In this way it is possible to draw up a table showing how many of the original 100 women will have one, two or three or more abortion in succession. Making this assumption, the chances of second pregnancy continuing one abortion is 78% after 2 abortion 62% and after 3 abortion 27% and after 4 abortion 6%. This progressive fall in the spontaneous abortion cure rate means that after three successive abortions there is an overwhelming likelihood that a truly recurrent cause is present (Malpas).

Later on Macgregor and Stewart (1939) have modified some details of this theory\(^{36}\). They sum up their examination of the problem with the statement that in a series of cases with at least two successive abortions, but including a number with three, the expectation of the abortion in next pregnancy is 65%. The view of Malpas, MacGregor and Stewart have been widely accepted for many years and as a result an unduly gloomy prognosis has often been given. It is now an established fact that the abortion incidence predicted by this way does not confirm to what occur in practice.

Goldzieher and Benigno (1958)\(^{37}\) in a critical review of the subject attached the Malpas formula and claimed that it was only after four consecutive abortions that any appreciable alteration in the abortion rates was observed.
Mann (1959) also criticized the inaccuracy of mathematical prediction of abortion sequence. He commented on the fact that results varying from good to excellent had been achieved by many different therapies. Similar views were expressed by Stallworthy (1959)\textsuperscript{38}.

The implantation of the conceptus, the support of embryonic development and the continuation of pregnancy depends on a complex interaction of hormonal effect on the ovary and the uterus. When a woman presents with two or more first trimester spontaneous abortion, a persistent or recurrent endocrine defect must be ruled out.

Among the hormonal causes hypothyroidism has been reported to cause both infertility and increased rate of fetal loss. In 1951 Jones and Delfs reported 63.5\% prevalence of hypothyroidism in habitual abortus based on the measurements of basal metabolic rate (BMR) and blood cholesterol levels\textsuperscript{39}. In 1962 Greenman and co-workers uncovered a history of spontaneous abortion or stillbirth in six of seven women with a low serum butanol extractable iodine.

Using current radio-immunoassay techniques to measure thyroid functions. Tho and colleagues in 1979\textsuperscript{40} and Harger and associates in 1983\textsuperscript{41} failed to demonstrate conclusive evidence of thyroid disease in any of the 219 women they evaluated.
Although thyroid function assessments are simple and relatively inexpensive, their utility in diagnosing recurrent abortion is so small that justification in asymptomatic women is difficult. However, the prevalence of thyroid antibodies among women having two or more consecutive spontaneous abortion justifies measurement to help to diagnose autoimmune cause of recurrent abortion.

Evidence for carbohydrate intolerance leading to recurrent miscarriages also is poorly substantiated. In fact, there is no data that support a role for subclinical or adequately controlled diabetes mellitus in cases of pregnancy wastage.

Crane and Wahl studied the overall incidence of spontaneous abortion among 154 diabetic pregnant mothers from 1977 to 1980 and compared them with a matched control group, and there was no increase incidence of recurrent abortion in diabetic patients.

For most women with recurrent first trimester spontaneous abortions the routine performance of a glucose tolerance test is therefore not indicated. For a patient with an unexplained second trimester or third trimester pregnancy loss or with clinical signs of diabetes mellitus, an investigation of carbohydrate intolerance is warranted.

So among the endocrine defects inadequate luteal phase remains the important cause for recurrent abortions.
Luteal phase defect was defined in 1949 by Jones in patients with reproductive failure

Jones and Delfs in 1951 reported a 35% incidence of luteal phase deficiency in patients with recurrent abortions.

Botella Llusia (1962) found that 38% of women with three or more consecutive abortions had a poorly developed secretory endometrium, compared with a 6% incidence in infertile women.

In a series heavily weighted towards genetic abnormalities, Tho et al (1979) reported that 23% of women with two or more histologically documented abortions or one or more abortions with a phenotypically abnormal child had dys-synchronous endometrial development on biopsy study.

