REVIEW
OF
LITERATURE
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The study of place of magnesium in medicine is complicated by the fact that its requirement in the body is influenced by a number of factors. During periods of rapid formation of tissues the magnesium requirement goes up as in the pregnant state. Conditions that interfere with magnesium absorption and enhance its urinary excretion increases magnesium requirement. Pregnancy is an altered physiological state with increased metabolic rate. Simultaneously high intake of calcium, phosphates, proteins and vitamin D increases the magnesium requirement. With so many factors influencing the absorption and excretion of this element and also the amount needed for metabolic processes it remains a controversial question as to what the normal requirement is? To determine the magnesium status it is necessary to establish the normal value.

Magnesium is a light white metal of atomic number 12 and atomic weight 24. It is extremely reactive and invariably present in all living cells. The adult human being has whole body content of 25 gms of magnesium (Wacher and Valluze 1958). Half of total magnesium is in the skeleton, rest of it is intracellular. However the total magnesium in extracellular fluids represents only 1% of magnesium in the body.
Magnesium contributes for stabilization of highly ordered organization of macromolecule of DNA, RNA and ribosomes. Genetic information stored in DNA is transcribed into messenger RNA which in turn translates that information into amino acid sequences in the newly synthesized proteins.

The physical integrity of DNA helical appears to depend upon magnesium. The physical size of RNA aggregates is controlled by the concentration of magnesium and polypeptide formation cannot proceed unless magnesium concentration is optimal. All these functions depend upon the ability of magnesium ions to form chelates. The magnesium competes with calcium within cell for calmodulin activation. During contraction calcium binds to calmodulin and resulting complexes activates myosin light kinase.

This is primarily due to influx of calcium from extracellular fluid via voltage gated channels, for magnesium acts at this site. The fundamental role of magnesium in all biological processes therefore seems to be that of chelating agent.

Magnesium has important effect on central nervous system and neuromuscular transmission. It is a depressant of central nervous system and low magnesium level may evoke increased irritability, confusion and convulsions. The central nervous system and the myoneural depression
produced by magnesium can be antagonised by calcium activation which bring about uterine contractions.

Magnesium also possess local anesthetic activity and depresses myoneural transmission by reducing the quantal release of acetylcholine and by antagonizing its depolarizing effect at the motor end plate and by reducing the excitability of the muscle cell membrane. Magnesium is also important for stabilization of lysosomal membranes. Magnesium has been associated with neuromuscular conduction in heart and muscles (O’Walaas 1950) and thromboembolic phenomenon due to oral contraceptives (Dale and Simpson 1972).

Magnesium acts by having common transport system with calcium at membrane receptor sites modifying Sodium Potassium ATPase channels.

Plasma concentration of magnesium is normally maintained within very narrow limits it being predominantly an intracellular ion. The laboratory detection of clinical magnesium deficiency is very difficult because the magnesium levels often differ slightly from normal even in presence of clinically demonstrable deficiency.

Since there are multiple factors that influence the absorption and excretion of magnesium as well as the amount needed for metabolic processes, it is not surprising that there is disparity as to what is the exact
magnesium requirement during pregnancy. Increased intake and metabolism of calcium, phosphates, vit D and protein each increases the magnesium requirement.

There is so great a variation in the normal values of serum magnesium cited by different authors that it is difficult to cite exactly what is normal. The main point for the controversy is that different authors have used different methods of determining the serum magnesium in normal subjects & several conditions are associated with altered magnesium levels. There is evidence that the physicochemical state of the magnesium in the serum may deviate from normal in several condition associated with magnesium deficit (Bajpai et al 1967 G I Telman et al 1969, Silverman et al 1954.)

**SERUM MAGNESIUM LEVELS IN NORMAL NONPREGNANT SUBJECTS**

Plass & Borget (1923) were amongst the earliest workers to report on the magnesium content of blood in the human beings. In this series of healthy woman the average value of serum magnesium was found to be 2.3 mg%.
Becher & Bomskov (1932) found the range of serum magnesium in normal healthy individuals as 1.8 – 2.3 mg% and 1.7 – 2.6 mg% respectively.

