided into two groups: group A comprised of 75 women (40 primigravidae and 35 multigravidae) and group B comprised of 77 women (37 primigravidae and 40 multigravidae). The mean age, parity, and weight were comparable in both groups (Table 1).

Adverse reactions to intravenous iron sucrose

After the first dose, 5 of the 75 women in group A (6.7%) and 15 of the 77 women in group B (19.5%) reported minor adverse reactions, such as giddiness, generalized itching/burning, local pain, gastrointestinal

symptoms (such as nausea), burning at the infusion site, swelling in extremities, and chest discomfort (Figures 1a and 1b). Two women in group B required intravenous hydrocortisone 100 mg when they developed rashes and GI symptoms lasting more than 20 minutes, and all symptoms and signs resolved within 20 minutes of administering the hydrocortisone. Major side effects necessitating hospitalization was not reported by any women.

In group A, 19 women lost to follow up, including 2 with adverse reactions. In group B, 22 women lost to follow up, including 4 with adverse reactions after the first dose.

In group A, 10 women did not come for the second injection but came after 4 weeks for regular antenatal checkup, 7 came for the second injection but did not come for Hb estimation after 4 weeks, and 2 attended neither the second dose of injection nor the subsequent antenatal checkup.

In group B, 7 women did not come for the second injection but continued to come for further antenatal checkup, 12 came for the second injection but did not attend the Hb test after 4 weeks, and 3 failed to attend both the second injection and Hb estimation after 4 weeks.

Hb changes in response to intravenous iron sucrose

Both groups had comparable pretreatment levels of Hb (group A: mean Hb = 9.3 g/dL [SD = 0.8] and group B: mean Hb = 9.2 g/dL [SD = 0.7]).

The posttreatment Hb level was measured in all women who were available for follow-up (group A: n = 56 and group B: n = 55). Both groups showed a statistically significant (P<.05) increase in Hb level at 4 weeks as compared to baseline (group A: mean Hb = 10.2 g/dL [SD = 0.8] and group B: 10.3 g/dL [SD = 0.7]; Table 2).

Mean changes in Hb level in the two groups posttreatment were 0.92g/dL (SD = 0.75) and 1.10g/dL (SD = 0.87) in groups A and B, respectively. The differences in changes in mean Hb level between the groups after treatment was not statistically significant (P = .227).

Change in severity of anemia in response to intravenous iron sucrose

Change in severity of anemia in response to intravenous iron sucrose was assessed women who received both doses of iron sucrose and attended for Hb estimation at 4 weeks (56 in group A and 55 in group B). Changes in group A were as follows: 3.6% women were in the severe anemia category prior to the treatment, whereas, at 4 weeks there were none; the prevalence of moderate anemia decreased from 76.8% to 19.6%; rates mild anemia increased from 19.64% to 66%; and 14.3% of women with mild anemia were rendered nonanemic. The corresponding changes in group B were as follows: there were no women with severe anemia at baseline; the prevalence of moderate anemia decreased from 81.8% to 18.2%; whereas, mild anemia increased from 18.2% to 67.3%; and 14.5% of women with mild anemia at basement were rendered nonanemic (Figures 2a–c).

Comparison of cost between slow intravenous infusion and the bolus push technique

Costs involved in the infusion method included the costs of 100 mL normal saline (0.9%), intravenous set, cannula, and infusion and bed occupancy charge for 1 hour (30 minutes infusion + 30 minutes observation) amounting to Indian rupees (INR) 200 per injection in group A. In group B, the cost of 10 mL saline (0.9%) and syringe with needle was INR 30. Thus, the bolus push technique was seven times cheaper than the slow infusion technique.

Discussion

The case for establishing supplementation programs that can effectively eradicate IDA during pregnancy in developing countries cannot be overstated. In India, where maternal mortality is as high as 350 to 450 per 100,000 live births (a figure similar to that found in Europe 200 years ago), anemia is estimated to lead to 20% of all maternal deaths.[8–10] The often unrecognized consequence of maternal IDA is the impact

on the fetus, newborn, child, and subsequent adult. Anemia and iron deficiency during pregnancy are associated with large placental weight and a high placental ratio (ratio of placental weight to birth weight), both of which are predictors of adult hypertension.[11,12] In newborns, IDA is associated with poor performance in the Bayley Mental Development Index.[13] Although nutritional factors may be contributory, it is likely that IDA during infancy and early childhood is largely secondary to maternal iron deficiency during pregnancy. The definitive solution is to eradicate iron deficiency during or before pregnancy. The increasing prevalence of IDA during pregnancy nearly 40 years after the initiation of IFA program is an indictment of the failure of this program and the urgent need to explore alternative approaches.

Data from this study corroborated previous reports from developed countries on the safety and efficacy of intravenous iron sucrose during pregnancy.[14] Challenges posed by attempts to use iron sucrose as a vehicle for the mass eradication of IDA in developing/underdeveloped areas include the cost of drug and method of its administration, logistics of administering several infusions of the drug to women who need it most, compromising compliance, and potential concerns about adverse reactions and how they might be handled in such settings. In the present study, authors sought to evaluate ways in which these impediments might be overcome. If iron sucrose could be used on a mass scale, this would eventually drive down the cost of drug, especially if generic formulations could be developed. This is a challenge for the government and pharmaceutical industry. The use of bolus push technique has potential for cost savings because it does not require hospital bed and other paraphernalia associated with the conventional infusion technique of iron sucrose administration. This study showed that bolus push technique is indeed a feasible approach, with similar efficacy to the conventional technique, and corroborated the previous report by Macdougall et al[15] who demonstrated the safety of 200 mg iron sucrose administered as a 2-minute bolus push in a total of 2297 injections. It was observed that, as in this study, a higher incidence of adverse reactions with bolus push technique was reported, but all the adverse reactions were minor in nature. From the cost aspect, the current finding that the bolus push technique is seven times cheaper than the conventional slow intravenous infusion increases the possibility that its use could render iron sucrose affordable for use on a mass scale as indicated by the experience of its use in patients on hemodialysis in India.[16]

Apparent limitations in this study included the measurement of Hb level at 4 weeks instead of 6 to 8 weeks, use of a blanket dose of 400 mg iron sucrose irrespective of each woman's pretreatment Hb level rather than individual calculations, failure to exclude other causes of anemia in the study population, and use of Hb estimation without serum ferritin values to define iron deficiency anemia. However, the study design was driven by the need for pragmatism—the need to evaluate treatment approaches that would be applicable to low-resource settings. Therefore, if Hb levels were measured at longer than a 4-week interval, a more significant increase in the Hb levels would have been observed. However, the authors selected the duration of 4 weeks because leaving a larger time gap would mean a higher loss to follow up. At present, 200 mg is the maximum IV iron sucrose dose considered safe for administration at one sitting. Current practice is that the required iron dose is calculated for each woman based on her Hb deficit and prepregnancy weight. In a rural setting, if the mean Hb level for most of the women in the initial stages of pregnancy is 9.0 g/dL and their mean weight of is 46.0 kg, calculations indicate that a single dose of 200 mg iron sucrose would increase the Hb level to >11 g/dL. It is generally stated that in pregnancy an additional 500 mg iron is required to replenish stores.[17] Researchers in this study gave an additional 200 mg of iron sucrose, although this would be insufficient to replenish the stores. By doing so, they treated anemia in women, leaving some spare albeit inadequate amount of iron for stores in those women who came back for the second dose of 200 mg. Also, this approach indicated the need for future evaluation of a single bolus dose. If the 400 mg dose (or higher) could be safely administered in a single bolus push, the woman would not need to return for several infusions, compliance no longer becomes an issue, and efficacy would be virtually guaranteed, and costs are substantially reduced. With regard to failure to exclude other causes of anemia, from a pragmatic point of view, it is known that in rural settings such investigations are rarely conducted,

whereas the most common cause of anemia in such settings is known to be iron deficiency (Divakar et al; personal communication). The authors aimed to evaluate a treatment regimen in a manner that would reflect how such treatment might be administered on a mass scale.

The WHO/Indian Council of Medical Research criteria, which are based on Hb and do not include serum ferritin, were used to define iron deficiency anemia in the present study. Unpublished data showed improved ferritin estimates after intravenous iron sucrose in an urban population. Therefore, the authors were confident that the increase in Hb would also be reflected in appropriate increases in serum ferritin.

The rate of loss to follow up was very high in the present study. However, there was no correlation between the incidence of adverse reactions and rate of loss to follow up. Therefore, it can be concluded that this high loss rate reflects what really does happen in practice—there is a high failure to complete treatment courses or comply with treatment. This has major implications for any program designed to use IV iron sucrose to eradicate IDA in pregnancy, because women who need the treatment most (Hb <9 g/dL) are the ones who would need several visits if the iron sucrose were to be administered by several divided doses as per current convention. It is believed that a key potential solution might be to evaluate the use of a single dose of IV iron sucrose administered by the bolus push technique.

Conclusion

The bolus push technique for administration of intravenous iron sucrose may represent a cost-effective approach to the eradication of iron deficiency anemia during pregnancy in low resource settings. Further studies are required on optimal iron sucrose dose regimens that could be administered as single total dose infusions.

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Is Vacuum–assisted Delivery a Safer Option for Delivering a Floating Head at Cesarean Section?

Mrutyunjaya B Bellad,* Pramila Koli, Anita Dalal

Abstract

Objective: To evaluate the safety and effectiveness of delivery of floating fetal head at cesarean section using vacuum extractor.

Methods: Study design: A prospective case series. Place: KLES Hospital and MRC, Belgaum. Period: December 2009 to June 2010. Inclusion criteria: Singleton term pregnancy, elective/early labor cesarean sections. Exclusion criteria: Known medical diseases, unwilling to participate. Intervention: Use of vacuum for delivery of fetal head at cesarean section. Procedure: After incision on the uterus, a vacuum cup of 65 mm diameter was gently applied to the fetal head at the most prominent visible part of the head. After ensuring that no other structure is caught between the cup and the fetal head a negative pressure of 600 mm Hg was created (usually within a minute) a gentle traction was applied. Outcome measures: Maternal: Estimated blood loss, uterine incision extension.

Neonatal: Apgar score, hyperbilirubinemia, injury (such as evidence of scalp abrasions, bruising, and cephalhematoma, subgaleal, or intracranial hemorrhages).

Results: A total of 25 women underwent cesarean section (20 were elective and 5 were in early and active labor) and the procedure was successful in 24 (96%) cases. The mean visually estimated blood loss was 800 mL (range 600–1000 mL). There were neither extension of uterine incision nor any increased neonatal complications.

Conclusion: The use of vacuum extractor for the delivery of floating fetal head at cesarean section is a safe and effective alternative. However, a larger randomized controlled trial is required to confirm these findings.

Key Words: Vacuum-assisted delivery, floating head, cesarean section

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Introduction

Delivery of floating fetal head, poses real challenge even to an experienced obstetrician. Different measures such as allowing the fluid to drain till the head gets fixed to incision, use of fundal pressure by assistants/anesthesiologists, and use of forceps/vectis are taken. Since the rapid creation of negative pressure during vacuum-assisted vaginal delivery has become safer method, the same principle was attempted in the present series. Vacuum-assisted delivery has been used in the cesarean section from the time when other methods were not successful in delivering the fetal head.[1] The present case series is an attempt to use the same technique during cesarean section to deliver the floating fetal head because it is easy to perform and under direct vision. The objective of this case series was to evaluate the effectiveness and safety of the vacuum-assisted fetal head delivery during cesarean section. If proved beneficial, it has wider implications as it eases the process of fetal head delivery.

Methods

The present case series is carried out at Teaching hospital attached to J. N. Medical College, Belgaum between December 2009 and May 2010. Pregnant women at term, with singleton pregnancy and planned for a cesarean section, were included in the study.

Inclusion criteria: Singleton term pregnancy, elective/early labor cesarean sections.

Exclusion criteria: Known medical diseases, not willing to participate.

Outcome measures: The outcome measures were the ease of fetal head delivery, estimated blood loss for the procedure, evidence of uterine extension, neonatal complications such as birth asphyxia (Apgar scores), neonatal hyperbilirubinemia, and trauma (including evidence of scalp abrasions, bruising, and cephalhematoma, subgaleal, or intracranial hemorrhages). Also, the time (in minutes) was noted from uterine incision to delivery of the neonate.

Procedure: After the incision on the uterus, a vacuum cup (Figure 1) of 65 mm diameter was gently applied to the fetal head at the most prominent visible part. After ensuring that no other structure is caught between the cup and the fetal head a negative pressure of 600 mm Hg was created (usually within a minute) with machine (Figure 1) and traction was applied.

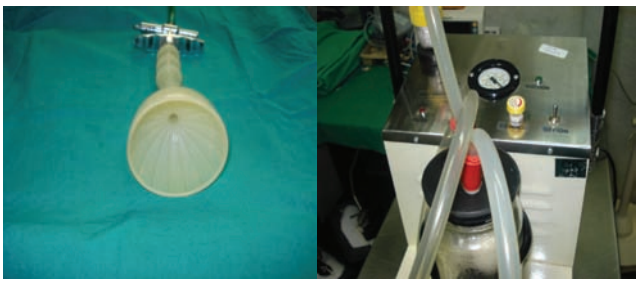

Figure 1. Vacuum cup and suction apparatus.