The corpus luteum is an unusual endocrine gland, diverse in function and important for successful reproduction in all mammalian species. Lutectomy before 7 weeks of gestation causes abortion in most women (Csapo A.I., 1972). The substance secreted by the corpus luteum responsible for successful pregnancy was shown as early as 1929 by Allen and Corner to be progesteron. Further evidence that corpus luteum function necessary for implantation and early embryo growth can be replaced by hormones alone, comes from
studies of women receiving donor oozytes\textsuperscript{47,48} (Sauer, M.U., 1992; Meldrum, 1993).

In 1991 Asrinbekova, Karpova & Mylashko studied the state of sex hormone reception in the endometrium of women with late habitual abortion and found that the oestrogen receptor/progesteron receptor ratio in the cytosol in the endometrium at secretory phase of menstrual cycle was higher in cases of patients with habitual abortion than in normal non-pregnant females.

In 1993 Bopp & Shooue\textsuperscript{49} diagnosed luteal phase defect when mid luteal serum progesteron level $\leq$ 10 ng/ml and advised endometrial biopsy when progesteron levels are $\geq$ 10 ng/ml in patients with habitual abortion & unexplained fertility.

In 1994 Jordan Craig, O., Cliflor O.K. studied luteal phase defect and concluded that luteal phase defect is relatively uncommon but important cause of infertility and habitual abortion\textsuperscript{50}. They recommended tests for determination of LPD is a mid-luteal phase though serum progesterone level $\leq$ 10 ng/ml or sum of three progesterone levels that is $\leq$ 30 ng/ml. The endometrial biopsy is a second time test that is only recommended when LPD needs to be evaluated in a treated cycle (ovulation induction or supplemental progesterone).
Intra-uterine Growth Retardation:

It was not until about 30 years ago that physicians first recognized that runting or fetal growth retardation was a human as well as animal phenomenon. In 1961 Warkany\textsuperscript{51} and co-workers reported normal values for infant weights, lengths and head circumferences and defined fetal growth retardation.

In 1962, WHO introduced the term low birth weight for all babies weighing less than 2500 gm as a single category.

Gruenwald (1963) reported that approximately one third of low birth weight infants were mature and their small size could be explained by chronic fetal distress probably due to placental insufficiency\textsuperscript{52}.

In 1963 Lubchenco and co-workers\textsuperscript{53} from Denner published detailed comparisons of gestational age to birth weights is an effort to derive norms for expected fetal size and therefore, growth at a given gestational week.

Battaglia and Lubchenco (1967) then classified small for gestational age (SGA) infants as those whose weights were below the 10th percentile for their gestational age.
Large for gestational age infants had weight above the 90th percentile for their gestational age. These defined as small for gestational age were shown to be at increased with for early neonatal death (Koops and associates, 1982)\textsuperscript{54}.

The impact of population differences on fetal growth standards cannot be over emphasized. Golderberg and associates (1989 b) reviewed studies on fetal growth published in the English literature since 1963 and in part due to population differences concluded that there is currently no single national standard for fetal growth retardation.

Kramer (1987)\textsuperscript{55} reviewed 895 studies on fetal growth in English and French languages published between 1970 and 1984 and concluded that there was great confusion and controversy despite the profuse number of studies.

Problems with growth retarded fetuses - Wennergren and co-workers (1988) analysed the neonatal performance of 160 infants defined to be growth retarded because of their birth weight was at or two standard deviation from the mean. In most cases (83%) growth retardation had been suspected antenatally by birth weight less than 2 standard deviation of the mean for that period of gestation. Hypoglycemia and hypothermia occurred
frequently. The major hazard of growth retardation were stillbirth and fetal distress. Similar observations have been made by Villar and colleagues (1990)\textsuperscript{56} for growth retardation at term and by Vesser and associates (1986) between 25 and 34 weeks.

Autopsy findings in small for gestational age infants have revealed two basic pattern of impaired fetal growth (Gruenwald, 1963; Naye and Kelly, 1966). One of these is designated as symmetrical growth retardation because all body organs tends to be proportionately reduced in size and asymmetrical when some body organs are more affected and then others.

