Ann. Ist. Super. Sanità, vol. 29, n. 1 (1993), pp. 69-76

Maternal diseases and congenital malformations

Sandro GIARDINA, Angela CONTARINI and Bruno BECCA

Divisione di Ostetricia e Ginecologia, Unità di Fisiopatologia della Riproduzione, Ospedale Civile, Ravenna, Italy

Summary. - During intrauterine life the health conditions of the fetus are closely related to those of the mother. Hence, maternal diseases and especially endocrine-metabolic unbalances may have a negative impact on the fetus. Major maternal pathologies include: diabetes, hyperthyroidism, hypothyroidism, phenylketonuria, lupus erythematosus, epilepsy and antiepileptic drugs.

Key words: congenital malformations, diabetes, thyroid diseases, phenylketonuria, lupus erythematosus, epilepsy.

Riassunto *(Malattie materne e malformazioni congenite).* - Durante la vita intrauterina le condizioni di salute fetale sono strettamente correlate a quelle della madre. Pertanto, le malattie materne e specialmente gli squilibri endrocrino-metabolici possono avere un effetto negativo sul feto. Tra le più importanti patologie materne vi sono: il diabete, l'ipertiroidismo, l'ipotiroidismo, la fenilchetonuria, il lupus eritematoso, l'epilessia e i farmaci antiepilettici.

Parole chiave: malformazioni congenite, diabete, malattie tiroidee, fenilchetonuria, lupus eritematoso, epilessia.

Diabetes

Thanks to the improvement achieved in the treatment of diabetes after the discovery of insulin and the consequent possibility to normalize glycemic homeostasis, there is an increasing number of pregnant women suffering with this disease who are capable of concluding gestation successfully. Hence, there was a drastic reduction in the maternal-fetal risk related to this disease: the perinatal mortality rate dropped from 65% at the beginning of our century to the current 2-4%, while maternal mortality, that accounted for 30%, has become practically non-existent. At present the risk of spontaneous abortion (30% in diabetic pregnant women compared to 15% in the general population) and that of fetal malformations represent the major complications during diabetic pregnancy [1-7]. The incidence of malformations in infants born to mothers with clinical diabetes is significantly higher than the control population (2-3%), ranging from 6 to 9% according to different studies [2, 4, 6, 7], while paternal diabetes does not seem to be decisive when the mother is healthy [2]. An analysis of the incidence of malformations, while considering the duration of maternal diabetes, shows the influence of the seriousness of maternal disease on the frequency of malformations; in particular, a higher risk was noticed in the presence of vascular complications [8]. The etiological role of maternal diabetes in malformation pathology is still being studied. Some authors have considered the assumption that a genetic factor might play a major role in the increased incidence of fetal malformations [6]. The fact that it was not possible to demonstrate a difference in the incidence of malformations among controls and the infants born to diabetic fathers, while on the contrary a wide range of malformations was found in the offspring of mothers that were clearly diabetic, makes the incidence of a genetic component unlikely.

The theory that is currently held is the one considering the alteration of the maternal metabolic environment due to hyperglycemia and/or a higher presence of ketone bodies, as pathogenetic [4].

Studies performed *in vitro* and on mouses and rats, into which diabetes had been experimentally induced, demonstrated that in the presence of hyperglycemia there was a significant increase in malformation pathology that was not affected by the subsequent administration of insulin [9-11]. Similar dose-depending teratogenous effects were found in mouse embryonal cultures in the presence of β-hydroxybutyrate, the most common ketone body [11].

The presence of an excessive number of ketone bodies and/or hyperglycemia seems to interfere with glycolisis and lastly the use of energy for embryonal development.

The most recent findings suggest an assumption that considers an altered balance in the activation of potential regulatory factors (somatomedines) [12].

The clinical confirmation of the metabolic theory is that the presence of a high maternal glycosiled hemoglobin in the first three months is associated with an increased incidence of fetal congenital malformations, while a good glycemic balance in the organogenetic period reduces the number of malformations to levels that can be juxtaposed to those of a physiological pregnancy [13-17].

The spectrum of malformations is wide and heterogeneous, and this points to a totally aspecific teratogenous effect.

It was undoubtedly pointed out that most abnormalities occur between the 4th and 7th week of embryonal development [14].

Notwithstanding the heterogeneity of the malformations observed (Table 1) [7, 14], the caudal regression syndrome shows a relative risk that is markedly higher (about 1%) [18].

It was assumed that the first mistake in development, leading to the caudal regression syndrome, is a defect in the formation of the medioposterior axial mesoderm before the 5th week of embryogenesis [18].

This syndrome is also highly variable: from sirenomelia to imperforate anus; the latter is a less serious expression of this sequence of malformations [18].

