ORIGINAL ARTICLE

Role of human chorionic gonadotrophin to prevent repeated early pregnancy loss

E Saha[1], F Begum[2], ZF Jesmin[3]

Abstract

Early pregnancy loss is a frustrating experience for both the patient and the physician. Approximately 5% of couples trying to conceive have 2 consecutive miscarriages and approximately 1% couples have 3 or more consecutive losses. Objective of this study is to determine whether therapy with dydrogesterone or Human chorionic Gonadotrophin hormone (HCG) in history of repeated pregnancy loss during the first trimester of pregnancy will improve pregnancy outcome. This is a prospective open comparative study.Women having early pregnancy presenting to a private clinic with history of early pregnancy loss, having no medical disorder were included in this study. Eligible subjects were randomised to receive either dydrogesterone 20mg daily or injection Human Chorionic Gonadotrophins (HCG) 5000 iu intramuscularly at 72 hours interval up to fourteen weeks of pregnancy or no additional treatment. Follow up of those patients were done with transabdominal ultrasonography. Hundred women were recruited. There was no statistically significant difference between the three groups with regard to pretreatment status. The continuing pregnancy success rate was higher in women treated with dydrogesterone (79.17%) and highest with Injection Human Chorionic, Gonadotrophin (86.36%) compared with women received no treatment (70%), (p=0.358). Hormonal support with either dydrogesterone or Human Chorionic Gonadotrophin may increase the chances of a successful pregnancy in women with a history of spontaneous abortion.

Bang Med J Khulna 2015; 48 : 7-10

Introduction

Early pregnancy loss is a frustrating experience for both the patient and the physician. Early pregnancy loss is unfortunately the most common complication of human gestation occurring in as many as 75% of all women trying to conceive. Spontaneous abortion defined as the loss of pregnancy before viability of the foetus, is estimated to occur at a rate of approximately 15%.1 Recurrent abortion is defined as the loss of three or more consecutive pregnancies.[1] ASRM (American Society for Reproductive Medicine) practice committee report redefined recurrent pregnancy loss in January, 2008 as two or more consecutive spontaneous abortions. Evidence indicates that after one spontaneous abortion, the risk of a second abortion is approximately 23%. after two spontaneous abortions, the risk of another is 38% and after three, the risk is increased further to 55%.[2-3] It is estimated that as many as 5% of couples trying to conceive have two consecutive abortions and 1-2% have three or more.[4]

The etiology of early pregnancy loss varies and is often controversial. No explanation can be identified in approximately 40-50% of women with recurrent abortion.[3] In cases of unexplained repeated pregnancy loss, several supportive therapies have been advocated. These include bed rest,[5] abstention from coitus and a simple wait and watch policy, as well as treatment with progesterone or human gonadotropin.[6,7] Progesterone deficiency is recognized to be associated with insufficient endometrial maturation and inadequate regulations, such as interleukins. Support with progestogen may therefore help to establish an adequate immune response in early pregnancy and prevent pregnancy loss. Dydrogesterone is an orally active progesterone that is similar to endogenous progesterone.[7] Human chorionic gonadotrophin (HCG) works by increase secretion of endogenous progesterone. It have less side effect but it is available only in injection form. The aim of this study was therefore to compare the efficacy of supportive therapy with dydrogesterone or Human

1. Eti Saha FCPS, Assistant Professor (Obs & Gynae), Khulna Medical College & Hospital.
2. Fouzia Begum MCPS, Consultant (Obs & Gynae), Khulna Medical College Hospital.
3. Zannatul Ferdous Jesmin FCPS, Assistant Professor (Obs & Gynae), Khulna Medical College & Hospital.

Chorionic Gonadotrophin (HCG) in women with history of pregnancy loss in first trimester.

Methods

Pregnant women of first trimester presenting in a private clinic of Khulna between 2009 to 2013, who had experienced spontaneous abortions were enrolled. All the patients included in this study were seen by author and were included in this prospective randomised open study. The women were required to have been investigated after their last abortion and to be scheduled to attend the clinic for antenatal care. Only those women for whom apparently no explanation could be found for their abortions were included. Exclusion criteria: patient having medical disorder-chronic nephritis, chronic hypertension, diabetes mellitus, SLE, antiphospholipid syndrome and patient having no history of abortion were excluded from this study. All women provided verbal informed consent.