Factors regulating fetal growth are mainly genetic and racial. The neonates of the Indian and Chinese weigh less than those of Europeans or the Africans (Ashcroft and Desai, 1976)\textsuperscript{57}. The fetus growth is also influenced by the maternal weight, height, age, parity and duration of gestation. Social deprivation influences height and shorter women are not optimal reproductor as far as support of fetal growth is concerned (Gruenwald, 1968).

Apart from fetal cause of intra-uterine growth retardation maternal and placental causes are important. Hypertension during pregnancy causes intra-uterine growth retardation. It varies with mean arterial pressure at
4-6 months - higher it is, lower the birth weight (Page and Christiansson, 1976).

Boyd & Scott (1985) showed that compared to normal, the placentae in pre-eclampsia and intra-uterine growth retardation were of a lower volume of parenchyma and villous surface with increased areas of infarction.

Poor maternal nutritional status also affects fetal growth. Pregnancy weight of 40 kg or below, poor weight gain in pregnancy (less than six kg). Anaemia (Hb. less than 8 gm/dl) in pregnancy and mid-arm circumference (less than 20 cm.) were associated with low birth weight babies (Jayam et al, 1984). Acute starvation restricts fetal growth with birth weight of 300-400 gm. due to loss of body fat (Hytten, 1979) with nutritional supplements (Calories protein, iron and folic acid) in the 2nd half of pregnancy, there is fetal oocyst gain of over 200 gm. compared with controls (Venkatachalam, 1962; Iyengar & Rajalakshmi, 1974; Lachting et al, 1975).

Biale (1983) studied lipolytic activity in the placenta of chronically deprived fetuses, concluded that lipoprotein lipase activity was significantly greater in placentas of pre-eclamptic women and in placenta of intrauterine growth retarded fetuses.
Iwaszkiewicz, Pawlowska (1986)\textsuperscript{62} found that pregnancy complicated by intra uterine growth retardation, the free fatty acids concentration in amniotic fluid was almost three times higher than in normal pregnancy.

In 1980 Economide & Crook\textsuperscript{63} showed that small for gestational age fetuses had hyper-triglyceridemia and hypoglycaemia and hypoinsulinemia.

Recently Berg, Ronald, Sande (1994)\textsuperscript{64} found that high lipoprotein(a) | Lp(a) | level in maternal serum can interfere with placental circulation and causes fetal growth retardation.
MATERIAL AND METHODS
MATERIAL AND METHODS

Present study was carried out in the Department of Obstetrics & Gynaecology and Department of Medicine, M.L.B. Medical College, Jhansi, during the period of 1994-1995.

Selection of cases -

Females of reproductive age group attending O.P.D., antenatal clinics, admitted in antenatal wards or labour room directly formed the main groups for the study. Patients were clinically examined and investigated and were divided into two main groups A and B.

Group A was further divided into two sub-groups:

Group A₁ : Patients with normal uncomplicated pregnancy during 1st or early IIInd trimester.

Group A₂ : Patients with history of habitual abortion.

Group B was also further divided into three sub-groups:

Group B₁ : Healthy normal pregnant females during IIIrd trimester.

Group B₂ : Patients with intra-uterine growth retardation (IUGR) who had normal vaginal delivery.

Group B₃ : Patients with intra-uterine growth retardation (IUGR) who had caesarean section.
Group A:

Group A₁: Comprised of 7 healthy females of reproductive age with normal pregnancy i.e. without any complication either obstetrical or medical.

Group A₂: Comprised of 25 pregnant females of reproductive age with history of three or more consecutive spontaneous abortions.

Group B:

Group B₁: Comprised of 7 healthy females of reproductive age with normal pregnancy i.e. without any complication either obstetrical or medical.

Group B₂: Comprised of 8 pregnant females with IUGR, who had normal vaginal delivery.

Group B₃: Comprised of 17 pregnant females with IUGR, who had caesarean section.