During delivery, number of pop-offs were noted. Also, uterine incision extension and size of the skin incision were observed.

Results

A total of 25 women underwent vacuum-assisted fetal head delivery at cesarean section. Of these, 20 were elective and 5 were in active labor. The technique was successful in 24 (96%) cases. In one case, pressure could not be generated to optimal level even with repeated attempts (3 times), so slippage and subsequent pop-offs were noted. This case was delivered manually. The mean blood loss, as estimated visually, was 800 mL (range 600–1000 mL). None of the cases had extension of uterine incision. No neonatal complications (such as neonatal Apgar scores, neonatal hyper-bilirubinemia and trauma) were noted. The delivery of the head was slow and well under control. As the series advanced, the size of the skin incision was reduced by 2 to 3 cm. Advantages noted with this procedure were ease of fetal head delivery, without increasing the size of incision (head + hand in manual and head + forceps in forceps), uniform pressure to the uterine incision during extraction, and slow and controlled delivery of the fetal head.

Discussion

A total of 25 women underwent cesarean section (20 elective and 5 in active labor where the vacuum was used to assist delivery of the fetal head). The procedure

was successful in 96% (24 out of 25) of cases. None of the cases had uterine extensions and neonatal complications, similar observations were noted in other studies. The mean visually estimated blood loss in the present case series was 800 mL, ranging between 600 and 1000 mL. These findings were comparable with those in a previous study that recorded mean blood loss of 680.9 mL.[2] The blood loss was not excessive, probably because the bleeding from the cut surface of uterine incision was controlled by the uniform pressure of the head when traction was exerted.[3] There was no report of postpartum hemorrhage. No uterine incision extension was observed in the present study. This finding was in corroboration with that of earlier studies.[2,4] Neonatal outcomes revealed no adverse outcome with regard to neonatal Apgar scores, hyperbilirubinemia, and trauma. The slippage of cup and subsequent pop-offs during the delivery was observed in only one case (4%) in the present study, which was comparable to observations in other studies. However, in a study conducted in 1960s, the slippage rate was noted to be 25%, probably due to the use of slow generation pressure method.[2,3] In that study, Malmstrom metallic cup was used as compared to silastic cup in the present series. Proper placement of the cup and assurance that no other structure is caught between the fetal head and the cup before generating the pressure is vital for the safety and success of vacuum-assisted deliveries of the floating fetal head during cesarean section. Advantages observed with this procedure include ease of fetal head delivery (avoids fundal pressure from assistants/anesthesiologists), without an increase in the size of incision (head + hand in manual and head + forceps in forceps), uniform pressure to the uterine incision during extraction, and slow and controlled delivery of the fetal head.[2,3] Smaller skin incision was an additional advantage observed in the present study.

Limitations: The major limitations of the present study were the sample size and the performance of the procedure by a single person. A larger randomized controlled trial with adequate sample size will answer this research question in an effective manner.

Conclusion

From the present study, it was evident that the vacuum-assisted fetal head delivery during cesarean section is safe and effective without increasing maternal and neonatal complications. However, the outcomes may be confirmed with randomized controlled trial before the procedure is used routinely, as it is associated with other advantages (smaller skin incision and no fundal pressure-associated stress and complications).

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Advances in the Management of Female Infertility

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Introduction

Infertility primarily refers to the biological inability of a person to contribute to conception.[1] Infertility is medically defined as a lack of conception following at least 1 year of unprotected sexual intercourse. Couples with primary infertility have never been able to conceive, whereas secondary infertility refers to difficulty in conception after at least one conception. Infertility is a multidimensional problem with social, economic, and cultural implications. The magnitude of the problem calls for urgent action, particularly when in the majority of cases the infertility is avoidable.

Burden of the disease

Infertility is not fatal but it carries with it an additional burden of social stigma and a sense of personal failure. It is a global health issue affecting approximately 8% to 10% of couples. It is estimated that globally 60 to 80 million couples suffer from infertility every year[2] of which probably between 15 and 20 million are from India alone.[3] The incidence of infertility is associated with geographic differences. In some west-African communities, infertility rate is around 50%, while in some western European countries it is 12%. Likewise, differences are observed in terms of infertility rates in developed (3.5%–16.7%) and less developed countries (6.9%–9.3%). It has also been observed that the causes are related to geographical differences. In Western countries, the most common risk factor of infertility is age, while in Africa it is sexually transmitted diseases.[4-7]

Etiology

The main etiological factors in infertility are anovulation, tubal factor, and endometriosis. Anovulation accounts for about 20% of primary infertility and 15% of secondary infertility. Tubal-factor infertility accounts for about 15% of primary infertility while 40% of secondary infertility. Endometriosis accounts for about 10% of primary infertility and 5% of secondary infertility.[8] Male factor infertility contributes 25% of primary infertility and 20% of secondary infertility. Unexplained infertility (10%) is a term used to describe couples with infertility in which standard investigations including semen analysis, tests of ovulation, and tubal patency have failed to detect any gross abnormality.

Causes of failure to ovulate

Ovulatory disorders are one of the most common reasons of female infertility, and they account for 30% of female infertility cases. Hormonal problems are the most common causes of anovulation. In approximately 50% of the cases of anovulation, the ovaries do not produce normal follicles in which the eggs can mature. Ovulation is rare if the eggs are immature and the chance of fertilization becomes almost nonexistent. Polycystic ovary syndrome (PCOS) is the most common disorder responsible for this problem. Hypothalamus is responsible for sending signals to pituitary gland, which, in turn, sends hormonal stimuli to ovaries in the form of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to initiate egg maturation. Failure of hypothalamus to trigger and control this process results in formation of immature eggs. This is the cause of ovarian failure in 20% of the cases. Malfunction of the pituitary gland due to physical injury, a tumor, or any chemical imbalance in the pituitary gland may result in anovulation. Scarred ovaries due to infection, invasive, or multiple surgeries for repeated ovarian cysts may cause the capsule of the ovary to become damaged or scarred, such that follicles cannot mature properly and ovulation does not occur. Premature menopause is a rare and unexplained cause of anovulation. Thyroid disorders, such as hypothyroidism and hyperthyroidism, may lead to menstrual irregularities and ovulation disorders. Chronic debilitating diseases such as cancer and AIDS may lead to anovulation.

Causes of poorly functioning fallopian tubes

Tubal-factor infertility is the single cause among 85% of infertile couples in Africa, 44% in Latin America, 39% in Asia, and 36% in developed countries.[9] Tubal disorders range from mild adhesions to complete tubal blockage. The main cause of tubal damage includes: Infections caused by bacteria and viruses, which get usually sexually transmitted and cause inflammation resulting in scarring and damage (eg, Chlamydia trachomatis, gonorrhea). Abdominal diseases may cause inflammation of the abdominal cavity which can affect the fallopian tubes and lead to scarring and blockage. Ectopic pregnancy may also cause tubal damage.

Endometriosis

Approximately 10% of infertile women are affected by endometriosis. It is a progressive disease that occurs when the endometrial tissue lining the uterus grows outside the uterus and attaches to the ovaries, fallopian tubes, or other organs in the abdominal cavity.

Additional factors

Conditions such as uterine fibroids, polyps, adenomyosis, and Asherman syndrome may lead to obstruction of the uterus and fallopian tubes. Congenital abnormalities, such as septate uterus, may lead to recurrent miscarriages or the inability to conceive. Physical causes include diabetes, pain during intercourse, or infection in females. Cervical mucus defects or dysfunction can cause sub-fertility. The cervical mucus acts by transporting and storing spermatozoa. Spermatozoa require an adequate amount of clear, fluid mucus to protect them from the acidity of the vagina and help them in moving to the upper genital tract. Cervical mucus may also contain antisperm antibodies, which prevent sperm moving into the upper genital tract. Various psychological reasons such as worry about poor sexual performance or emotional or financial stress may lead to lower libido and less frequent sexual intercourse.

Impact of lifestyle factors on fertility

Female age is the most important determinant of spontaneous conception and treatment-related conception.[10] The number of competent oocytes in the ovaries declines with increasing age. Fertility begins to decline in females from the age of 30 years, although the reduction in fertility is greatest in women in their late 30s and early 40s.[11] Significant association is observed between smoking and reduced fertility among female smokers.[12] Some of the negative reproductive consequences associated with smoking include: Quicker depletion of ovarian follicles, conception delay, increased risk of

spontaneous miscarriage in both natural and assisted conception cycles, and increased risk of birth defects.[13] There are a number of prescribed, over-the-counter, and recreational drugs that are known to impact fertility. Nonsteroidal anti-inflammatory drugs are known to inhibit ovulation.[12] Cytotoxic chemotherapy drugs cause ovarian failure in some women. Marijuana has an adverse effect on ovulation, and cocaine can adversely affect tubal function.[14] Obesity and overweight are associated with decreased pregnancy rate, increased requirement of gonadotropins, and higher miscarriage rate. A high body mass index is also associated with adverse pregnancy outcomes such as gestational diabetes and hypertension.[15] Psychological stress has negative impact on female reproductive performance. Intake of caffeine at high levels has a negative effect on reproductive performance. Alcohol consumption has been reported to reduce fertility, although the level of consumption associated with risk is unclear.[16] Exposure to lead and repeated exposure to radiation may also result in infertility.

Investigations

Assessment of ovulation, evaluation for tubal patency, and semen analysis are the three major basic investigation aims for infertile couples. Tests of ovulation include basal body temperature monitoring, ultrasound examination to detect the number, size, and shape of the egg follicles, followed by monitoring the growth of follicles, and LH surge monitoring. Luteal phase testing is conducted to assess whether the uterus prepares itself properly to receive and carry a fertilized egg. Postcoital test is done to assess any problem in the interaction between a woman's cervical mucus and her partner's sperm.

Blood and urine tests are taken to evaluate hormone levels. High FSH and LH levels and low estrogen levels suggest premature ovarian failure. High LH and low FSH may suggest PCOS or luteal phase defect. High FSH and high estrogen levels on the third day of the cycle predict poor success rates in older women trying fertility treatments. LH surges indicate ovulation. Blood tests for prolactin levels and thyroid function are also measured as these hormones indirectly affect fertility.[17-19] Tests for autoimmune disease, such as hypothyroidism and diabetes, are considered in women with recent ovarian failure that is not caused by genetic abnormalities.[20,21]

Evaluation of uterine cavity and patency of tubes is assessed by hysterosalpingogram. Limitation of this test is that it does not aid in the characterization of uterine wall or ovarian pathology. Evaluation of ovarian, uterine wall, and adnexal pathology is done by ultrasound examination of pelvis. Limitation of this test is that additional imaging may be needed for presurgical characterization and localization of pathology. Sonohysterogram allows visualization of endometrial lining and intra cavity defects. Magnetic resonance imaging guides interventional radiology and surgical management of infertility by identifying size, number, and location of pathology. Pelvic environment visualization with laparoscopy is done to identify the underlying cause of infertility.

Treatment

The treatment of infertility includes

- Advice (the timing of intercourse or reduction of stress factors)
- Administration of drugs to enhance the reproductive cycle
- Procedures that treat underlying causes of infertility

Fertility drugs are often used alone as initial treatment to induce ovulation. If they fail as sole therapy, they may be used with assisted reproductive procedures, such as in vitro fertilization (IVF), to produce multiple eggs (superovulation). According to the American Society for Reproductive Medicine, fertility drugs can be divided into three main categories: Medications for ovarian stimulation, medications for oocyte maturation, and medications to prevent premature ovulation.[22,23]

Clomifene citrate is an anti-estrogen, which may be prescribed for women with unexplained infertility and women with PCOS, and may also be used to stimulate the development of multiple eggs for use with assisted reproductive technologies (ART) such

as intrauterine insemination (IUI).[24] Clomifene acts by blocking estrogen, which triggers the pituitary to produce FSH and LH. This boosts follicle growth and release of the egg. A maximum of six cycles of clomifene citrate is recommended.[25] This relates to the number of cycles within each course of treatment. Side effects of clomifene include ovarian cysts, hot flashes, nausea, headaches, weight gain, and fatigue. There is a 5% chance of having twins with this drug, and a slightly increased risk of miscarriage.[26] Tamoxifen is an anti-estrogen that works in a similar way to clomifene citrate.

If the patient fails to respond to clomifene treatment, gonadotropins are the next treatment option. Gonadotropins induce follicle development and ovulation. They are also used to induce development and ovulation of multiple follicles in women undergoing ART such as IVF, or superovulation and IUI.

Gonadotropins include:

- Human menopausal gonadotropins
- Human chorionic gonadotropins (hCG)
- Follicle-stimulating hormone
- Gonadotropin-releasing hormone (GnRH) analogs (GnRH agonist and GnRH antagonists)

Gonadotropins are used to induce follicle development and ovulation in women. An injection of hCG may be given to some women being treated with clomifene citrate to help trigger release of the egg. Adverse effects of gonadotropins include a higher risk of miscarriage, ovarian hyperstimulation syndrome (OHSS), multiple gestation, ectopic pregnancies, and adnexal torsion. Other possible side effects include headaches, abdominal pain or bloating, breast tenderness, swelling or rash at the injection site, and mood swings.