A detailed obstetric history was obtained from each women at baseline including number of pregnancies, live births, still births, abortion, ectopic pregnancies and hydatiform moles. A detailed past medical and surgical history were obtained. All women also underwent the following assessment: pelvic ultrasonography both trans abdominal and trans vaginal, blood grouping and Rhesus factor, complete blood count, erythrocyte sedimentation rate, thyroid function tests (T3,T4,TSH), anti nuclear antibodies, serum prolactin level, VDRL, urine routine and culture examination & semen analysis of husbands of those who had history of secondary subfertility.

The women were randomised to receive oral dydrogesterone (Duphaston 10 mg b.I.d), Intramuscular hCG (Profasi, Pregnyl, Choragon, HCG every 72 hrs interval) or no additional treatment (controls). Treatment was started as soon as possible after confirmation of pregnancy by urine pregnancy test and or pelvic ultrasonography and continued until fourteenth (14th) gestational weeks. All women received standard supportive care including folic acid supplementations and recommended bed rest and were followed routinely in outpatient basis with trans abdominal ultrasonogram at 8th an 14th gestational week. The women were only admitted in hospital during the treatment period if they had vaginal bleeding or a medical conditions that required hospital treatment.

Calculated data was checked and edited. Finally data was entered into the computer for statistical analysis by using MS Excel & Chi square tests. Calculated data were arranged in systemic manner and presented in various tables.

Results

A total of 150 women with a history of early pregnancy loss presented to the clinic between January 2009 to December 2013. Of these, 100 women (66%) were found to have apparently no explanation for their spontaneous abortion.

Table I

Patients distribution in treatment group (n-100)

Groups	Treatment received	No. of patients (n-100)(%)
Group-A	Dydrogesterone	48(48)
Group-B	Human chorionic gonadotrophin (HCG)	22(22)
Group-C	No additional treatment	30(30)

Table I shows patients distribution in treatment group those who received dydrogesterone were included in group A (48%), those who received injection HCG were included in group B (22%) and no additional treatment were in group C (30%).

Table II

Age distribution of patients

Age	Group-A (n-48)(%)	Group-B (n-22)(%)	Group-C (n-30)(%)
19 years or less	4(8.33)	0	1(3.33)
20-25 years	26(54.17)	8(36.37)	6(20)
26-30 years	15(31.5)	7(31.82)	18(60)
31 yrs or more	3(6.25)	7(31.82)	5(16.67)

Table II shows age distribution of patient of three groups. There was no patient of less than 20 years in group B, who received HCG. Age group 20 to 25 years in group A who received dydrogesterone (n-26), group B (n-8), group C (n -6). Age group 26 to 30 years n-18 in group C, where as 32% in group A & B. More than 30 years old lady in group B about 32%,where as 6% in group A and 17% in group C.

Table III

Marital life of patients

Age	Group-A (n-48)(%)	Group-B (n-22)(%)	Group-C (n-30)(%)
<5 years	24(50)	7(31.82)	15(50)
5-9 years	18(37.5)	11(50)	10(33.33)
10 yrs or more	6(12.5)	4(18.18)	5(16.67)

Table III shows marital life of patients of different group. Marital life less than five years in group A & C were 50%,where as in group B 32% of patients. Marital life five to nine years in group B were about 50%, in group A 38% & in group C 33% of patient. 10 years or more marital life in group A 13%, group B 18%, group C 17% of patients.

Table IV

History of early pregnancy loss among groups

Number of early pregnancy loss	Group-A (n-48)(%)	Group-B (n-22)(%)	Group-C (n-30)(%)
History of one abortion	31(64.58)	9(40.91)	19(63.33)
History of two abortion	12(25)	7(31.82)	8(26.67)
History of three abortion	2(4.17)	5(22.73)	3(10)
History of more than three abortion	3(6.25)	1(4.54)	0

Table IV shows history of early pregnancy loss in patients of different groups. History of one abortion is about 65% in group A, where as 41% in group B, and in group C 19%. History of two abortion in group A about 25%, in group B 32% whereas in group C 27%. History of three early pregnancy loss in group A was about 4%, in group B 23%, in group C 10%. History of more than three abortion in group A about 6% where as 5% in group B & no patient in group C.

