

AN OBSERVATIONAL STUDY FOR EARLY DETECTION OF INTRAUTERINE GROWTH RESTRICTION IN PREGNANCY USING ULTRASONOGRAPHY AS A TOOL IN FIRST TRIMESTER

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ABSTRACT

BACKGROUND

In a country like India, Intrauterine Growth Restriction (IUGR) is a serious problem by engulfing a major expenditure for health by increasing mortality as well as day-to-day morbidity. My intention of this study is to find out IUGR in early trimester upto 13 weeks of pregnancy, so that we can implement any corrective measures so that rate of IUGR will be minimal and also its adverse consequences.

MATERIALS AND METHODS

1120 patients were chosen from an Institute of Infertility Clinic of Kolkata who were free of any medical or surgical problem and conceived by In-Vitro Fertilisation (IVF) due to unexplained infertility having singleton pregnancy. Patient was chosen from IVF, so that exact date of conception can be found to rule out the fallacy of calculating the period of gestation on the basis of menstrual history of patient, which was sometimes approximated. Out of 1120 patients 725 had no clinical pregnancies, rest had undergone ultrasonography. A serial Ultrasonography was done every month and the parameter of crown rump length, femur length, abdominal circumference, head circumference, estimated foetal weight and period of gestation was recorded along with the Amniotic Fluid Index and birth weight (all were delivered by Caesarean Section at 34 - 35 weeks).

RESULTS

Out of 395 patients, 65 had midterm pregnancy loss; 2 patients delivered IUGR babies, one having history of Oligohydramnios with Oesophageal Atresia and another having Antepartum Haemorrhage with low-lying placenta with anaemia. Four patients were in accordance with normal variant in early trimester become IUGR due to Gestational Diabetes Mellitus (Controlled), Chronic Hypertension. Four patients delivered mild IUGR babies suffering from Nutritional Deficiency because of Morning Sickness (Pyridoxine given) and Hyperprolactinaemia (Bromocriptine given along with amino acid supplement), and 275 patients have positive correlation among CRL and birth weight. Rest 45 mothers had negative correlation having normal CRL, but low birth weight.

CONCLUSION

Although out of 55 LBW deliveries author found positive correlations only in 10, most of the cases has got negative correlations making the study inconclusive with the hope of scope for further study on adverse effect of procedure of assisted reproductive technique.

KEYWORDS

Crown-Rump length, Assisted Reproductive Technique, In-Vitro Fertilisation, Intrauterine Growth Restriction.

HOW TO CITE THIS ARTICLE: Roy D. An observational study for early detection of intrauterine growth restriction in pregnancy using ultrasonography as a tool in first trimester. *J. Evolution Med. Dent. Sci.* 2017;6(53):4012-4016, DOI: 10.14260/Jemds/2017/867

BACKGROUND

Foetal growth is characterised by sequential pattern of tissue growth, differentiation and maturation. Lein and Santolaya-Forgas (1998) have classified the phases of growth as that of cellular hyperplasia (conception till 16 weeks), hyperplasia and hypertrophy (16 - 32 weeks) and the last period of hypertrophy only (32 weeks onwards) without any increase in cell number.¹

Intrauterine Growth Restriction (IUGR) refers to a condition, in which a foetus is unable to achieve its genetically determined potential size. By definition, IUGR is

said to be present in those babies whose birth weight is below the 10th percentile of the average for the gestational age.²

World Health Organisation (WHO) estimates that globally about 25 million Low-Birth Weight (LBW) babies are born in each year. Among those 2 - 8% are born in developed countries and some in developing region (Africa). In fact, South Asia has the highest prevalence of LBW and the latest projection indicates more than half of the world's LBW babies are born here.²

In India data collecting from Institutional and community deliveries show wide regional variations of prevalence of LBW from 2.7% (Madhya Pradesh) and 5.1% (Assam) to a high of 24.7% (Tamilnadu) and 40% (Orissa).³

The world summit for children had set a goal of reduction of the LBW prevalence to less than 10%⁴ associated with a higher rate of multiple births,^{5,6} which in turn is associated with LBW.⁷ In addition, studies have suggested that there is a higher rate of low birth weight among singleton infants conceived with assisted reproductive technology than among

Financial or Other, Competing Interest: None.