Uterine fibroids may be treated with GnRH analogues. GnRH analogues work by controlling the bleeding and reducing the size of the fibroids.[27] Although they effectively reduce bleeding and decrease fibroid size, they can only be used for up to 6 months as they can cause osteoporosis.[28,29] Therefore, they are used mainly in reducing fibroid size before surgery to make the operation easier. Endometriosis appears to be an estrogen-dependent condition and treatment with ovulation suppression agents such as oral contraceptives may be useful in some cases.

Ovulation can be induced surgically by a procedure called ovarian drilling or ovarian diathermy. This procedure is useful in women with PCOS who are resistant to clomifene treatment.[30] A blockage or damage inside the fallopian tubes can be treated using various surgical procedures depending on the location of blockage and type of damage. Salpingolysis or fimbriolysis can be done by laparotomy (through the abdomen) along with the use of a microscope to magnify the area or by laparoscopy. Salpingolysis and fimbriolysis involve releasing the fallopian tubes from adhesions by cutting the adhesions out by surgical diathermy. A salpingectomy may be used to treat an ectopic pregnancy or an infection in the fallopian tube, although the more conservative procedure, salpingostomy, may be the preferred option. Tubal anastomosis involves surgical removal of a blocked section of a tube and then rejoining the freshly open ends that were on either side of the removed section. If the blockage in the fallopian tubes is limited, treatment by conducting a tubal canalization by fluoroscopy or through a hysteroscope may be performed. Surgery may be required to treat uterine abnormalities, such as uterine fibroids, intrauterine adhesions, septate uterus, and endometriosis.

Intrauterine insemination is the process of inserting sperm into the woman's uterus. This technique requires that the woman have normal fallopian tubes and a uterus. It is particularly useful where women have deficient cervical mucus, ovulatory dysfunction, or endometriosis; or there is male factor infertility or unexplained infertility.[31] The success of IUI depends on several factors including the cause and duration of infertility, ages of partners, and sperm quality. The procedure is timed to coincide with the release of an egg or eggs (ovulation) in a natural or a stimulated cycle. It is often used before resorting to more complex and invasive ART.

The first successful fertilization of human eggs in the laboratory was in 1978. The ART is only used after the proper selection of patients and explaining the failure rates of this methods.[32] The definition of ART

according to the Center for Disease Control is all fertility treatments in which both eggs and sperm are handled. ARTs have proved increasingly effective in treating many types of female infertility.

In vitro fertilization involves taking medication to stimulate the ovaries to produce more eggs than usual. Eggs are then retrieved and mixed with the sperm in a laboratory dish and incubated for 2 to 3 days. The aim is for the sperm to fertilize the eggs to form embryos. One or two of these embryos are then placed inside the woman's uterus using a fine plastic tube passed through the cervix. Any other embryos that have formed in the dish can be frozen (cryopreserved) for future use by the couple who produced them. This avoids having to repeat the ovulation stimulation and harvesting procedure, which can be risky and uncomfortable. When the IVF-ET is performed in women with tubal infertility the success rate per cycle varies between 20% and 30%. IVF is a useful treatment in women with damaged fallopian tubes, unexplained infertility, endometriosis, and male infertility. It may also be used after several failed attempts with ovulation induction or IUI. IVF may be offered as a first-line treatment in women of older maternal age, irrespective of the cause of infertility. The success of IVF treatment is dependent on many factors. These include patient factors such as age, weight, and pregnancy history, and variations in IVF procedure such as the number of embryos transferred and the method of embryo transfer used.

The gamete intrafallopian transfer (GIFT) technique involves collecting eggs and sperm in the same way as for IVF. The eggs and sperm are then mixed together in a dish and immediately transferred to the fallopian tubes. This is done laparoscopically through a small incision in the abdomen, or by a catheter passed through the cervix. This allows the sperm to "naturally" fertilize the egg inside the woman's fallopian tube or uterus. GIFT is effective in women aged >40 years. It is less valuable with low-quality semen.[3] Zygote intrafallopian transfer is a similar procedure like GIFT, in which the newly fertilized egg (or zygote) is transferred to the women's fallopian tubes.

Intracytoplasmic sperm injection (ICSI) involves injecting a single sperm directly into the cytoplasm of an egg. ICSI is a useful technique for couples that have been unsuccessful with IVF, or where the quality or number of sperm is too low for normal IVF to be successful. In couples considering ICSI, genetic counseling is indicated due to the higher incidence of genetic abnormalities in men with severe male infertility.

Ovarian hyperstimulation syndrome is a rare but very serious adverse effect of ART. Multiple-gestation pregnancies are much more common after infertility treatment than after natural conception and increase the risk for maternal complications. Multiple-birth infants are at increased risk for low birth weight, preterm delivery, infant death, and disability among survivors.[33,34] Around 4% of women who become pregnant after assisted conception will have an ectopic pregnancy.[35]

In vitro maturation (IVM) involves taking immature eggs from un-stimulated or minimally stimulated ovaries and maturing them in the laboratory for 1 to 2 days. When the eggs have matured, they are fertilized using ICSI and transferred to the womb a few days later. IVM eliminates the risk of OHSS as it does not require ovarian stimulation.

In hyperprolactinemia, high levels of prolactin suppress the pulses of GnRH, and therefore prevent ovulation. Such patients are treated with Dopamine agonists (bromocriptine and cabergoline). Adverse effects associated with dopamine agonists include nausea, headache, dizziness, abdominal pain, and tiredness.[36]

Ayurveda in the Management of Infertility

Materia medica of Ayurveda is extensive, with more than 700 herbs described in detail in the ancient texts. The herbs and herbal mixtures utilized in Ayurveda are prepared by using various parts of plants (eg, roots, leaves, fruits, bark, seeds, etc.). Herbs are sometimes used alone but more often in combination to provide synergistic effects and mitigate toxic side effects. Acharya Sushruta has described four essential factors for fertilization, that is, Ritu (fertile period), Kshetra (healthy reproductive organs), Ambu (proper nutrition),

and Beeja (healthy sperm and ovum). In female infertility, ovum is referred as beeja. Novel procedures like basti and uttar basti and many herbs have been used to treat infertility. Also, herbs have the potential to add to the existing treatment options. Many herbal formulations have been used in the treatment of infertility. In this article, the role of Evecare syrup in the treatment of female infertility has been discussed.

Evecare syrup in the treatment of infertility

Evecare is a natural-ingredient formulation recommended for the management of uterine disorders. Evecare regularizes endogenous hormonal secretion, corrects the cyclical rhythm, and normalizes bleeding. It exhibits gonadotropin-agonist activity that helps in ovulation, enhances endometrial receptivity, and thus, is helpful in female infertility. Evecare has a regularizing influence on the menstrual cycle by virtue of its uterine-stimulant action. Evecare's stimulatory effect on ovarian tissue helps regularize endogenous hormonal secretion, enhances the repair of endometrium, and thus, controls abnormal uterine bleeding. Anti-inflammatory action of Evecare has a healing effect on the uterus and its antispasmodic action alleviates pain. The immunomodulatory and hematinic properties of Evecare are beneficial in anemia and generalized weakness associated with uterine disorders. It renormalizes FSH and LH required for the well-being of women. It has anti-inflammatory, analgesic, central depressant, vasodilator, and spasmolytic activities, which will be helpful in the management of various painful conditions during menstruation. All these activities provide support for premenstrual syndrome and other painful menstrual conditions. Also, Evecare is useful in improving the quality of life.

Pharmacological actions of principal herbs

Saraca indica

Saraca indica, which is rich in tannins and other glycosides, is used in treating different uterine disorders such as menorrhagia, dysmenorrhea, post partum hemorrhage, and leucorrhea.[37]

Dashamoola

This is an aqueous extract of a combination of 10 plant roots known to be clinically beneficial in various disorders, which may be helpful in various conditions related to menstruation.[38] Herbs that are used in the traditional preparation of Dashamoola such as Clerodendrum phlomidis and Premna integrifolia have been found to possess tonic and anti-inflammatory activities, which improve the quality of life.[39]

Symplocos racemosa

Symplocos racemosa contains betulinic, oleanolic, acetyl oleanolic, and ellagic acids. Trials have shown that the bark extract reduces the frequency and intensity of both pregnant and nonpregnant uterine contractions, suggesting its benefits in menstrual irregularities.[40] The same is used in different gynecological problems like menorrhagia, frequent abortions, reduced libido, lecorrhea, and vaginal ulcerations.[41] Also, studies suggest its role in renormalizing FSH and LH required for the well-being of women.[42]

Tinospora cordifolia

Tinospora cordifolia has anti-inflammatory, analgesic, and spasmolytic activities that are helpful in the management of various painful conditions during menstruation.[43] It also regularizes menstrual flow.[41]

Solanum nigrum

Solanum nigrum has analgesic, anti-inflammatory, antispasmodic, central depressant, and vasodilator activities. All these activities provide support for premenstrual syndrome, and other painful menstrual conditions.[44,45]

Boerhaavia diffusa

Boerhaavia diffusa possesses potent antifibrinolytic and anti-inflammatory properties that indicate its use in menstrual disorders like menorrhagia.[46,47] It is also used in dysmenorrhea.[41]

Asparagus racemosus

Asparagus racemosus is very useful in menorrhagia as well as in threatened abortion.[41] Studies have shown that the extract blocks the uterine contraction and spontaneous motility, blocking the pitocin sensitive receptors. This activity can be helpful for using the

same as uterine sedative and to treat different menstrual problems like dysmenorrhea.[48]

Cocos nucifera

According to folk medicine, coconut juice (*C nucifera* L., Arecaceae) is claimed to contain several different compounds with various therapeutic properties. It also postulated that tender coconut juice has phytoestrogen-like effect. This has been proven in one of the trials which showed that *C nucifera* possesses estrogen-like activity and may be helpful in various menstrual irregularities.[49] Results demonstrated that *C nucifera* and its fractions have antinociceptive and anti-inflammatory activities, which confirm the popular use of this plant in several inflammatory disorders and, thus, may be helpful in dymenorrhea.[50]

Aloe vera

Aloe vera is reported to provide therapeutic benefits during menstruation suppression. It is used in spasmodic dysmenorrhea because of its antispasmodic activity.[51] Intragastric administration of Aloe vera powder at a dose of 60 mg/kg improved the fertility rate in rabbits, it also improved the fertility in women, which establishes the use of Evecare in assisted conception. Also, anti-inflammatory activity helps in various gynecological disorders.[52]

Santalum album

The bark of *S album* contains triterpene and palmitate including a- and b-santalol. Traditionally, the same is used in various menstrual irregularities.[53] Extract of *S album* has antioxidant activity and is also used as adaptogenic activity and may be helpful in debilitating conditions that may occur due to excessive menstrual bleeding.[54]

Acacia arabica

The bark of *A arabica* is reported to have catechin, epicatechin, dicatechin, quercetin, and gallic acid. Trial has shown that the extract has antioxidant activity and may be helpful in renormalizing the hormonal imbalances in the body which leads to regular menstrual cycle.[55]

Cyperus rotundus

Tubers of *C rotundus* exhibit estrogenic activity. They also induce relaxation of the isolated uterus as noted in an animal study indicating its role in relieving spasmogenic pain associated with uterus. Also, its anti-inflammatory and analgesic activities ensure better therapeutic action.[56] The rhizomes of *C rotundus* have been used in traditional medicine as an estrogenic and anti-inflammatory agent for the treatment of women's diseases. Previous phytochemical studies on *C rotundus* have led to the identification of more than 60 sesquiterpenes besides flavonoids, furochromones, triterpenes, and sterols. The extract of the rhizomes of *C rotundus* showed acetylcholinesterase inhibitory activity as well as inhibition of nitric oxide and superoxide production activity.[57]

Hemidesmus indicus

A saponin from *H indicus* is found to have anti-inflammatory and antinociceptive activities in both acute and sub-acute conditions which may be helpful in inflammatory condition of reproductive system and also believed to be helpful in minimizing menstrual difficulties.[58,59]

Triphala

Triphala, an ancient herbal blend, is one of the most commonly used herbal remedies in Ayurveda, an Indian system of medicine. Triphala is the homogenous mixture of three fruits—*Emblica officinalis*, *Terminalia chebula*, and *Terminalia belerica*. It is found to be a rich source of vitamin C, ellagic acid, gallic acid, chebulinic acid, etc. Studies confirm its anti-inflammatory and antimicrobial activities, which may be helpful in various gynecological inflammatory disorders.[60] The extract of Triphala possesses the ability to scavenge free radicals such as DPPH and superoxide. The phenolic compounds present in this extract are mostly responsible for their radical scavenging activity, and may be helpful in controlling various hormonal influences that result in menstrual irregularities.[61]

Adhatoda vasica

Extracts of *A vasica* have anti-inflammatory activity and will be helpful in managing various inflammatory changes of the genito-urinary system, which in turn may be therapeutically supportive in extending comfort.[62] Vasicine was found to have a uterotonic

activity in different species including human beings. It was shown that the effect was influenced by the degree of priming of the uterus by estrogens. Vasicine initiated rhythmic contractions of human myometrial strips from both pregnant and nonpregnant uteri. Trials suggest that the effect is as comparable to that of oxytocin and methergin. Various ethnopharmacology approaches show that it is used because of its styptic activities and used in various bleeding disorders.[63]

Rubia cordifolia

Rubia cordifolia is used for the treatment of vertigo, insomnia, hematemesis, and menstrual disorders. Phytochemical examinations have shown that it produces triterpenoids, anthraquinones, cyclopeptides, and phenolics. It also has antioxidant and antimicrobial activities, suggesting its usefulness in various gynecological disorders.[64]

Trikatu

Trikatu is an Ayurvedic preparation containing black pepper, long pepper, and ginger, which is prescribed routinely for a variety of diseases as part of a multidrug prescription because of its bioavailability enhancing activity.[65,66]

Bombax malabaricum

Preliminary phytochemical tests have shown the presence of glycosides and tannins in the root, stem, and leaf of *B malabaricum*. Hot aqueous extract of the seeds showed moderate oxytocic activity on gravid and nongravid isolated rat uteri and on guinea pig and rabbit uterine strips.[67] Mangiferin extracted from *B malabaricum* shows antioxidant and analgesic activities and may be helpful in various gynecological disorders.[68]

Shilajeet (purified)

Shilajeet has been used as a rejuvenator and an adaptogen for thousands of years, in one form or the other, as part of traditional systems of medicine in a number of countries.[69] Trials on Shilajeet indicate that it acts as a prospective modifier of analgesic tolerance. All these activities may be helpful in providing support in menstrual disorders.[70]

Following trials have been conducted to evaluate the safety and efficacy of Evecare syrup in the treatment of infertility.