Wacker and Fohrig (1932) reported this value to be 2.4 mg%. A little higher values for serum magnesium were reported by Greenburg et al (1933) who found these values to be from 2.0 – 3.6mg% the mean value being 2.74mg%.

Sohi(1933) set the limits from 1.0 – 3.0 mg% in approximation which were more in accordance to those of Becher and Bomskov. Walker and Walker (1936) reported values ranging from 1.6 – 3.0 mg% the mean value being 2.2mg%.

Velluz and Velluz (1934) Cope (1936) and Brookfield (1937) reported the same. Their mean value was 2.00, 2.06 and 2.04 mg%. respectively. Bernstein and Simkins (1940) recorded 2.13 mg% as the mean value of serum magnesium in their normal female individuals.

Haury (1942) observed that the normal range of serum magnesium in his series was between 1.7 and 3.0mg%. He also analysed and compared the mean serum magnesium values of various authors and commented that those values stood in the vicinity of 2.4 mg%.
Simons et al (1947) Orange and Rhein (1951) and Polonowski (1953) reported comparable readings about the serum value of magnesium. Their findings were 1.9 to 2.4 mg%, 1.8 to 2.2 mg% and 1.87 mg% respectively.

Andreason (1957) observed the range of serum magnesium in normal non pregnant women to vary from 1.53 to 2.21 mEq/l with a mean value of 1.87 ± 0.17 mEq/l.

Hall et al (1957) estimated serum magnesium level in 30 non pregnant women of child bearing age and free from cardiovascular and renal disorders. This mean value was reported to be 1.87 ± 0.20 mEq/l. Haunter found serum magnesium mean values to be 1.90 mg% in normal female cases.

Achari et al (1961) estimated serum magnesium levels in 100 normal subjects and reported that the normal serum magnesium in their cases was ranging between 1.80 to 3.20 mg% with mean of 2.38 ± 0.35 mg%. The value closely approximated that found by Haury (1940).

A series of 52 samples of blood from normal healthy individuals were studied by Roychoudhary, Khan, Bose & Habibe (1962) for the estimation of serum magnesium. These worker reported mean value of 2.32 ± 0.108 mEq/l. This value was higher than those reported by Hall & Haunter.
Laha et al (1963) determined magnesium levels in 100 normal adults and reported that normal serum magnesium in their cases ranged from 1.73 to 3.00 mg% with a mean of 2.41 ±0.34 mg%. They employed chemical methods for magnesium estimation.

Goldsmith and Goldsmith (1966) in a series of 77 normal women found serum magnesium fluorometrically to be 1.73 ± 0.15 mEq/l. In a series of 62 normal subjects analysed by atomic absorption by Lida, Fawa and Wacher (1967) gave an average value for serum magnesium of 1.81 ± 0.18 mEq/l.

Jain et al (1969) studied serum magnesium level by chemical methods in renal disease. Their study included 59 cases of various types of renal diseases and results were compared with magnesium level in serum in 20 normal persons. Their normal values of serum magnesium ranged from 1.54 to 2.80 mg% with a mean of 1.94 mg%.

Bajpai et al (1970) using Titan yellow method estimated serum magnesium in their control cases. There value ranged from 1.63 to 2.25 mEq/l, the mean value being 1.69 ± 0.16 mEq/l.