Submission 07-06-2017, Peer Review 25-06-2017,

Acceptance 27-06-2017, Published 03-07-2017.

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DOI: 10.14260/Jemds/2017/867



naturally conceived singleton infants⁸⁻¹⁰ or among all infants in the general population.¹¹⁻¹⁵

Aims and Objectives

To correlate the CRL in the first trimester in foetuses conceived by In-Vitro Fertilisation (IVF) with the incidence of IUGR near term or with birth weight that is low for gestational age.

First trimester study for IUGR will be done for earlier monitoring of pregnancy with the hope of best outcome. For accurate prediction of IUGR in first trimester based upon LMP (which is often erroneous), we have taken the help of pregnancy by in-vitro fertilisation.

MATERIALS AND METHODS

Study Population

All women who conceived through assisted reproduction (IVF) in the period between September 2008 and August 2010 was recruited for this study.

Author assessed the relationship between discrepancy in the observed and expected size of the foetus in the first trimester and the birth weight, duration of pregnancy and risk of delivering a small for gestational age infant among a large prospective/concurrent cohort of women with a known date of conception. All the relevant data of those patients with IVF pregnancy were collected.

Place of Study

The data was collected from the Assisted Reproduction Unit, the Obstetrics Unit and the Sonography Unit of one Institute of Reproductive Medicine situated at Salt Lake City, Kolkata.

Inclusion Criteria

- Maternal age between 19 - 35 years (to exclude age-related problems on pregnancy).
- Single viable embryo or foetus (conceived by IVF) present when the first ultrasound scan is performed (9 - 11 weeks of amenorrhoea, because after that frequent movement of embryo may create error in CRL measurement).

Exclusion Criteria

- A history of rhesus isoimmunisation.
- Essential hypertension.
- Cardiac disease.
- Diabetes mellitus.
- Other medical problems.
- Non-viable embryo or foetus at first scanning.
- Multiple pregnancy (second sac seen on ultrasonography).
- Antenatal detection of foetal abnormality.
- Therapeutic termination of pregnancy.
- Postnatal detection of foetal abnormality.

The above cited cause may affect the growth rate of embryo and the statistical analysis directly or indirectly.

Method of Study

1120 patients were selected from Institute of Reproductive Medicine, Salt Lake, Kolkata taking prior consent in prescribed form who came with the complaint of pregnancy loss or infertility (primary/secondary).

The patients were divided into two broad groups on the basis of quality of endometrium (by Polymerase chain reaction of endometrium taken by dilatation and curettage of uterus done during pre-conceptual checkup) - (a) Normal endometrium and (b) Abnormal endometrium.

The patient with normal endometrium again was divided on the basis of seminal plasma quality (reactive oxygen status estimation), oocyte quality (from spindle view appearance in meiosis) and embryo quality.

After embryo transfer serial hormonal studies (mainly β -HCG) was done on 'O' day, 7th day and on 14th day. On and from 6th week, CRL was measured by perabdominal USG.

The scans in the present study was obtained by real-time ultrasonography by using 3.5 MHz transabdominal transducer through a full urinary bladder. Ultrasound was used to measure foetal CRL before 14 weeks (between 59 and 83 days after conception) by the sonographer using electronic calipers on a frozen image on a monitor. The CRL was then to be converted to the equivalent number of days of gestational age on the basis of the formula currently recommended by the British Medical Ultrasound Society for first-trimester estimation of gestational age.