Clinical trial 1

Enhancement of conception rate by Evecare after ovulation induction by clomifene citrate followed by IUI[71]

Aim

The study was conducted to evaluate the role of Evecare after ovulation induction by clomifene citrate followed by IUI.

Methodology

Inclusion criteria

Patients in the age group of 25 to 32 years, who underwent ovulation induction by clomifene citrate and hCG followed by IUI and who were willing to give informed consent were included in the study.

Exclusion criteria

Patients who were unwilling to give informed written consent were excluded from the study.

Study procedure

Fifty infertile women were enrolled in the study. All the patients were given 50 mg clomifene citrate for 5 days starting from day 3 to day 7 of the menstrual cycle (day 1—day of menstruation). From day 8, follicular and endometrium developments were monitored with the use of transvaginal probe (7.5 MHz). When the follicle size reached 18 mm or >18 mm diameter, 10,000 IU hCG was injected intramuscularly. After 36 hours of hCG injection, IUI was performed after sperm wash by swim-up technique with normozoospermic husband/donor semen. The patients were divided into two groups of 25 patients each. Group 1 received Evecare 2 tablespoonfuls, twice daily for a period of 16 days after IUI and group 2 was placebo group. The investigations included TSH, FSH, LH, prolactin, and E2 levels.

Results

The results of the investigations showed that except for prolactin and E2 levels all the other values increased. The conception rates were high in the Evecare-treated group. Out of the 25 patients, who took placebo only 7 conceived (28%). The rate of conception in Evecare therapy was 64% (16 out of 25).

Conclusion

Results of the preliminary study indicate that infertile patients undergoing follicular stimulation followed by hCG administration and subsequently undergoing IUI followed by Evecare treatment indicate that the conception rate can be significantly increased in infertile patients undergoing assisted conception.

Clinical trial 2

Clinical evaluation of Evecare syrup in the treatment of infertility in women: An open study[72]

Aim

The aim of this study was to evaluate the clinical efficacy and safety of Evecare syrup in the management of infertility in women.

Methodology

Inclusion criteria

Infertile women in the age group of 30 to 45 years who failed to conceive after a minimum of 3 years of regular intercourse without contraception were included in the study.

Exclusion criteria

Patients having anatomical defects of uterus and/or cervix, uterine malignant tumors, evidence of malignancy, history of uterine surgery, pituitary tumors, and renal failure; patients with problem in the male partner; and patients who were unwilling to sign the informed consent form were excluded from the study.

Study procedure

Hundred infertile patients were included in the study. Routine physical and gynecological examinations, laboratory tests, and hormonal assays of FSH, LH, progesterone, and estrogen were carried out before and after the treatment. Patients were administered Evecare syrup at a dosage of 10 to 15 mL twice daily for a period of 6 months. No other medications were given to these patients.

Results

Results of the study showed a significant increase in the levels of estrogen and progesterone hormones and no change in the levels of FSH and LH after 6 months of treatment with Evecare syrup. Out of the 100 enrolled patients, 17 patients conceived at the end of the treatment (significance, $P<.0001$). No clinically significant adverse effects were observed or reported.

Conclusion

Results of this study indicated that Evecare helps in conception and corrects hormonal imbalances in infertile women without causing any adverse effects. Thus, Evecare syrup was found to be safe and effective in the treatment of infertility in women.

Clinical trial 3

Evaluation of efficacy and safety of Evecare syrup in infertility due to PCOS[73]

Aim

The aim of the study was to evaluate the efficacy and short- and long-term safety of Evecare syrup in women suffering from infertility due to PCOS.

Methodology

Inclusion criteria

Hundred women aged >18 years with infertility (who were not able to conceive even after stopping contraception for >1 year) due to PCOS with symptoms such as hirsutism, acne, and obesity, and their infertility proven with laboratory investigations (ultrasonography or hormonal assay) were included in the study provided they were willing to sign the written informed consent and comply with the study procedure.

Exclusion criteria

Women aged >45 years, who had tubal obstruction with anatomical defects in the reproductive system and had a history of significant pelvic inflammation were excluded from the study. Individuals with any associated liver, kidney, or cardiac diseases, and who were not willing to sign the written informed consent and comply with the study procedures were also excluded from the study.

Study procedure

Patients were randomly divided into Evecare and placebo groups of 50 patients each. A detailed report of

medical history and clinical examination that included vaginal and cervical smear examinations were taken. Laboratory investigations included estimation of blood sugar, cholesterol, and testosterone levels. Ultrasonographic examination was performed to examine the ovarian follicles in the ovaries. All the patients received either Evecare syrup at a dosage of 2 to 3 teaspoonfuls twice daily or a similar looking placebo at the same dosage for a period of 6 months. Normal sexual intercourse was advised to influence conception.

Results

Results of the study showed a significant improvement in the clinical presentations of PCOS in the Evecare group and reduction in the levels of testosterone and LH, whereas an increase in the levels of FSH was observed. Out of the 50 cases, 18 patients conceived after the treatment. Also, hemoglobin and cholesterol levels showed a significant improvement with Evecare treatment. The number and the size of the follicles were also significantly reduced.

Conclusion

This study indicated a significant improvement in the clinical presentations of PCOS in Evecare syrup treatment group, which was further substantiated by hormonal evaluation tests. No adverse effects were reported or observed during the entire study period. Therefore, from the above findings, it can be concluded that Evecare syrup is safe and effective in women suffering from infertility due to PCOS.

Conclusion of the Review

On the basis of the results of the clinical trials reviewed, it may be concluded that Evecare syrup is safe and efficacious in the treatment of infertility. Beneficial effects are due to the synergistic action of all the herbs present in it. Evecare regularizes endogenous hormonal secretion, corrects the cyclical rhythm, and normalizes bleeding. It exhibits gonadotropin-agonist activity that helps in ovulation, enhances endometrial receptivity, and thus is helpful in female infertility. Evecare has a regularizing influence on the menstrual cycle by virtue of its uterine stimulant action. It exerts anti-inflammatory, analgesic, vasodilator, and spasmolytic activities, which can be helpful in the management of painful conditions during menstruation. The medicinal properties of the herbs also help to correct menstrual disorders, infections, dysfunctional uterine bleeding, and ovulatory defects, and also improve general health by correcting anemia and enhancing immunity, thereby treating infertility. Thus, Evecare syrup is found to be safe, efficacious, and cost-effective in the treatment of infertility in women.

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Current Concepts in the Management of Recurrent Respiratory Tract Infections

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Introduction

Recurrent respiratory tract infections (RTIs) are common in patients of all ages and are associated with high morbidity and high rates of medical consultations. Although not usually life-threatening in adults, these infections represent a major medical concern in terms of high morbidity and absenteeism from work. More than 10% of all young children suffer from recurrent upper and lower respiratory tract infections.[1,2]

The upper respiratory tract consists of airways from the nostrils to the vocal cords in the larynx, including the paranasal sinuses and the middle ear. Most common infectious diseases of upper respiratory tract include rhinitis, sinusitis, ear infections, acute pharyngitis or tonsillopharyngitis, epiglottitis, and laryngitis. Rhinitis and bronchitis are the most common recurrent RTIs observed in adults. The lower respiratory tract includes the continuation of the airways from the trachea and bronchi to the bronchioles and the alveoli. Lower respiratory tract infection includes pneumonia, lung abscess, acute bronchitis, and emphysema. The two most common infections are pneumonia and bronchiolitis. The World Health Organization (WHO) estimates that 2 million deaths due to pneumonia occur every year in children aged <5 years.[3]

Definition of recurrent RTI includes three or more infections per fall-winter semester.[4,5] Viruses are usually the primary pathogens involved in recurrent RTIs, and superinfection with bacteria are frequent. Viral etiology includes infection from rhinoviruses, respiratory syncytial viruses, parainfluenza and influenza viruses, human metapneumovirus, adenoviruses, and corona viruses. The most common bacteria involved are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus Pyogenes*, and *Moraxella catarrhalis*.[6] The bacterial flora that colonize the upper respiratory tract, in health as well as during illness, contain >600 different strains of aerobic and anaerobic bacteria, that interact in a synergistic or antagonistic fashion. Viral agents can act synergistically with potential bacterial pathogens and normal flora. These interactions may involve sharing of metabolites, exchange of genetic material, and influence of extracellular enzymes and other compounds produced by some pathogens on their partners.[7]

Apart from the infectious agents, other important etiological factors include recurrent exposure to viral infections to which the child has very less immunity, unhealthy and obstructive tonsils and adenoids or persistent sinusitis, immaturity of the immune system in children susceptible to upper respiratory infections, and a possible inherited allergic background that can sometimes be demonstrated by the parental history. There are many predisposing factors, such as impaired host immunity, zinc and iron deficiency, smoking, environmental pollution, and occupational or climatic factors, for recurrent RTIs.[8] Repeated lower RTIs in the first 3 years of life show a positive association with wheezing up to the age of 7 years.[9]

Except during the neonatal period, respiratory infections are the most common causes of both illness and mortality in children aged <5 years, with an average of 3 to 6 episodes of RIs annually regardless of economic and geographic situation.[10,11] Preschool children may contract 4 to 6 RTIs during a period of 1 year. A careful study of history is essential and may reveal the etiology of recurrent infections, thus leading to appropriate treatment. Most common symptoms of RTIs include cough, sore throat, runny nose, nasal congestion, sneezing, headache, low grade fever, facial pressure, and mouth breathing. Cough that often occurs on exposure to cold air, warm air, or both and paroxysms of coughing during exercise is common. Mouth breathing is frequent, caused by nasal obstruction due to edematous turbinates or hypertrophy of the adenoids, leading to the development of the characteristic adenoid facies in the child.

A wide spectrum of diseases influences the respiratory tract directly or indirectly, by causing recurrent infections. The immune system is not at its full maturity at birth and may not be totally developed until school going age. The most common serological abnormality reported in children with recurrent infections is partial deficiency of immunoglobulin A (IgA) or immunoglobulin G (IgG) subclass. Humoral immunodeficiency diseases such as transient hypogammaglobulinemia of infancy and IgG subclass deficiency are also common conditions that increase susceptibility to recurrent infections.[12] Most of the children with recurrent respiratory infections do not have an immunodeficiency; however, they often have deficient antibodies.[13]

The current management of recurrent RTIs is based on curative measures. Antibacterial and antiviral chemoprophylaxis is only exceptionally appropriate in the treatment of RTIs. However, these treatments do not prevent the recurrence of infections. Antibacterials have several drawbacks when used for the treatment of recurrent RTIs. Antibacterials are ineffective against viral infections, do not enhance defense mechanisms of the host against subsequent infections, and induce bacterial resistance with prolonged use. Also, the efficacy of surgery is unclear; many trials and reviews attempted to define the role of ear, nose, and throat surgery (such as tonsillectomy, adenoidectomy, and myringotomy with/without placement of tympanostomy tubes) in the prevention of recurrent upper RTIs with poor results. The role of xylitol in prevention of childhood acute otitis media remains controversial.[14] Oligosaccharides have shown to prevent bacterial mucosal attachment, colonization, and infection in in vitro and animal experiments.[15]

Immunotherapy has been used to boost the immune system and provide protection against microbial infections. Bacterial immunostimulants containing bacterial lysate (OM-85 BV, LW 50020) or components of bacterial cells (ribosomal extracts) were shown to induce a nonspecific response (ie, intensification of phagocytosis) and orchestrate both cellular (B- and T-cell stimulation) and humoral responses (antibodies and proinflammatory cytokines production). The duality of their immunomodulatory activity mimics or, to a certain extent, repeats the immune response evoked by the intrusion of a pathogen into the human body, which is initially nonspecific, but subsequently becomes specific. However, their clinical efficacy in the prevention of RTIs is still debated.[16]

Each recurrence increases the risk of complications and due to its considerable health and economic burden and the progressive resistance to antibiotic treatment, there is an urgent need for cost-effective management of recurrent RTIs.