Singh et al (1979) used Titan yellow in 75 non pregnant cases, and a mean value of 2.097 ± 0.056 mg% was reported.
Summary of serum magnesium reported by some recent authors and the method of estimation employed in normal subjects.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of Workers</th>
<th>Magnesium concentration in serum</th>
<th>Method Employed for estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pile et al (1952)</td>
<td>1.65mEq/l</td>
<td>Chemical</td>
</tr>
<tr>
<td>2.</td>
<td>Montgomery (1960)</td>
<td>1.71mEq/l</td>
<td>Flame Photometry</td>
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<tr>
<td>3.</td>
<td>Rangam et al (1961)</td>
<td>1.68± 0.27mg%</td>
<td>Chemical</td>
</tr>
<tr>
<td>4.</td>
<td>Kalgi (1962)</td>
<td>Males 2.14mEq/l Females 2.34mEq/l</td>
<td>Chemical</td>
</tr>
<tr>
<td>5.</td>
<td>Roychaudhry (1962)</td>
<td>2.32 ± 0.108 mEq/l</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>6.</td>
<td>Laka et al (1963)</td>
<td>2.41 ±0.34mg%</td>
<td>Chemical</td>
</tr>
<tr>
<td>7.</td>
<td>Linder et al (1963)</td>
<td>1.4 to 2.2 mg%</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>8.</td>
<td>Benarzie et al (1964)</td>
<td>1.68mg%</td>
<td>Chemical</td>
</tr>
<tr>
<td>9.</td>
<td>Pradhan et al (1964)</td>
<td>1.68mg%</td>
<td>Chemical</td>
</tr>
<tr>
<td>10.</td>
<td>Radha Krishnan (1964)</td>
<td>2.17mEq/l</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>11.</td>
<td>Gharparusal et al (1966)</td>
<td>2.01mEq/l</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>12.</td>
<td>Zutshi (1966)</td>
<td>1.87 ± 063mEq/l</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>13.</td>
<td>Khanna et al 9 19660</td>
<td>2.0mEq/l</td>
<td>Titan Yellow</td>
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<tr>
<td>14.</td>
<td>Jain et al (1969)</td>
<td>1.94mg%</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>15.</td>
<td>Bajpai et al (1970)</td>
<td>1.66 ± 0.16 mEq/l</td>
<td>Titan Yellow</td>
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<tr>
<td>16.</td>
<td>Potnis et al (1977)</td>
<td>2.080 ± 0.368mg%</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>17.</td>
<td>Singh et al (1977)</td>
<td>2.097 ± 0.056mg%</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>18.</td>
<td>Rizvi et al (1979)</td>
<td>2.68 ± 0.396 mg%</td>
<td>Titan Yellow</td>
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<td>19.</td>
<td>Khan et al (1987)</td>
<td>2.53 ± 0.30mg%</td>
<td>Titan Yellow</td>
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<tr>
<td>20.</td>
<td>Sarin et al 91987</td>
<td>2.25 ± 0.12mg%</td>
<td>Titan Yellow</td>
</tr>
<tr>
<td>21.</td>
<td>Verma et al (1989)</td>
<td>2.52 ±0.28mg%</td>
<td>KlettSummers photoelectric colorimetric</td>
</tr>
</tbody>
</table>
Rizvi et al (1979), Sarin et al reported serum magnesium level in their non pregnant case. Their value was $2.68 \pm 0.39$ mg% and $2.25 \pm 0.12$ mg% respectively.

Khan et al (1987) used titan Yellow method and reported a value of $2.53 \pm 0.30$ mg% Manju Verma et al (1989) used Klett submersion photoelectric colorimetric method in 25 non pregnant women a mean value of $2.52 \pm 0.28$ in preovulatory phase and $2.41 \pm 0.27$ mg in ovulatory phase was reported by them.

**SERUM MAGNESIUM LEVEL IN NORMAL PREGNANT WOMEN:**

The earliest available data on the serum magnesium content of animal or human tissue during pregnancy came from the work of “Sichal” who in 1899 published data concerning the chemical composition of human embryo and fetus at various stages of pregnancy.

Krebs and Briggs (1923) reported on blood magnesium level in pregnant women from 8-40 weeks of gestation. The magnesium concentration in their value varied between 2.1 to 2.7mg%.

In another study published in the same year Lass & Boeg et al (1923) measured serum magnesium in 40 pregnant women at various stages of pregnancy and compared their values with those of normal non pregnant women. Although the serum magnesium level of non pregnant women
appeared to be quite constant, with an average value of 2.35 mg%, that of pregnant women fell to an average of 2.1 mg% by the end of pregnancy.