Table V

Outcome of pregnancy among groups

Outcome of pregnancy	Group-A (n-48)(%)	Group-B (n-22)(%)	Group-C (n-30)(%)	P value
Alive pregnancy	38(79.17)	19(86.36)	21(70)	0.358
Pregnancy loss	10(20.83)	3(13.64)	9(30)	

Outcome of pregnancy in each group is shown in table V. Abortion were in the control group C is (30%), in dydrogesterone group A is (20.83%) where as hCG receiving group B (13.64%).

No adverse effects were reported during treatment with dydrogesterone or hCG. P/V bleeding occur during study time in the 9 patients of group A , 10 patients of group B, 10 patients of group C.

Discussion

During normal pregnancy, there is an adaptation between the trophoblast, which acts as allogenic tissue due to parental genetic contribution and the mother. Some recent research suggests that the immunologic interaction between mother and fetus appears to be beneficial for foetal and placental growth and development and limits trophoblast invasion. This is result of immunotolerance and immunosuppression. First, the placental tissue (syncytiotrophoblast) that contacts with maternal tissue lacks the ability to activate the immune system. Second, the placenta tissue (cytotrophoblast) dose not stimulate major histocompatibility complex (MMC) antigen formation because of the presence of human leukocyte, antigen G (HLA G). Therefore the mother creating immunotolerance does not normally produce harmful anti paternal antibodies. Certain cytokines (transforming growth factor beta [TGF-B] and interleukin 10), prostaglandin E2, hCG and steroid hormones appear to have immunosuppressive activity in normal gestational tissue.[8]

Failure of this immune system adaptation results in alloimmune rejection of the foetus. It has been proposed that women with recurrent abortion have a deficiency in maternal blocking antibodies or abnormal uterine and decidual suppressor natural killer cells.[7] Progesterone is also important in maintaining the pregnancy throughout the nine months by inhibiting myometrial activity and preventing T cell mediated rejection.[8] It is a debate that hormonal therapy may be beneficial in women with unexplained repeated pregnancy loss.

The finding of current study clearly support the use of a progestogen or hCG in those women. Both therapies were significantly more effective than standard supportive care alone in preventing repeated spontaneous abortions. Similar findings were detected by EL Zibdeh.[7] There was a review done by RHL (The WHO reproductive health library) on progestogen for preventing miscarriage. The review suggest that progestogen therapy may be beneficial for women who have experienced recurrent miscarriages.[9]

In one study shows that dydrogesterone inhibits the production of the Th1 cytokines IFN-g and TNF-µ from lymphocytes and up regulates the production of the Th-2 cytokines IL-4 and IL-6, inducing a Th-1 to Th-2 cytokine shift and also induced the production of progesterone induced blocking factor (PIBF).[10] PIBF mediates the immunological effects of progesterone and dydrogesterone in pregnancy, so result show usefulness of dydrogesterone in women with history of recurrent miscarriage.[11]

In one study done by Kalinka etal showed pregnancy outcome in dydrogesterone treated women was not significantly different from that of healthy controls.[12] Some studies show dydrogesterone appears to have beneficial effects in women with threatened miscarriage.[13]

Another study shows that abortion rate in dydrogesterone receiving group is 17.5% whereas

25% in untreated group13, in this study abortion rate is 21 % in dydrogesterone where as 30% in untreated group (C).

In another study, similar to our study, shows that abortion were significantly less common in dydrogesterone group (13.4%) than in the control group (29%); there were no statistically differences between the hCG group and control group.[7]

One meta analysis suggested a statistically significant reduction in miscarriage rate using hCG.[14] In our Study abortion rate is much less in hCG group about 14% than dydrogesterone group (21%) & untreated group (30%). Since p value is 0.358, so study result is insignificant. Our study suggests that there is no association between hormone use and pregnancy status that is hormone has no significant impact on pregnancy status.