The results of all ultrasound scans obtained were to be entered into a computer database along with details of the women's medical, gynaecologic and obstetrical history, antenatal complications and pregnancy outcome. The difference between the actual and predicted CRL will be expressed as the difference in days of gestation (Δ GA) - that is the estimated post-conception age according to CRL minus the actual number of days post-conception based on the day of embryo transfer. A negative value indicates a smaller than expected foetus.

Estimated foetal weight (Ultrasonographically) and relevant investigations were done every month.

1120 patients were selected from Institute of Reproductive Medicine, Salt Lake, Kolkata taking prior consent in a prescribed form who came with a complaint of pregnancy loss or infertility (primary/secondary).

Maternal characteristics to be studied were maternal age, height and weight in the first trimester; body mass index; number of previous terms and preterm deliveries, miscarriages and abortions. Complications of pregnancy excluded are preterm delivery, pre-eclampsia, preterm premature rupture of the foetal membranes, preterm labour, placental abruption and placenta previa.

After delivery, Ballard Scoring (birth weight, newborn length, head circumference, abdominal circumference, etc.) were measured to detect whether it is IUGR for the gestational age, which also show negative CRL in early trimester.

Delivery of a small for gestational age infant was defined as birth weight below the 10th percentile for gestational age.

Statistical Analysis

Statistical Analysis was performed with Statistical Package for the Social Sciences (SPSS Software).

A linear correlation with Pearson 'r' coefficient has been utilised in a statistical method to calculate the correlation between LBW at delivery with CRL at 9 weeks-

- A. The Odd Ratio between CRL (Positive or Negative), BW at 35 weeks (Normal or low) is 0.00625. We can calculate 'p' value from Odd ratio, which is 0.00621.
- B. Rate Ratio= Incidence in LBW with (-) CRL against incidence in LBW with (+) CRL= 0.1818.
- C. Risk Ratio= Mother having negative CRL at 9 weeks against mother having positive CRL at 9 weeks= 0.22 which is < 1.
- D. CRL at 9 weeks True Positive (TP)= 275, False Positive (FP)= 45, True Negative (TN)= 10, so the
- E. Specificity= 0.01819
- F. Positive predictive value of USG to detect normal birth weight is 0.859

RESULTS

1120 patients are taken from an Institute of Infertility Clinic situated at Salt Lake Kolkata, West Bengal who are free of any medical or surgical problems and conceived by In-Vitro Fertilisation (IVF) due to unexplained infertility having singleton pregnancy. Patient was chosen from an IVF, so that exact date of conception can be found to rule out the fallacy of calculating the period of gestation on the basis of menstrual history of patient, which was sometimes approximated. Out of 1120 patients 725 has no clinical pregnancies or pregnancy related complications, rest had undergone ultrasonography.

Out of 395 patients, 65 had midterm pregnancy loss. Two patients delivered IUGR babies, one having history of Oligohydramnios with Oesophageal Atresia and another having Antepartum Haemorrhage with Low-Lying Placenta with Anaemia. Four patients were in accordance with normal variant in early trimester become IUGR due to Gestational Diabetes Mellitus (Controlled) and Chronic Hypertension. Four patients delivered mild IUGR baby suffering from Nutritional Deficiency because of Morning Sickness (Pyridoxine given) and Hyperprolactinaemia (Bromocriptine given along with amino acid supplement), and 275 patients have positive correlation among CRL and birth weight. Rest 45 mothers had negative correlation having normal CRL, but low birth weight.

The outcome of the study has been represented in tabulated form below:

Result	Birth Weight
Normal	275
IUGR	55

Table 1. Final Result of 330 Study Group

Result shows normal birth weight, approximately 91.62%, which is acceptable. It shows IUGR approx. 1.52%, less than normal suggesting better option of combating IUGR!

CRL at 9 Weeks	Low Birth Weight
Normal value	45
Negative value	10

Table 2. Relation of Crown Rump Length with Low Birth Weight

Out of 55 deliveries having Low Birth Weight, 10 cases shows negative CRL which is 18.19%.