Wolf et al (1937) measured serum magnesium in pregnant women between 2nd and 9th months of pregnancy and found a decrease in the concentration of the ion at the end of pregnancy. The value being between 1.5 to 1.7 mg%.

In a more extensive study Hall (1952) determined serum magnesium in 294 pregnant women from 11 weeks of gestation upto term and in 30 cases at 6 weeks postpartum. As compared with the mean value of normal non-pregnant women (1.87 ± 0.29 mEq/l) serum magnesium was depressed during pregnancy, falling as low as 1.6 mEq/l.

Achari et al (1961) measured serum magnesium levels in normal pregnant women. The level lies between 1.70 to 3.20 mg% with a mean value of 2.41 ± 0.36 mg%. The serum magnesium level approximated the value of normal subjects. They obtained a value of p<0.08 which indicates that the value of serum magnesium of normal subject does not significantly differ from those of pregnant women.

De-Jorge and his collaborators (1965) found that serum magnesium levels in 99 pregnant women fell continuously from level of about 1.6 mEq/l in the 2nd month to about 1.2 mEq/l in 8th months while the normal non-pregnant value was 2.00 mEq/l.
Celli Arcella (1966) in a study of 159 women also found a marked fall in serum magnesium during pregnancy with the maximum depression during 3rd trimester.

Hurley and Cozen (1976) in studies with pregnant rats made observations similar to those of De Jorge et al (1966) in female rats feature at term, had higher plasma magnesium level than did their mothers (3.16mg% as compared to 2.64mg%).

De Joerge and his collaborators (1965) looked into account the hemodilution of pregnancy in analyzing women. The value of magnesium concentrations averaged to 1.878 mEq/l during the first month of pregnancy and fell progressively to 1.392 mEq/l at term as compared with a normal value of 2.087mEq/l. After correlation for hemodilution however hypomagnesaemia was seen only in first 120 days of gestation and in the last month.

Potnis et al (1927) measured serum magnesium levels in normal pregnant women at various stages of pregnancy. In the first trimester, the value rises slightly to 2.096 ± 0.197mg%. There after continuous fall is observed, the value reaches to 2.025 ± 0.435mg% in second trimester. It continues to fall in third trimester up to a levels of and 1.874 mg% ± 0.30mg%.
Rizvi et al (1979) determined serum magnesium in first trimester, second trimester and third trimester of pregnancy $2.40 \pm 0.21$, $2.26 \pm 0.24$ and $1.86 \pm 0.30$ mg% respectively. There is significant fall in serum magnesium levels in second trimester of pregnancy but a highly significant fall is observed in third trimester of pregnancy.

Singh et al (1979) determined serum magnesium level in 78 normal pregnant women. They found serum magnesium level of $2.06 \pm 0.073$ mg% in first trimester, $1.88 \pm 0.042$ mg%, in second trimester of pregnancy.

Sarin et al (1987) studies found the levels of serum magnesium in normal pregnancy to a value of $2.08 \pm 0.16$ mg%.

**SERUM MAGNESIUM LEVEL IN DIFFERENT TYPE OF ABORTIONS, PRETERM LABOUR & PREGNANCY INDUCED HYPERTENSION:**

There is some evidence that serum magnesium levels may be indicative of pathological states of pregnancy.

Stefaine (1968) found that serum magnesium in women during 9 months of pregnancy was significantly lower than in normal non-pregnant women ($1.93$ as compared to $2.16$ mg%). However in women with threatened abortion it was still lowered to a value of $1.52$ mg%.
In a series of studies Dumont and his collaborators (Dumont 1966-Dumont and Bernard 1966, Dumont et al 1977) serum magnesium level in pathological and hyperexcitable states including threatened abortion, premature labour, pregnancy induced hypertension cases as well as insomnia & anxiety, hypomagnesemia was found in 35 to 17% of such cases.

Ryvkis (1967) studied electrolyte metabolism in women with abortion cases. He found lowered values of serum magnesium with value of 1.7mg% in normal pregnancy. At the same time urinary excretion of magnesium was also decreased.