Septilin in the Management of Recurrent RTIs

Septilin possesses immunomodulatory and anti-inflammatory properties, which potentiate the nonspecific immune responses of the body. Septilin stimulates phagocytosis by macrophage activation, increases the polymorphonuclear cells, and helps overcome infection. Septilin builds up resistance to infection and prevents reinfection. Septilin's stimulatory effect on the humoral immunity increases the antibody forming cells, thereby increasing the secretion of antibodies into the circulation.

Pharmacology

B mukul or *Commiphora mukul* showed a wide range of inhibiting activity against both Gram positive and Gram negative bacteria.[17]

Maharasnadi quath has analgesic, anti-inflammatory, and antipyretic properties.[18]

T cordifolia reduces IL-1b production and inhibits TNF-a, and hence, is a potent anti-inflammatory agent.[19] *T cordifolia* reverses chemically induced immunosuppression providing immunomodulatory support. *T cordifolia* has potent immunomodulatory and immunostimulatory activities, which increase the levels of antibodies and activate macrophages.[20,21]

R cordifolia has immunomodulatory effect that occurs through suppression of iNOS protein.[22]

E officinalis has shown immunomodulatory and antibacterial activity against test bacteria.[23,24]

G glabra has anti-inflammatory action similar to hydrocortisone and other corticosteroid harmones.[25] It also enhances immunostimulation.[26]

Trikatu, an Ayurvedic formulation comprising of a 1:1:1 ratio of dried fruits of *Piper nigrum* and *Piper longum* and rhizomes of *Zingiber officinale*, is widely used to enhance the bioavailability of drugs.[27]

The essential oil from *S lappa* root exhibits strong antiseptic and disinfectant activity against Streptococcus and Staphylococcus. The root extract possesses astringent and antiseptic activity.[28]

Various parts of *Moringa pterygosperma* such as leaves, root, seeds, bark, fruits, and flowers acts as antipyretic, anti-inflammatory, antiulcer, antispasmodic, diuretic, antioxidant, antibacterial, and antifungal activities and are being used for the treatment of different ailments in the indigenous system of medicine, especially in South Asia.[29]

Shankha bhasma has antioxidant action and reduces gastric irritation.[30]

Several clinical trials have been conducted to evaluate the efficacy of Septilin in recurrent RTIs.

Clinical trial 1

Clinical trial of Septilin in recurrent upper respiratory tract infections in children[31]

Aim

This study was conducted to evaluate the efficacy and safety of Septilin tablet in the treatment of recurrent upper RTIs.

Methodology

Inclusion criteria

Thirty cases of recurrent upper RTIs were selected from a pediatric outpatient clinic. Only those patients who were treated earlier with various antibiotics but failed to show improvement were included in the study.

Exclusion criteria

Patients who were unwilling to give informed written consent were excluded from the study.

Study procedure

After detailed physical examination and routine investigations such as hemoglobin, total and differential white cell counts, and throat swab for culture and sensitivity, patients were given Septilin, 1 tablet twice a day in younger and three times a day in older children for a period of 12 weeks. Patients were asked to report at any time if symptoms recurred and at monthly intervals for check up and collection of tablets. After 12 weeks of treatment, all patients were followed up for another 6 months for the frequency of recurrence of symptoms.

Results

Fifteen (50%) patients showed an excellent response. There was complete disappearance of symptoms with no recurrence after initiating Septilin therapy. Nine (30%) children showed good response with no recurrence of attacks during therapy, but had one or two mild attacks of cough during 6 months of observation period. However, the attacks were mild and did not require the use of antibiotics. Six (20%) patients showed poor response. There were no side effects noted in any of the cases. All patients showed a steady gain in weight during the study period.

Conclusion

Septilin was found to be very useful in the management of recurrent upper RTIs in children. Significant improvement was observed in 80% of the cases treated with Septilin. It is a cost-effective and safe drug well tolerated by children and is safe for long-term use without any side effects.

Clinical trial 2

Clinical trial of Septilin syrup in recurrent upper respiratory tract infections (URTIs) in Children[32]

Aim

This study was planned to evaluate the efficacy and safety of Septilin syrup in the management of recurrent upper RTIs of suspected viral etiology.

Methodology

Inclusion criteria

Twenty infants and children aged 9 months to 5 years with upper RTIs of suspected viral etiology were included.

Exclusion criteria

Patients who were unwilling to give informed written consent were excluded from the study.

Study procedure

The enrolled patients underwent routine blood counts, throat cultures, and chest x-ray whenever indicated. Patients started treatment with Septilin syrup with an initial dosage of 1 teaspoon BID in infants and 2 teaspoon BID in children. Subsequently, the dosage was increased to 1 teaspoon TID in infants and 2 teaspoon TID in those children who did not show a significant improvement. The treatment was given for 12 to 16 weeks in most cases.

Results

The average frequency of recurrent attacks prior to Septilin therapy was 4 per patient. Ten (50%) patients showed an excellent response while the remaining 10 (50%) patients exhibited a good response. The latter group comprised all 5 of the patients aged between 3 and 5 years and 5 of the patients were <3 years and required an augmentation of the liquid dose and prolongation of therapy for a further period of 8 to 12 weeks. Avoidance of antibiotics was possible in most of the cases (75%); the remaining 25% had to be given antibiotic coverage in addition. None of the patients could be categorized as being in the poor response group. During follow-up, there was a significant improvement in the symptoms in most patients and all the patients reported good appetite with concomitant weight gain. No adverse effects were observed.

Conclusion

Septilin syrup is as effective as Septilin tablets in the management of recurrent upper RTIs. Septilin syrup was palatable and acceptable to patients and parents, with no untoward side effects. Improved appetite and weight gain were also observed. Therefore, Septilin syrup may be safely and efficiently utilized for the management of recurrent viral upper RTIs.

Clinical trial 3

Septilin for recurrent tonsillopharyngitis in infants and children[33]

Aim

The aim of this study was to evaluate the efficacy and safety of Septilin in the treatment of children with repeated attacks of acute tonsillopharyngitis, using Septilin and antibiotics during the acute phase, preven-

tion of acute exacerbations, and eradication of chronic infections from the throat by prolonged use of Septilin.

Methodology

Inclusion criteria

Children in the age group of 6 months to 5 years with repeated attacks of acute tonsillopharyngitis whose parents were willing to sign informed consent were included in the study.

Exclusion criteria

Children without tonsillopharyngitis and whose parents were unwilling to give informed consent were excluded from the study.

Study procedure

Thirty children who had repeated attacks of acute tonsillopharyngitis at intervals varying from a few weeks to months were included. Therapy with Septilin was instituted after 7 to 10 days of antibiotic treatment for the acute phase patients. Septilin was administered at a dosage of ½ tablet TID for 2 weeks and ½ tablet BID for following 6 to 7 weeks in children aged 6 to 12 months. In children aged 13 to 24 months, Septilin was administered at a dosage of ½ tablet QID for 2 weeks and ½ tablet TID for following 6 to 7 weeks. In children aged 25 months to 5 years, Septilin was administered at a dosage of 1 tablet TID for first 2 weeks followed by 1 tablet BID for 6 to 7 weeks. Patients were followed up for a period of 6 to 9 months.

Results

Results showed that 80% of children had a remarkable reduction in the number of throat infections after Septilin, as compared to the number of attacks before giving Septilin in spite of repeated administration of antibiotics. Before Septilin therapy, 11 children used to get 2 to 4 attacks of sore throat per month. With Septilin treatment only 3 children had these numbers of attacks. Improvement in physical growth and development, increase in appetite and sense of general well-being were also observed. Side effects of Septilin were rare and mild.

Conclusion

From the above study, it can be concluded that administration of Septilin for 6 to 8 weeks after acute throat infection reduces the recurrence rate, promotes growth of the children, creates a feeling of well-being, and minimizes the repeated use of antibiotics and the need for tonsillectomy. Side effects of Septilin were rare and mild.

Conclusion of the Review

Based on the results of the clinical trials conducted on Septilin, it is evident that Septilin is safe and effective in the treatment of recurrent RTIs. Its immunomodulatory, anti-inflammatory, antioxidant, and antimicrobial properties potentiate the nonspecific immune responses of the body and prevent the recurrence of infections. Septilin augments granulocyte-macrophage differentiation, natural killer activity, and antibody dependent cytotoxicity. These effects are due to the synergistic action of all herbs used in the formulation of Septilin. Adverse events were negligible in Septilin-treated patients and did not necessitate withdrawal of the drug. The overall drug compliance was very good. It is also a safe and effective adjuvant to antimicrobials in the management of recurrent infections. When co-prescribed with antibiotics, Septilin ensures faster recovery and reduces the duration and cost of therapy, in addition to preventing reinfections. Therefore, it may be concluded that Septilin is a safe, effective, and economical medication in the treatment recurrent RTIs.

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PERINATOLOGY • Vol. 12 • No. 2 • Jul–Sep 2011

Picture Quiz

Can you make the correct diagnosis?

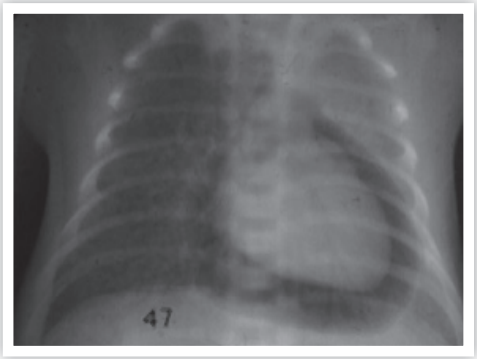

Figure 1

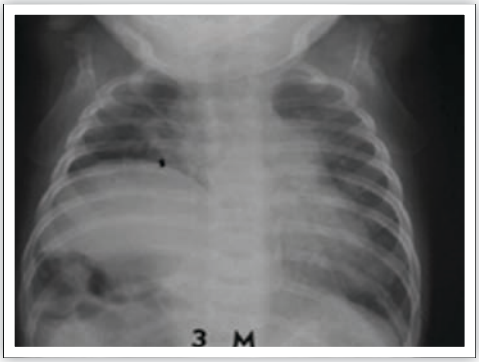

Figure 2

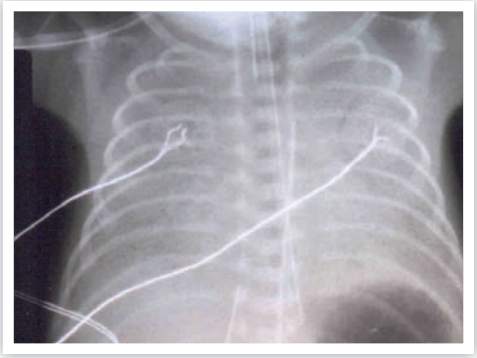

Figure 3

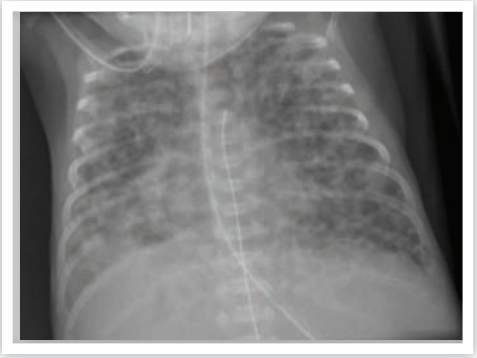

Figure 4

Self-assessment Quiz

Which of the following statements are true?

1. Amniotic fluid

a. alphafetoprotein concentration increases to term
b. bilirubin concentration increases to 36 weeks of gestation
c. is hyperosmolar to fetal plasma
d. is mainly formed from fetal urine
e. urea concentration increases to term

2. Amniotic fluid

a. first appears at 7 weeks of gestation
b. reaches a maximum volume at 38 weeks
c. during early pregnancy has a composition similar to maternal plasma
d. passes through fetal skin up to 36 weeks of gestation
e. has an acid pH

3. In the fetal circulation

a. the ductus arteriosus carries blood to the lungs
b. there is one umbilical vein
c. oxygenated blood passes through the foramen ovale
d. the ductus venosus carries blood with a lower PO2 than the umbilical arterial blood
e. the ductus arteriosus closes during the last 4 weeks of pregnancy

4. The fetal testes

a. secrete testosterone
b. are necessary for the formation of the mesonephric (Wolffian) ducts
c. produce Mullerian inhibitory factor
d. are distinguishable from fetal ovaries 30 days after fertilization
e. contains cells that have migrated from the yolk sac

5. The neonatal mortality rate

a. only includes deaths in the first week of life
b. includes all deaths in the first 4 weeks of life
c. does not include infants born at <24 weeks of gestation
d. is expressed as deaths per 1000 live births
e. is deaths in the first year of life per 1000 live births

6. The stillbirth rate

a. does not include fetuses dying in utero before 24 weeks of gestation
b. includes any infant born dead after 24 weeks of gestation
c. is expressed as deaths per 1000 pregnancies
d. includes all cases of abortions
e. includes neonates born alive weighing <500 g

7. The perinatal mortality rate

a. is the number of stillbirths and neonatal deaths per 1000 live births
b. is the number of stillbirths and deaths in the first week of life per 1000 total births
c. excludes major congenital abnormalities
d. includes all abortions after 20 weeks of gestation
e. does not include first week deaths of infants weighing <500 g

Picture Quiz Answers

Figure 1: Pneumopericardium

Pneumopericardium is one of the rare types of air leak syndromes observed in newborns. Pneumothorax is the most common. Other types include pneumomediastinum, pneumoperitoneum, surgical emphysema, and pulmonary interstitial edema (PIE). They most often occur in babies on supportive ventilation. Pathophysiology includes barotrauma in a dysmature lung. PIE occurs usually after prolonged ventilation and may lead to chronic lung disease. Very rarely, air leak syndromes may occur spontaneously. Pneumopericardium may occur as a complication of pericarditis. Complication of pneumopericardium includes cardiac tamponade that leads to hypotension, shock, and heart failure. Ultrasound guided drainage can be done.