In contrary, 45 cases showed positive CRL which is 81.12% which is acceptable hardly.

CRL at 9 Weeks	LBW	In %	Conclusion
Normal value	45	13.64	Not acceptable, contradictory to general observation may be due to the effect of IVF
Negative value	10	3.03	Acceptable

Table 3. Correlation of Crown Rump Length with Low Birth Weight among 330 Samples

Out of 55 LBW deliveries, author found negative CRL in 10; most of the cases has got positive CRL making the study inconclusive with the hope of scope for further study on adverse effect of procedure of assisted reproductive technique. So out of 330 patients, 45 although having normal CRL had Low Birth Weight which was about 13.64% which was significant.

In 10 patients out of 330 had negative CRL having Low Birth Weight, which is about 3.03% is also significant.

In the Correlation of Negative CRL with LBW

Pearson 'r' Coefficient is 0.7457; 95% confidence interval is 0.2186 to 0.9359; P value (two tailed) is 0.0133; which shows the correlation is significant (alpha=0.05); R square is 0.5561.

In the Correlation of Positive CRL with LBW

Pearson 'r' coefficient is -0.08666; 95% confidence interval is -0.3708 to 0.2123; P value (two-tailed) is 0.5714 which shows correlation is not significant; R square is 0.007510.

Statistical Analysis was performed with Statistical Package for the Social Sciences (SPSS Software)

DISCUSSION

LBW (less than 2500 g) and birth weight that is low for gestational age are associated with increased perinatal morbidity and mortality,¹⁶ short- and long-term childhood morbidity and mortality¹⁷⁻¹⁸ and a range of cardiovascular and metabolic disease in later life.¹⁹ Consequently, the factors determining birth weight (other than gestational age) are clearly clinically and biologically important. IUGR is aetiologically associated with various maternal, foetal and placental factors, although such an association may not be present in many cases. Maternal factors include hypertensive disease, autoimmune disorders, certain medications, severe malnutrition and maternal lifestyle including smoking, alcohol and cocaine abuse. Foetal aetiologies include aneuploidy, malformation syndrome related to abnormal genomic imprinting, perinatal viral or protozoan infections, preterm birth and multiple gestations. Placental factors may involve many conditions including anatomical, vascular, chromosomal and morphological abnormalities. Also some uterine malformations have been linked to impaired foetal growth.

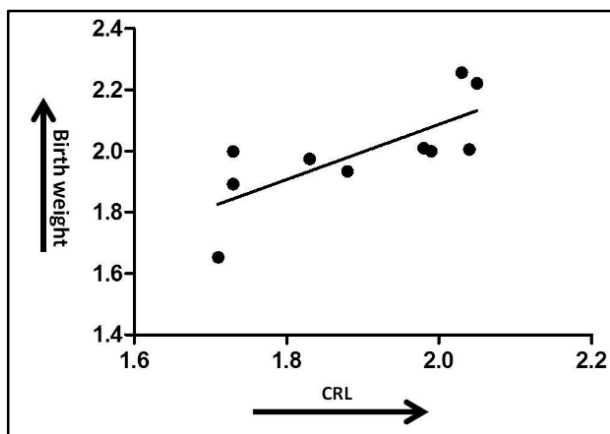
However, considering a higher incidence of unexplained IUGR at term in singleton babies conceived by assisted reproduction, it remains unclear whether the risk of LBW among this infant is a direct effect of the procedure involving such technology^{20,21} or reflects some other factors related to the underlying infertility of the couples who conceive using these procedures.²²⁻²⁴

It has previously been suggested that variations in foetal size are largely determined in the second half of pregnancy.²⁵ However, a single study has shown that foetuses that were smaller than expected in the first trimester (on the basis of menstrual history) were at increased risk of being LBW.²⁶ This has been interpreted as indicating that impairment of foetal growth begins in the first trimester.