There are some shortcoming in this study. Study group are small in number. In Khulna we have no facilities for TORCH screening, anticardiolipin antibodies, antiphospholipid antibodies, Lupus anticoagulant antibodies test and chromosomal analysis. So patient were not screened properly. Some patient cannot afford human chorionic Gonadotrophin (HCG) which is costly. HCG is parenteral in form and inconvenient to some patient. So randomisation of patient was not properly done. About 50% of the patients of study group were delivered by author. So congenital abnormality of foetus and complications during late pregnancy and labour were not included in this study. Dydrogesterone use during pregnancy have no link with birth defect.[15]

Outcome of pregnancy only observed upto fourteen weeks of pregnancy- alive pregnancy or loss. In this study group women who received HCG injection 10 of 22 women developed p/v bleeding but one miscarriage occured of them, in contrast only 9 of 48 women of dydrogesterone group developed threatened abortion.

Dydrogesterone has a number of advantages over micronised progesterone and other available synthetic progestogens in term of Pharmacokinetic parameter, safety, tolerability and convenience.[7]

Conclusion

Though the result of study is statistically insignificant, but it provides that dydrogesterone is cost effective and convenient to patient due to oral form & improvement of outcome of pregnancy near to hCG. So that dydrogesterone can be a treatment option in women in first trimester in pregnancy who have history of spontaneous abortion of unexplained cause. Similar studies with large number of patients are warranted to establish universal adaptation guideline in all women to prevent early pregnancy loss.

References

1. J. L. Ecker, M. C. Laufer, J. A. Hill. Measurement of embryotoxic factors is predictive of pregnancy outcome in women with a history of recurrent abortions, Obstet Gynecol 1993;9: 84-87.
2. G. M. Stirrat. Recurrent abortion: definition and epidemiology, Lancet 1990; 336: 673-675.
3. Parihard M, Bharath M. Recurrent Spontaneous Abortion: Current choices in treatment, Principles & practice of obstetrics & Gynaecology for postgraduate, 3rd Edition, Volume-1 Editors Pankoj Desai, N. Malhotra Jaypee brothers, Medical Publishers LTD. New Delhi, India, 2008, p. 164-172.
4. Regan L, Braude PB, Trembath PR. Influence of past reproductive performance on risk of spontaneous abortion, Br. Med. J 1989; 299:541-545.
5. Aleman A, Althabe F, Belizan J. Bergel E. Bed rest during pregnancy for preventing miscarriage, Cochrane data base Syst Rev. 2005.
6 Qureshi NS, Edi-Osagie EC, Ogbo V, Roy S, Hopkins RE. First trimester threatened miscarriage treatment with hunman chorionic gonadotrophins: a randomised controlled trial, BJOG 2005; 112: 1536-41.
7. El Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion, Journal of Steroid Biochemistry & Molecular Biology 2005; 97(5):431-434.
8. Gilbert ES, Manual of high risk pregnancy and delivery, fifth edition; MOSBY, an imprint of Elsevier, St Louis, Missouri 2011; 314.
9. Thach TS. Progestogen for preventing miscarriage, RHL commentary, The WHO reproductive Health Library; Geneva: World Health Organisation. 2009.
10. Raghupathy R, Mutawa EA, Makhseed M, Azizieh F, Bartho JS. Modulation of cytokine production by Dydrogesterone in lymphocytes from women with recurrent miscarriage, BJOG 2005; 112; pp. 1096-1101.
11. Gruber CJ, Huber JC. The role of dydrogesterone in recurrent (habitual) abortion, J. Steroid Biochem Mol Biol 2005; 97: 426-430.
12. Kalinka J, Szekeres-Bartho J. The impact of dydrogesterone supplementation on hormonal profile and progesterone induced blocking factor concentrations in women with threatened abortion, Am J Reprod immunol 2005; 53:166-171.
13. Zibdeh EL, Yousef LT. Dydrogesterone Support in threatened miscrriage. J. Maturitas. 2009; 65: S 43-46.
14. Morley LC, Simpson N, Tang T. Human chorionic gonadotrophin (hCG) for preventing miscarriage. Cochrane Database of Systematic reviews 2013 issue 1.
15. Queisser-Luft AH. Dydrogesterone use during pregnancy: Over view of birth defects reported since 1977, Early Human development .2009;85: 375-377.