Figure 2: Eventration of the right dome of the diaphragm

Eventration of the right dome of the diaphragm is a congenital abnormality. It may present as respiratory distress or remain silent and can be observed on chest x-ray taken for some other indication. Sometimes, it may present with respiratory distress after many months or years. Respiratory tract infections may have exaggerated symptoms due to this abnormality. Surgical repair can be undertaken as an elective procedure.

Figure 3: Hyaline membrane disease

Hyaline membrane disease is also known as respiratory distress syndrome, observed most commonly in preterm and low birth weight babies. This is due to deficiency of a substance called "surfactant" and leads to change in surface tension of the alveoli causing atelectasis. Severe cases may proceed to respiratory failure, requiring supportive ventilation. Low lung volume, ground glass appearance of lung fields, and air bronchogram are the characteristic radiological findings. Exogenous surfactant preparations (natural extracts and synthetic) can be instilled intratracheally.

Figure 4: Chronic lung disease

Chronic lung disease is honey comb appearance of lung fields on chest x-ray of babies who have received prolonged period of supportive ventilation. The presence of immature lungs with barotrauma could be the etiology. The damage to the lung tissue by oxygen free radicals is also implicated. They are usually oxygen dependent for a long time. Diuretics, nebulization with bronchodilators, and steroids can be used. Neonatal nutrition should be improved. Gentle ways of supportive ventilation (continuous positive airway pressure [CPAP]), avoidance of high pressures during supportive ventilation, and optimum usage of oxygen can be used to prevent this complication.

Self-assessment Quiz Answers

Question 1: D, E

Alphafetoprotein is maximal at 13 weeks and bilirubin at approximately 24 weeks. The amniotic fluid is mainly formed from fetal urine and reflects the maturing fetal kidney, becoming progressively more hypo-osmolar and containing increasing concentrations of nitrogenous products such as urea.

Question 2: B, C

Amniotic fluid appears 7 days after fertilization and reaches a maximum volume at 38 weeks. During early pregnancy, the composition is similar to that of maternal plasma. However, as the fetal kidney matures, it becomes more like fetal urine. The pH is always greater than seven. Fetal skin is permeable until keratinization takes place at 24 weeks.

Question 3: B, C

The ductus arteriosus carries blood from the pulmonary artery to the aorta (ie, bypassing the lungs). If it closes during pregnancy, the infant would develop pulmonary hypertension; it closes after delivery. The single umbilical vein (two arteries) carries oxygenated blood from the placenta to the ductus venosus and portal veins, through the inferior vena cava to the right atrium, directly through the foramen ovale to the left atrium.

Question 4: A, C, E

Germ cells originate beneath the epithelium of the yolk sac and migrate to the genital ridge. In the male, testis is identifiable from 7 weeks after fertilization. Testosterone is produced which sustains rather than causes formation of the Wolffian ducts, which also appear in females. Mullerian inhibitory factor is produced which prevents development of the fallopian tubes, uterus, and vagina.

Question 5: B, D

The neonatal mortality rate includes all deaths in the first 4 weeks after delivery, regardless of the gestation at delivery. It is expressed as a rate per 1000 live births.

Question 6: B

Stillbirths include all babies born dead after 24 weeks of gestation, whenever the death occurred. Abortions occurring before 24 weeks are not included and neither are babies showing signs of life at birth irrespective of their weight. It is expressed as a rate per 1000 total births.

Question 7: B

The perinatal mortality rate includes all stillbirths, babies born dead after 24 weeks, and all first week deaths. Any baby showing signs of life at birth who dies within 7 days is included. It is expressed as a number per 1000 total births (live and dead).

PERINATOLOGY • Vol. 12 • No. 2 • Jul–Sep 2011

Neonatal Outcomes after Demonstrated Fetal Lung Maturity before 39 Weeks of Gestation

Elizabeth B, et al.

Obstetr Gynecol. 2010;116:1288-1295.

In this retrospective cohort study of women with singleton pregnancy delivered at 360/7 to 386/7 weeks after positive fetal lung maturity testing (based on amniotic fluid lecithin to sphingomyelin ratio) or at 390/7 to 406/7 weeks (without maturity testing), authors compared outcomes among neonates delivered after documentation of fetal lung maturity before 39 weeks and those delivered at 39 or 40 weeks. Primary outcome was composite including neonatal death, adverse respiratory outcomes, hypoglycemia, treated hyperbilirubinemia, generalized seizures, necrotizing enterocolitis, hypoxic ischemic encephalopathy, periventricular leukomalacia, and suspected or proven sepsis. There were 459 neonates delivered at 36 to 38 weeks and 13,339 delivered at 39 to 40 weeks; mean birth weight was 3107 ± 548 g and 3362 ± 439 g, respectively. The risk of the composite adverse neonatal outcome was 6.1% for the 36- to 38-week group compared with 2.5% for the 39- to 40-week group (RR 2.4; CI 1.7–3.5). It remains significant after multivariable adjustment (OR 1.7; CI 1.1–2.6). Data suggest that neonates delivered at 36 to 38 weeks after confirmed fetal lung maturity are at higher risk of adverse outcomes than those delivered at 39 to 40 weeks.

Prenatal or Postnatal Indomethacin Exposure and Neonatal Gut Injury Associated with Isolated Intestinal Perforation and Necrotizing Enterocolitis

Sharma R, et al.

J Perinatol. 2010;30:780-785.

In this prospective observation study, including infants born at gestational age ≥23 weeks with birth weight of 400 to 1200 g, authors examined the role of indomethacin in neonatal gut injury. Infants with isolated intestinal perforation (IIP) confirmed at laparotomy or autopsy or with necrotizing enterocolitis (NEC) were identified. Data suggest that prenatal exposure to indomethacin do not increase the rate of gut injury (n = 58). However, any postnatal indomethacin exposure (n = 611) increased the odds of IIP (OR 4.17; CI 1.24–14.08) but decreased the odds of NEC (OR 0.65; CI 0.43–0.97). Compared with NEC, IIP occurred at an earlier age (P<.05), and was more common (P<.05) among infants who received early indomethacin (first dose at <12 hours of age) to prevent intraventricular hemorrhage than among infants who were treated with late indomethacin for closure of a patent ductus arteriosus (PDA). Unlike the classic hemorrhagic ischemic lesions of NEC in which large areas of tissue were inflamed or necrotic, the IIP lesions were small and discrete. These data also suggest that PDA may contribute to NEC.

How Useful Are B-type Natriuretic Peptide Measurements for Monitoring Changes in Patent Ductus Arteriosus Shunt Magnitude?

Chen S, et al.

J Perinatol. 2010;30:780-785.

In this study, authors retrospectively analyzed the data of neonates who underwent paired BNO echocardiogram measurements (obtained from infants between 24 and 32 weeks of gestation with clinical suspicion of PDA). Data suggest that though individual BNP concentrations have significant relation to shunt magnitude (ROC-AUC: 0.85, n = 146), paired BNP-echocardiogram had only fair discriminating power for increase or decrease in shunt magnitude.

High-flow Nasal Cannula and Extubation Success in the Premature Infant

Miller SM, et al.

J Perinatol. 2010;30:805-808.

In this prospective, randomized pilot study, including 40 infants born between 26 and 29 weeks of gestation,

authors compared the effectiveness of Fisher and Paykel (FP) and Vapotherm (VT) high-flow nasal cannula (HFNC) in preventing reintubation either within 72 hours or <7 days after extubation of premature infants. Data did not reveal any difference between FP and VT in the extubation success of infants born between 26 and 29 weeks. The rate of extubation failure at 72 hours was 18% for FP and 9% for VT. The failure rate H7 day after extubation was 30% for FP and 27% for VT.

Fetal Growth Retardation and Risk of Febrile Seizures

Visser AM, et al.

Pediatrics. 2010;126:e919-e925.

This prospective study, based on data for 3372 subjects, revealed the association of fetal growth retardation with increased risk of febrile seizures in the first 2 years of life. Data suggest that children in lowest tertile of the transverse cerebellar diameter in second trimester and in the lowest tertile of all general growth characteristics (femur length, abdominal circumference, and estimated fetal weight) in third trimester were at increased risk of developing febrile seizures compared with children in the highest tertile (OR 2.87; 95% CI 1.31–6.28;OR 2.57; 95% CI 1.34–4.96, respectively).

Maternal Serum and Vaginal Fluid C-reactive Protein Levels Do Not Predict Early-onset Neonatal Infection in Preterm Premature Rupture of Membranes

Torbe A, et al.

J Perinatol. 2010;30:655–659.

This study was aimed to evaluate the usefulness of maternal serum and vaginal fluid C-reactive protein (CRP) determinations in the prediction of neonatal congenital infection. Fifty women between 24 and 36 weeks of gestation, complicated by preterm premature rupture of membranes (pPROM), were divided into two groups according to the presence (n = 14) or absence (n = 36) of early-onset newborns' infection. Data revealed that maternal serum and vaginal fluid CRP concentrations were comparable between both the groups. Maternal serum and vaginal fluid CRP determinations after preterm premature rupture of membranes (pPROM) are of poor predictive value in neonatal early-onset infection prediction.

PERINATOLOGY • Vol. 12 • No. 2 • Jul–Sep 2011

Congenital Megalourethra

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This report presents a rare case of congenital megalourethra. A 20-year-old primigravida with unremarkable medical and family history was diagnosed with fetal lower urinary tract abnormality at 35 weeks of gestation.

Initial ultrasonography (USG) evaluation showed a fetus with normal renal parenchyma but an abnormality in the lower genital tract (a cystic lesion between the scrotal sac, anteriorly, sized 3.2 × 3.6 cm), amniotic fluid index 8, and consistent fetal biometry with the gestational age. There were no additional findings.

A male neonate weighing 2750 g, with an Apgar score of 8 and 10 at 1 and 5 minutes, respectively, was delivered by caesarean route at 38 weeks. On physical examination, the baby had enlarged penis (penile length = 6.2 cm), fusiform shaped with redundant skin and testis descended. Spontaneous voiding of urine was difficult, with a poor urinary stream and a concomitant swelling on the ventral penile surface. Compression of the urethra caused dribbling of urine from the normally located meatus with stenosis. Renal function tests were within normal limits.

In the present case, USG of genitalia revealed absence of corpora cavernosa and spongiosum in the distal part of penile shaft with dilated urethra. Intravenous urogram showed normally positioned kidney but abnormally dilated penile urethra.

Congenital megalourethra is a rare anomaly characterized by severe dilatation of anterior urethra and lack of erectile tissue development of penis without evidence of distal obstruction.

Although the term congenital megalourethra was first used by Nesbitt in 1955, the first case was described by Obrinsky in 1949. The effects of megalourethra are not life-threatening; however, the associated anomalies are often life-threatening and influence the management and prognosis of the condition.

In the present case, it was surgically corrected through reduction urethroplasty with penile reconstruction. Postoperative period was uneventful.

Absence of corpora cavernosa confirmed the diagnosis of fusiform megalourethra. Baby was discharged on 10th day postoperation and was being followed up regularly and reported to be healthy.

Cystic Fibrosis: An Unusual Neonatal Pulmonary Presentation

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Introduction

Cystic fibrosis is a genetic disease caused by mutation in cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for chloride channel that is for production of thick and sticky mucus, sweat, and digestive juices.[1] Usually at birth, newborns with cystic fibrosis present with gastrointestinal complications such as meconium peritonitis, intestinal perforation, ileus, and abdominal calcifications.[2] Although respiratory complications are common with cystic fibrosis in older infants, there are sporadic reports of life-threatening respiratory symptoms at birth in neonates with cystic fibrosis. This is a case report of a newborn with hypoxic respiratory failure with pulmonary hypertension and severe atelectasis.