Finally, to reduce the risk of malformations, diabetic women must plan their pregnancy in a periconceptional metabolic situation of good glucidic compensation [17, 19, 20].

With regard to the gestational diabetes, this condition does not entail a higher risk of malformations, given that carboidrate metabolism is normal in the early phases of pregnancy [2].

Table 1. - Malformations observed in infants born to mothers with overt diabetes

Caudal regression syndrome
Skeletal muscle apparatus
Lower limb defects
Great vertebrae defects
Genitourinary apparatus
Agenesis/genital hypoplasia
Hydroureteronephrosis
Agenesis/renal hypoplasia
Central nervous system
Spina bifida
Cardiovascular apparatus
Botallo's duct
Sectoatrial defects

Hyperthyroidism

The frequency of hyperthyroidism during pregnancy has been estimated at 0.04%-1.4% [21].

The causes of hyperthyroidism are multiple (Table 2), but in the large majority of cases of pregnant women (95%) it is due to diffuse toxic goiter or Flajani-Basedow-Graves disease, with autoimmune pathogenesis [21, 22]. This pathological condition is caused by the production of thyrostimulating antibodies that recognize TSH receptor as an antigen and, by interacting with it, entail an activation of thyroid follicular cells.

The immune system modifications due to pregnancy explain the frequent improvement of Graves' disease in the second part of pregnancy as well as the equally frequent reacutization during puerperium [23-25].

The diagnosis of hyperthyroidism starting during pregnancy is quite difficult, especially in mild and moderate forms, as the common findings of thyroid hyperfunction are often similar to the hyperdynamic modifications entailed by pregnancy (i.e. increased cardiac output, tachycardia, hyperemesis, pretibial edemas). Moreover, the normal weight loss characterizing hyperthyroidism may be less evident, owing to the weight gain that is typical of pregnancy [26].

Laboratory data shows an increase in T3 and T4 free fractions and a TSH reduction. Serumal measurements of thyrostimulating antibodies might be useful to evaluate the fetal risk of contracting the Graves' disease [21, 26, 27].

Diagnostic studies envisaging the use of I^{131} are contra-indicated in pregnancy, as radioiodine crosses the placenta and is concentrated by the fetal thyroid after the 10th week of development [21].

The main obstetric risk in women suffering from hyperthyroidism is premature labour [22].

On these conditions the use of tocolitic β-antagonist drugs is contraindicated, as said drugs - by further raising the activity of the sympathetic nervous system - may trigger a thyrotoxic crisis or cause fetal death [26].

Table 2. - Main causes of hyperthyroidism in pregnancy

Flajani-Basedow Graves' disease
Acute (subacute) thyroiditis
Hashimoto's thyroiditis
Toxic nodular goiter
Toxic adenoma

Premature infants with thyrotoxicosis may be small according to their gestational age (SGA), but they rarely show a respiratory distress syndrome, because pulmonary maturation is accelerated [28].

In cases of hyperthyroidism, maternal and fetal prognosis essentially depend on the time elapsing from the onset of the disease, the diagnosis and the start of an adequate therapy. Maternal morbidity, that is mainly represented by heart failure, is almost exclusively found in untreated forms [26].

Fetal prognosis can be particularly severe in case of inadequate treatment of the maternal disease, with an increase in perinatal or intrauterine mortality, prematurity, delayed growth, congenital neonatal hyperthyroidism following thyroid antibody stimulation or the accidental use of iodine in the early phases of pregnancy [21, 28].

Medical therapy makes use of thionamides that inhibit the synthesis of thyroid hormons by blocking thyroxin iodination. Given that said drugs block the synthesis but not the release of thyroid hormons, clinical response has a latency (3-6 weeks) depending on the disposal of the thyroid hormons already synthetized and stored in the colloid.

Metimazole and propylthiouracil should be mentioned among these drugs. The latter also blocks T4 conversion into T3, crosses the placental barrier more slowly, but it can cause fetal goiter and hyperthyroidism, though in a limited way [29].

A correlation was reported between intake of methimazole during pregnancy and onset of congenital defects, such as neonatal aplasia cutis [30]. Nevertheless, similar findings were not confirmed for carbimazole that acts *in vivo* by transforming itself into methimazole. Hyperthyroid pregnant women should be treated by constantly controlling serumal levels of thyroid hormons to avoid the risk of a fetal thyroid dysfunction.

Given that the analytical evaluation of the parameters of thyroid functional capacity on maternal serum and amniotic fluid does not provide final conclusions on fetal metabolic conditions, a serial control of fetal well-being using biophysical methods is required.