Intra Uterine Growth Retardation (IUGR):

This was defined on the basis of birth weight falling below 10th percentile or below 2 standard deviation of the mean for that period of gestational age. This group included pregnant women who had on clinical evaluation the fundal height of uterus did not correspond to the expected period of gestation (on the basis of LMP) being less by atleast four weeks, and later confirmed by ultrasonography.
Clinical Examination:

A complete clinical history of the above cases regarding age, parity, socio-economic status, literacy level, history of present illness, past history, obstetrical history, family history and dietary history were taken.

It was ensured that the patient did not suffer from any other diseases which caused increased cholesterol level such as coronary heart disease, kidney disease, liver disease or diabetes mellitus.

Complete general and systemic examination was done with special emphasis on general built of the patient, pallor, blood pressure, height and weight in kilograms.

The fundal height was assessed and the period of gestation was determined and it was ascertained if this corresponded to period of amenorrhoea as told by the patient.

Investigations:

Following investigations were performed.

Routine - Haemoglobin, TLC, DLC, ESR
- Blood group
- Blood sugar
- Blood urea
. Urine: Albumin,
    Sugar,
    Microscopic.

. Specific - VDRL
    - For TORCH infection
    - Ultrasonography.

Lipoprotein profile:
    - Serum total cholesterol,
    - Low density lipoprotein,
    - Very low density lipoprotein,
    - High density lipoprotein,
    - Serum triglyceride.

Period of collection of blood:

1. In normal uncomplicated pregnancy in 1st trimester cases, a fasting (12-24 hours) sample.

2. In normal uncomplicated pregnancy in IIIrd trimester cases at the time of admission and one week after delivery.

3. In cases of habitual abortions, a fasting sample.

4. In intra-uterine growth retarded cases, at the time of admission, and one week after delivery.
Method of collection of blood sample:

5 ml of blood was withdrawn from antecubital vein of the patient subjected to following conditions:

1. She has fasted for 12-14 hours before such sample was taken.

2. The blood was withdrawn without a minimal venous stasis in recumbent posture with all aseptic precaution.

3. After withdrawing the sample, it was allowed to settle for 1/2 an hour facilitating the serum to separate, then centrifuged and serum was preserved with standard precautions.

Estimation of lipid factors:

Various lipid factors - serum total cholesterol, (STC) serum triglyceride (STG), high density lipoprotein (HDL) were estimated with standard diagnostic kits while low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were derived from values of above mentioned lipids by formulae.

1. Serum Total Cholesterol - STC was estimated by commercial kits supplied by Ethnor. The basic principle is that cholesterol reacts with test solution of ferric perchlorate, ethyl acetate and sulphuric acid and gives a lavender coloured complex which is measured colorimetrically.
2. Serum Triglyceride (STG) - Serum triglyceride was estimated by acetyl acetone method. Principle behind is that triglycerides are determined by measuring glycerol after its liberation from fatty acid by saponification. Glycerol is oxidised or by sodium metaperiodate to formaldehyde which is directly proportional to the amount of triglycerides.

3. High density lipoprotein - HDL was estimated by utilizing commercial kits supplied by Ethnor. Basic principle is that the HDL cholesterol fraction is separated by using a precipitating reagent. The precipitate contains chylomicrons, VLDL, LDL which are removed by centrifugation. The supernatant contains HDL cholesterol which is estimated by HDL-C colour reagent which gives purple coloured complex which is measured colorimetrically at 560 nm. The intensity of colour developed is proportional to the concentration of HDL-C in the specimen under test.

4. Estimation of very low density lipoprotein - VLDL was estimated by formula given by Friedwald et al (1972) This formula is valid upto STG values to less than 400 mg/dl.

\[
\text{VLDL (mg/dl)} = \frac{\text{STG}}{5}
\]
5. Estimation of low density lipoprotein – LDL was calculated by the following formula given by Fredrickson D.A. (1972).

\[
\text{LDL (mg/dl)} = \text{STC} - \left( \frac{\text{STG}}{5} + \text{HDL} \right) \quad \text{or}
\]

\[
\text{LDL (mg/dl)} = \text{STC} - (\text{VLDL} + \text{HDL}).
\]