Case Report

A female infant was born by spontaneous vaginal delivery to a 23-year-old primigravida of Hutterite descent with a history of asthma and hypertension at 39 weeks of gestation. Complications during pregnancy included abnormal glucose tolerance test that was successfully treated with dietary management and group B streptococcal infection which was treated with antibiotics. The infant was born crying, with Apgar scores of 7 at 1 minute and 9 at 5 minutes. Thin meconium was observed at the rupture of membranes. After a few hours of birth, cyanosis was observed along with increasing respiratory distress with nasal flaring, grunting, and increased work of breathing. The oxygen saturation was <70% in high oxygen. Subsequently, the infant was intubated and placed on mechanical ventilator. Chest x-ray showed hypoaerated lungs with evidence of widespread atelectasis (Figures 1 and 2). There was no evidence of hyperinflation or air bronchogram. Oxygenation was not improved with the administration of two doses of surfactant. The echocardiogram showed evidence of persistent pulmonary hypertension. The baby was switched to high frequency oscillatory ventilation (HFOV) as there was no improvement with conventional ventilation. Inhaled nitric oxide at 30 parts per million was also added. In an attempt to improve oxygenation, the mean airway pressure was increased to 28 cm H_2O. Blood gases showed hypercardia and hypoxemia. Laboratory findings such as complete blood count, electrolytes, and serum lactate levels were normal except for an elevated creatinine of 89 μmol/L. Ionotropes were added to improve the blood pressure and circulation. Bilateral chest tubes were placed as there was a suspicion of layering of pleural effusion on the x-ray and

approximately 50 mL of clear fluid was drained from both chest tubes. Because of increasing hypoxemia in spite of 100% oxygen, the HFOV was stopped temporarily and baby was hand ventilated with high positive end expiratory pressures (PEEP), low ventilation rates, and high peak respiratory pressures. This showed clinical improvement. Subsequently, the baby was placed on the HAMILTON-G5 ventilator with a PEEP of 12, ventilation rate of 35, and pressures equivalent of hand ventilation. The baby continued to improve and within the next 48 hours weaned to 25% to 35% Fi02 lower pressures and was extubated on the fourth day. The ionotopes were weaned off, chest tubes were removed, and pleural fluid was found to be transudative. It was observed that the tracheal secretions were unusually thick and sticky and in large amounts during the first few days. The blood and tracheal aspiration cultures were negative.

The expanded neonatal screen suggested evidence of cystic fibrosis, which was confirmed at 3 weeks of age with a positive sweat chloride test. The baby was referred to cystic fibrosis clinic for further follow up and management and was doing well.

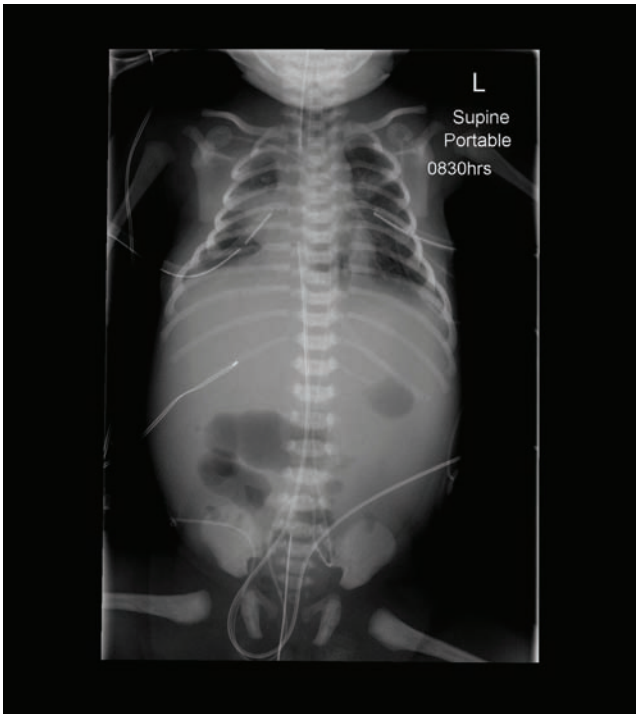

Figure 1

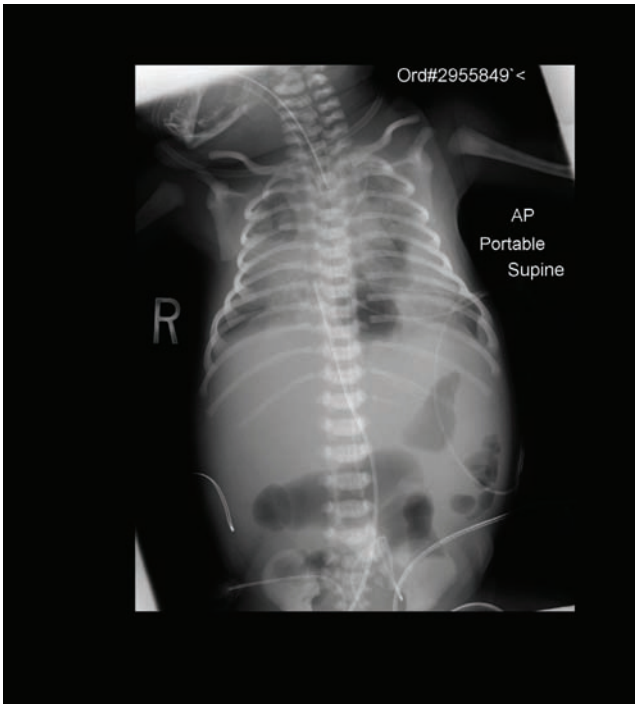

Figure 2

Discussion

The differential diagnoses in this case, included meconium aspiration with persistent fetal circulation, hyaline membrane disease, and sepsis. However, the chest x-ray findings were not consistent with any of these diagnoses. Evidence for severe atelectasis as observed (Figures 1 and 2) in the present case is not common with meconium aspiration syndrome. In addition, patchy atalectasis was observed along with hyperinflation. Cystic fibrosis may produce thick viscid mucus (mucus plugging) and predispose to severe atelectasis. The observation of thick, sticky secretions in this infant supports the possibility of cystic fibrosis. Further, the fact that high PEEP and slow ventilation rates appeared to ameliorate the symptoms, the abnormal mucus production of cystic fibrosis might be the reason for severe atelectasis in this infant. No evidence for local or systemic infection was observed and the cultures were negative. The possibility of hyaline membrane disease was unlikely as the infant was term and the symptoms

did not persist. It was supposed that the pleural effusion was not large enough to cause the atelectasis in this infant. Leaky capillaries from hypoxia may have caused the effusion.

There were no other pathophysiologic processes, except cystic fibrosis, that could explain the clinical presentation and findings.

Cystic fibrosis is a common congenital disease that is prevalent in Canadian population. Every year, approximately 3600 children are diagnosed with cystic fibrosis. It was believed that the unusual neonatal presentation of this infant was initiated by the pathophysiology of cystic fibrosis. It is important to recognize that at birth, neonates with cystic fibrosis may present clinical features similar to meconium aspiration with pulmonary hypertension. An unusual presentation at birth along with expanded newborn screening, suggestive of cystic fibrosis, may help to facilitate earlier diagnosis of cystic fibrosis. Institutional preventive treatment and appropriate follow up may help to decrease the long-term morbidity in infants born with cystic fibrosis.[3]

The literature review showed another case report.[4] In that report, a term infant needed extra corporeal membrane oxygenation to treat hypoxic respiratory failure. Severe atelectasis, hypoxemia, and hypercarbia were present in the previous study, which was similar to the present case. It is important to consider cystic fibrosis as a differential diagnosis in similar case presentations.

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Mixed Gonadal Dysgenesis with 45,X/46,XY/46,X,idic(Y)(p11.3) Mosaicism

Vijaya V Mysorekar,* Sundareshan T S, Padmalatha Kadamba, Jayarama S Kadandale

Abstract

This is a case report of an 11-year-old boy with mixed gonadal dysgenesis and 45,X/46,XY/46,X,idic(Y)(p11.3) mosaicism. The boy was short-statured and presented with hypospadias and a small phallus. He had an undescended, dysgenetic testis on the right and a streak ovary on the left side and bilateral rudimentary uterine tubes and vasa deferentia. The chromosomal mosaicism was detected on karyotyping and confirmed by fluorescence in situ hybridization (FISH) that showed 55% cells with XO, 36% cells with X,idic(Y), and 9% cells with XY. The abnormal Y chromosome showed duplication of the sex determining region Y (SRY) gene which is the testis determining factor (TDF) located on the short arm of Y chromosome. Such a combination of mixed gonadal dysgenesis with isodicentric Yp is extremely rare. The patient had been brought up as a male child.

Key Words: Mixed gonadal dysgenesis; mosaicism 45,X/46,XY; Y chromosome; isodicentric Yp; male pseudohermaphroditism

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Introduction

The term mixed gonadal dysgenesis was coined by Sohval[1] to describe a syndrome characterized by a unilateral abnormal testis that is usually intra-abdominal, contralateral streak gonad, persistent Müllerian structures, external genitalia that are always masculinized to some extent, and 45,X/46,XY mosaicism. Phenotypes of such individuals are varied such as phenotypic females with virilization, Turner-like females, phenotypic males with ambiguous genitalia or some stigmata of Turner syndrome, and almostnormal males.[2,3] This report describes a case of 45,X/46,XY mosaicism in combination with isochromosome of the Yp arm (isodicentric Yp or dicentric Yp), a rare abnormality where there is duplication of the p (short) arm of Y chromosome, with two centromeres, loss of variable amount of the q arm, and in some cases, duplication of the sex determining region Y (SRY) gene which is the testis determining factor (TDF) located on the short arm of Y chromosome.[3] Such a mosaic pattern is extremely rare and very few similar cases have been reported previously in the literature worldwide.

Case Report

An 11-year-old male presented with a history of passing urine from the base of the penis since birth and absence of testes in the scrotum. The boy was born to a nonconsanguineous couple and had a normal birth, development, and family history. On examination, his height was 120 cm (<3rd percentile) and weight was 23 kg (<3rd percentile). Systemic examination revealed no abnormality. His hematological and biochemical parameters were normal. On examination of the genitalia, the boy was found to have a small phallus, hypospadias at the base of the penis (perineal urethra), chordee attached at the base, and an empty scrotum. On diagnostic laparoscopy and right inguinal exploration, the right gonad measuring 1.5 × 1 × 0.5 cm^3 was found at the inguinal canal, and a fimbriated uterine tube was attached to it (Figure 1). Gonadal biopsy was done. Histopathological examinations revealed the structure of an immature testis which was composed of hypoplastic seminiferous tubules with thickened basement membranes (Figure 2). There was a significant germinal hypoplasia—the predominant cells were immature Sertoli cells and only a few spermatogonia. The interstitium showed abundant fibrosis along with Leydig cells.

Three weeks later, the boy underwent laparoscopic removal of a left gonadal streak with a uterine tube. Very thin vasa deferentia, which ended blindly, were found bilaterally. No prostate was observed in cystoscopic examination. Surgery and right orchidopexy were performed for chordee correction. The left gonadal streak was subjected to histopathological examination. Grossly, it measured 1.2 × 0.5 × 0.5 cm^3, and was grayish white in color. Microscopic examination showed compact fibrous tissue resembling ovarian stroma. Primordial follicles were absent.

Karyotyping of chromosomes in peripheral blood leukocyte cultures was done. Two cell lines, namely 45,X [20 metaphases] and 46,X,idic(Y)(p11.3)[10 metaphases], were observed in the 30 metaphases analyzed (Figure 3). Fluorescence in situ hybridization (FISH) showed a mosaic pattern: 55% cells with XO, 36% cells with X,idic(Y), and 9% cells with XY. The

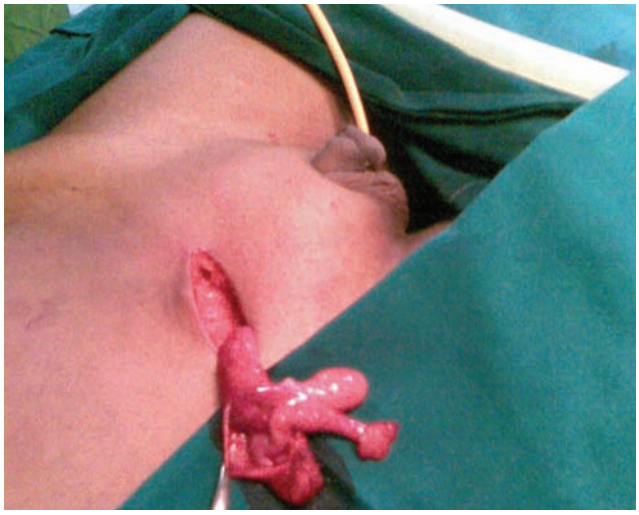

Figure 1. Right gonad at the inguinal canal, attached fimbriated uterine tube, and the small phallus.

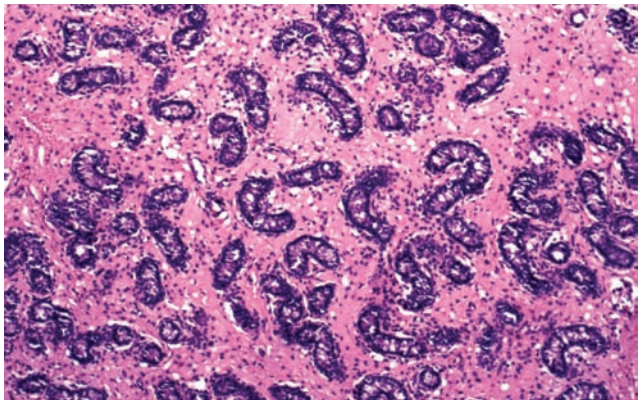

Figure 2. Immature testis composed of hypoplastic seminiferous tubules and interstitial fibrosis is seen (Hematoxylin and Eosin, x100).