A 1993 study demonstrated a correlation between first-trimester crown-rump length and birth weight.²⁷ Measurement with ultrasound is recognised to be a more accurate method of estimating gestational age in the first trimester of pregnancy than menstrual dating, owing to errors in the assumed date of conception based on the last menstrual period. With very rapid growth of the foetus during the first trimester- 1 mm per day at 7 weeks and up to 2 mm per day by 14 weeks, foetal measurement at this time when correlated with a correctly known gestational age should provide an accurate assessment of foetal growth and any restriction thereof. In women with a certain date of last menstrual period and a regular cycle and in women who conceive through assisted reproductive technology, pregnancies where the Crown-Rump Length (CRL) is smaller than expected may thus be benefited from closer monitoring, especially for abnormalities of foetal growth.

Graph 1 for Correlation of Negative CRL with LBW

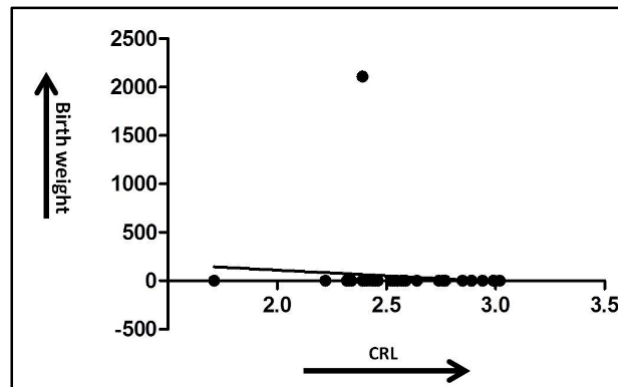
Number of XY pairs is 10; Pearson 'r' coefficient is 0.7457; 95% confidence interval is 0.2186 to 0.9359; P value (two-tailed) is 0.0133 which shows the correlation is significant (alpha= 0.05); R square is 0.5561.



Graph 1. X-Axis: CRL (cm), Y-Axis: BW (kg)

Graph 2 for Correlation of Positive CRL with LBW

Number of XY pairs is 45, Pearson 'r' coefficient is -0.08666; 95% confidence interval is -0.3708 to 0.2123; P value (two-tailed) is 0.5714 which shows correlation is not significant; R square is 0.007510.



Graph 2. X-Axis: CRL (cm), Y-Axis: BW (kg)

So, Inferences from this Observational Study are-

1. Odd ratio is 0.00625, which is < 1 indicating value of CRL has got limited predictive value to ascertain LBW at 35 weeks.
2. The P value, probability of occurrence of positive CRL with the normal BW is 0.00621 which is significant.
3. Rate ratio is < 1 indicating negative CRL at 9 weeks has got little predictive value for LBW at 35 weeks.
4. Risk ratio is < 1 indicating negative CRL, not correlating with LBW at 35 weeks.
5. Specificity is 0.01819, so USG is not a specific diagnostic tool to predict IUGR in early trimester by measuring CRL at least in this study!!
6. Positive predictive value of USG to detect normal birth weight is 0.859, which is acceptable.

Fallacies of this Study

1. Although, bias of counting period of Gestation on the basis of IVF can be done easily, but the drawbacks of using chemicals of Artificial Reproductive Techniques cannot be ruled out to project this data in normal population who conceived naturally.
2. Termination of pregnancy by 35 weeks (as the normal procedure of the concerned Institute) by Caesarean Section, author has to restrict herself for estimated foetal weight at 35 weeks and not the actual birth weight at 40 weeks.

ACKNOWLEDGEMENT

I express my gratitude to Dr. (Prof.) BN Chakraborty, I.R.M Salt Lake, Kolkata for giving scope for this study, constant encouragement and valuable guidance; and thanks to Dr. Arnab Bhattacharya, Assistant Prof., Anatomy, IPGME and R, Kolkata; and Mr. Jaidip Dutta B.C.E for statistical analysis.

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