Rasic et al (1966) found lower values in premature labour cases.

Gunther in 1981 showed that magnesium is an important cofactor of 300 different cellular enzymes and it acts as an activator of myosin ATPase and pregnant contractions.

In animal studies it was seen that increase in calcium and decrease in magnesium results in uterine contraction (Kochman 1921). Oxytocic effect of ergot and histamine was depressed by increase in magnesium ions (Frazer 1939). This results in low fertility, abortions and malformed IUGR babies (Cosla 1950 and Therley 1976).
Newman 1957 observed high concentration of magnesium in cord blood. Rasu et al (1966) had considered serum magnesium level as a parameter of the high risk of pregnancy involving preterm labour.

Singh et al (1979) studied serum magnesium in various types of abortion and found lower level of $1.727 \pm 0.050 \text{mg\%}$. Some decreased level reported by Sarin et al showed hypomagnesemia noted in 31.66 % cases having serum magnesium level below 1.6 mg%.

Huzar in 1981 proved that magnesium acts by competing with calcium for acting on calmodulin and reported serum magnesium level in preterm labour cases. He found lower result of serum magnesium 1.53mg% $\pm 0.58$ in 33 cases. There finding of hypomagnesemia in women with preterm labour are in agreement with the view of Potnis et al (1977) who believe that hypomagnesemia may play an etiological role in onset of preterm labour.

Magnesium probably competes with calcium within the cell which is responsible for bringing about uterine contractions. Potnis et al (1977) have attributed hypomagnesemia in certain pregnant women to a high intake of calcium orally. Since calcium and magnesium show a common transport system with calcium, it may be absorbed at the cost of magnesium and probably acts at the membrane receptor sites (Forman 1981).
The magnesium mediated augmentation of uterine blood flow may contribute towards stabilization of lysosomes, the labalization of which bring about synthesis of prostaglandins which initiate labour contractions.

Sarin et al (1987) studied serum magnesium in different types of abortion in 60 women. 31.66% i.e. 19 women had serum magnesium level below 1.6mg%. Mean serum magnesium level of threatened abortion cases was found to be 1.87 ± 0.13mg%, in inevitable abortion 1.69± 0.19mg%, in habitual abortion cases 2.02 ±0.30mg% and in missed abortion 1.94 ± 0.17mg%. Wynn & Wynn (1988) prepared details of daily intake of magnesium among pregnant women. The observation that the withdrawal of magnesium from the extracellular medium, caused vasconstriction in human umbilical vessels have led to hypothesis that magnesium deficiency during pregnancy may evolve the risk of developing pregnancy induced hypertension through uteroplacental constriction.

**ORAL MAGNESIUM SUPPLEMENTATION:-**

Elliot (1984) and Wilkins and co-worker (1986) demonstrated reasonable efficacies in analyzing role of oral magnesium in high risk pregnancy cases specially preterm labour.

Their study was done with oral magnesium gluconate given 1 gm four times daily and serum magnesium levels being measured initially and again
two weeks later. The data was then analysed with Fishers exact test and analysis of variance worked out. Magnesium is well tolerated with only mild gastrointestinal effects. It is inexpensive and patients were educated about signs & symptoms of contraction with repeated transvaginal sonography to study uterine activity.

A retrospective study by Condrat et al established a decrease of preterm labour from 11% to 4.9 % in women treated with addition of oral magnesium compared to standard tocolytics.

Spotling and Spotling were able to reduce preterm labour from 9% to 4.3% in women treated with magnesium aspartate.

Palla et al described a magnesium load test in which pregnant women were given intravenous magnesium and urinary excretion of this cation was measured. Retention of >20% of intravenous magnesium detected magnesium deficiency and such patients benefit from higher dosage of oral magnesium. Studies illustrate that magnesium may be measured in term of nutrient density. Nutrient density is the nutrient intake of the element in relation to total food calories. Several countries including Demark have implemented recommendation for magnesium supplementation during pregnancy.