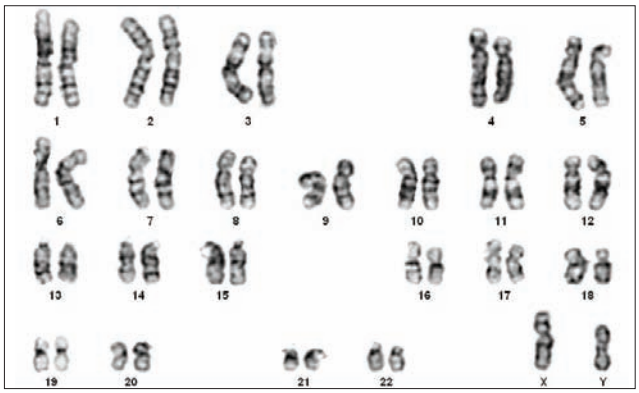

Figure 3. Karyotype 46,X,idic(Y)(p11.3).

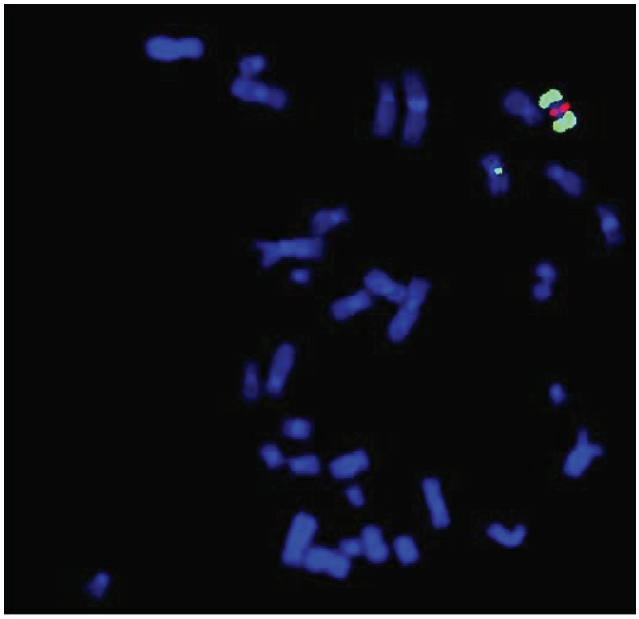

Figure 4. FISH using Y paint probe (green signal) and SRY probe (red signal). The two green signals indicate the duplicated p arm of the Y chromosome (isodicentric Yp). The two red signals indicate that there are two copies of the SRY. Centromeric probe X (CEP X) highlights the centromere of the adjacent X chromosome (green signal).

abnormal Y chromosome showed two FISH signals with the SRY probe (Figure 4), indicating the duplication of SRY. A final diagnosis of mixed gonadal dysgenesis with 45,X/46,XY/46,X,idic(Y)(p11.3) mosaicism (karyotype mos45,X/46,XY/46,X,idic(Y)(qter→cen →p11.3::p11.3→cen→qter) was made. Chromosomal study on skin fibroblast cultures and gonadal tissue cultures could not be conducted, as these facilities were not available.

The patient and his parents were counseled about his condition and they opted that he would be continued to be brought up as male. However, removal of his dysgenetic testis was contemplated due to its high malignant potential.

Discussion

This patient had a short stature, as in Turner syndrome, and all the features described in mixed gonadal dysgenesis. The case showed cell lines with idic(Y)(p11.3) in addition to 45,X/46,XY mosaicism, an extremely rare combination. A similar karyotype has been reported in a few other cases of mixed gonadal dysgenesis.[4–7] Other authors have described cases of mixed gonadal dysgenesis with 45,X/46,X,idic(Y)(q11.2) mosaicism.[8–10]

The present case had a 46,XY karyotype in the beginning, with some 46,X,idic(Y)(p11.3) cell lines developing in the embryo later on, as a result of mitotic nondisjunction. As abnormal Y chromosomes are inherently unstable during cell division, the 45,X line had arisen secondarily, following the loss of the dicentric Y chromosome in many cell lines.[3] This could explain the presence of a mosaicism of three cell lines, that is, 45,X/46,XY/46,X,idic(Y)(p11.3) in this patient. The dicentric Yp may indicate the duplication of SRY gene as observed in this case. However, the SRY gene is unevenly distributed in different tissues in the same individual, and the presence of SRY in a proportion of cells does not guarantee a male phenotype. The proportion of Y cell line with adequate SRY product present in the gonadal tissue determines the degree of differentiation of the testis. In the present case, the genetic constitution of the gonads is not known as karyotyping was performed only in peripheral blood leukocyte cultures.

As the testosterone secretion from the dysgenetic testis was insufficient, the male genital organs were incompletely developed. The failure of regression of the uterine tubes was due to the deficient production of Müllerian-inhibitory factor from the dysgenetic testis.

The presence of Y chromosome material in patients with dysgenetic gonads is known to increase the risk of gonadal tumors.[11] The most common tumor is the benign gonadoblastoma, which has the potential to progress toward invasive germ cell tumors, especially seminoma in testes and less frequently yolk sac tumor or embryonal carcinoma. Tumors commonly develop in the first or second decade, hence gonadectomy is recommended for these individuals.

Acknowledgement: The authors are grateful to Dr S Kumar, Principal, M S Ramaiah Medical College, for his kind support in developing this paper.

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Acephalus Acardiac Fetus—An Unusual Complication in a Twin Pregnancy

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Introduction

Acephalus acardiac twin is a very rare and unusual phenomenon occurring in monozygotic twin pregnancy, as an extreme form of twin-to-twin transfusion syndrome (TTTS). It appears in 1 in every 35,000 births with an average risk of 1% among monozygotic twins.[1] TTTS complicates 5% to 35% of monozygotic twin pregnancies with monochorionic placentation. This condition results from abnormal placental vascular anastomosis termed as twin reversed arterial perfusion (TRAP) sequence, first defined by Greenwald in 1942.[1,2] The "acardiac" twin bereft of the heart acts as a parasite and thrives from the potentially viable normal "pump" twin for its survival.

This is a case report of an antenatally undiagnosed case of acephalus acardiac twin with autopsy findings, of an unbooked primigravida admitted with labor pains.

Case Report

A 21-year-old primigravida was referred at 26 weeks of gestation from a private hospital in view of a threatened preterm labor and a scan result that revealed the possibility of one of the twins to be born dead and anomalous. Patient had conceived spontaneously and it was a nonconsanguineous marriage. Her clinical examination revealed a uterine size of 34 weeks tense abdomen suggesting polyhydramnios. Routine blood and urine tests were found to be normal. However, repeated ultrasound scan at this hospital during admission showed Fetus A corresponding to a gestational age of 27 weeks with no obvious anomalies with polyhydramnios. Fetus B showed a dead fetus with multiple anomalies of the skull, spine, and limbs. It was a monochorionic diamniotic placentation. Doppler study showed normal Pulsatile Index and Resistance Index values for Fetus A.

Patient delivered vaginally a preterm male baby by vertex weighing 1.08 kg—Twin A fetus or the pump twin, soon followed by the delivery of an acardiac fetus—Twin B fetus or recipient twin weighing 600 g on February 5, 2011. Twin A was admitted in NICU in view of extreme prematurity and died soon thereafter on postnatal third day. Placenta was monochorionic diamniotic weighing 500 g and was vellamentous

in type. Consent for autopsy was taken for the acardiac twin and the autopsy findings are as follows:

External examination showed no identifiable eyes, ears, nose, mouth, and mandible. Only one optic slit was present. Severe generalized subcutaneous edema was present. Upper limbs were absent. Single lower limb with club foot having four toes was observed. No anus or external genitalia was observed (Figure 1).

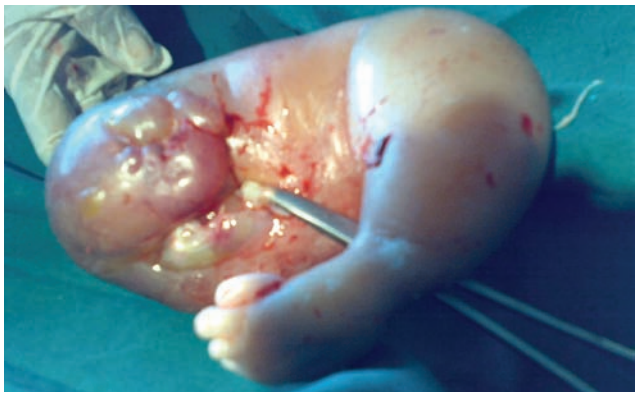

Figure 1. Gross anatomy of the acardiac twin.

Internal examination showed complete absence of brain which was replaced by a cyst filled with 6 mL of clear serous fluid. No neck, trachea, esophagus, or stomach was present. On dissection, seven ribs, bilateral kidneys, and 8 cm tubular intestinal segment were seen in the cephalic end of the coelomic cavity in the thoracic region. Thymus was also observed in the thoracic region. Cardia, liver, gall bladder, spleen, and pancreas were absent. No diaphragm was identified. Two small, brown, pea-shaped structures—adrenal gland and unilateral testis and epididymis were lying in the midportion of the coelomic cavity. Other testis and adrenal gland as well as ureter, urethra, and urinary bladder were absent (Figure 2).

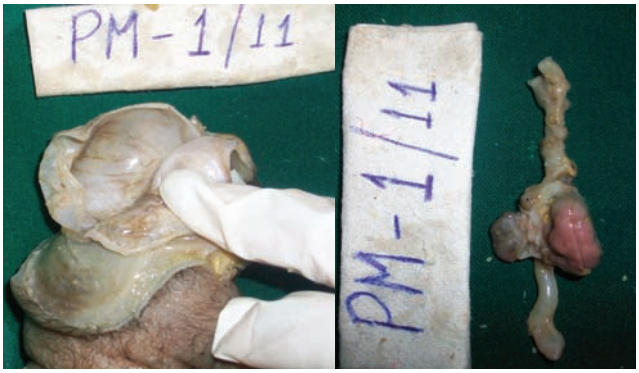

Figure 2. Autopsy of the acardiac twin showing eviscerated ill-formed organs.

Skeletal examination of the postmortem radiograph showed four fused cervical segments, nine thoracic segments with two hemivertebrae, seven ribs identified bilaterally, and five lumbar spinal segments with fusion of two (L4 and L5). Only right ilium, ischium, femur, tibia, fibula were visualized. Right foot showed one tarsal bone and four metatarsals. Four proximal phalanges, two middle phalanges, and a distal phalanx were identified in the right club foot. Left lower limb was not visualized (Figure 3). Hence, a final impression of acephalic acardiac fetus was made.

Figure 3. Postmortem radiography of the acardiac twin.

Discussion

Acardiac twin, also known as TRAP sequence is a rare and serious complication of twin pregnancy. This might be caused due to larger vessels on the outer surface of the common placenta, either through arterio-arterial or veno-venous communications. Blood is perfused from the pump twin to the acardiac twin by retrograde flow. Therefore, the acardiac twin receives deoxygenated arterial blood from the pump twin in a reverse direction. This inadequate perfusion of the blood flow in acardiac twin is responsible for a spectrum of lethal anomalies, such as acardia (absent heart), acephalus (absent skull), and severe maldevelopment of the upper body and excess of edematous connective tissue.[3] First, The pump twin though structurally normal has a high perinatal mortality of 50% to 70% because of high-output

cardiac failure (as it has to pump for both itself and the acardiac twin resulting in increased strain to its heart), second, because of polyhydramnios and rapid growth of the acardiac twin, risk of preterm delivery is increased where the expected fetal weight of the TRAP twin is 50% or more than the pump twin, as seen in our case.[4] This results in high-output cardiac failure in the pump twin showing signs of hydrops and critically abnormal flow patterns on Doppler Ultrasound.

Early sonographic prenatal diagnosis improves the survival of the normal twin (pump twin). It is worthwhile to try expectant treatment for the survival of the pump twin. Serial amniocentesis of the pump twin can be done to reduce the liquor quantity and congestive heart failure. Treatment of the mother with digoxin and indomethacin for congestive heart failure and to reduce the liquor quantity, respectively, is also suggested. Surgical intervention in the womb to separate the circulation systems of the twins has been proposed. In order to stop the blood flow to the acardiac twin, a high-energy radiofrequency ablation is used to destroy the blood vessels and surrounding tissues at the vascular connections between the twins. The other treatment available is fetoscopic placental laser surgery directed at the vascular connections between the twins.[5] The incidence of chromosomal abnormalities in the pump twin may be as much as 9%, and it should be excluded before offering fluoroscopic procedure.[6]

In the present case, because of the presence of polyhydramnios and the weight of the acardiac twin being more than 50% of the pump twin, patient experienced labor and the pump twin could not be salvaged due to extreme prematurity although it was structurally normal. This case is reported in view of its extreme rarity, absence of external genetalia in the acardiac twin.[6] There was difficulty in diagnosing the acephalus acardiac twin antenatally, as it was mistaken for a dead anomalous twin by sonography. Hence, expectant or interventional treatment could not be offered.

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