Ultrasound can prove a possible intrauterine delayed growth, while cardiotocography can point out an abnormally low (hypothyroidism) or high (hyperthyroidism) fetal heart rate.

Finally hyperthyroidism in pregnancy affects two patients: the mother who can be easily examined, evaluated and treated, and the fetus, whose conditions are more difficult to check in an altered intrauterine environment that can jeopardize its vitality, development and quality of postnatal life.

Therapeutical strategy must first of all aim at optimizing the risk benefit ratio for the fetus and the newborn.

The aim of preconceptional advice in women with a positive personal and family medical history for thyroid diseases is that of planning pregnancy after a final treatment of Graves' disease, or anyway, in case of a better thyroid hormonal balance.

Hypothyroidism

Hypothyroidism rarely complicates pregnancy, because the incidence of this pathology increases greatly in perimenopausal age and also because it may be a cause of reduced fertility in itself [22, 31].

Hypothyroidism is a clinical syndrome with multiple etiology. It can be due to a thyroid disease (primary hypothyroidism) with a marked rise in serumal TSH concentration, or to hypophyseal and hypothalamic alterations (secondary or tertiary hypothyroidism) with a consequent decreased TSH production.

The main causes of hypothyroidism in pregnancy are Hashimoto's thyroiditis, and iatrogenic consequences of surgery and/or radiotherapy and/or an overdosage of antithyroid drugs [1].

When maternal hypothyroidism occurs during pregnancy, it is generally in a mild form. Clinical diagnosis is quite difficult, as the typical signs, such as macroglossia, voice modifications and mixedema, are exceptionally found.

In several patients diagnosis is based on laboratory data.

TSH is constantly increased and its rise comes before the onset of clinical symptomatology.

FT3 and FT4 are lower than normal, but their modifications follow TSH rise.

The assessment of anthytiroid antibodies (anti-thyroglobulins and anti-microsomials) can be useful to confirm the diagnosis of primary hypothyroidism that often recognizes an auto-immune pathogenesis.

This determination can also be a fetal prognosis index, as antibodies easily cross the placental barrier and may cause alterations of fetal thyroid functional capacity [31].

Some authors found high antithyroid antibody titres in young mothers of children with Down's syndrome and assumed that antithyroid autoimmunity can predispose to aneuploidy in the conceptus [32, 33]. These observations did not obtain any experimental confirmation.

Even though a regular course of pregnancy and a normal development of conceptus do not seem to be incompatible with a condition of overt maternal hypothyroidism [34, 35], it is generally acknowledged that in hypothyroid women the incidence of abortion, intrauterine fetal death and congenital abnormalities in the offspring is markedly higher than in euthyroid pregnant women [31]. According to some authors, the

condition of maternal hypothyroidism is associated with an increased risk of preeclampsia [36], abruptio placentae, anemia and post-partum bleeding [21].

The mechanisms that may underlie the reproductive "failure" (considered as inability to bring an healthy fetus to full development) in hypothyroid women are being studied. The deficit of maternal thyroid hormons might entail a lower quantity of thyroxin available to the fetus. This is probably very important in the early stages of development [37, 38]. A second possibility is the damage of the transport mechanism at placentat level [31]. Lastly, in some geographical areas iodine deficit can be very important [39].

The incidence of congenital abnormalities in untreated hypothyroid women is almost three times higher that the one found in the general population (11.6% *vs* to 3%); for unknown reasons, it remains high even after replacement therapy [21, 31, 41-43]. The limited case series available does not allows us to draw any final conclusions. Based on these results it is however necessary to perform an accurate ultrasound screening of major congenital abnormalities in pregnancies complicated by hypothyroidism [44].

Finally, hypothyroidism in pregnancy surely entails an increased obstetrical and perinatal risk, but it does not justify in itself an alarming attitude. Maternal hypothyroidism is not an indication to perform invasive investigations of prenatal diagnosis. According to our current knowledge, TSH and thyroid hormons do no seem to cross the placenta in significant quantities. Hence, without an iodine deficit or insufficient exposure to anti-thyroid agents or congenital enzymatic defects of hormonal biosynthesis, it is thought that the functional capacity of the hypothalamic-hypophyseal-thyroid system is developed autonomously and regularly in the fetus [45]. An adequate and prompt replacement therapy improves maternal and fetal prognosis.

There is no direct correlation between maternal hypothyroidism and congenital hypothyroidism in the newborn, barring the case of the Hashimoto's disease or iatrogenic forms (due to administration of radioiodine or overdosage of antithyroid drugs) [22].

Congenital hypothyroidism is often caused by thyroid dysgenesia, enzymatic defects of hormogenesis or alterations of the fetal hypothalamic-hypophyseal axis [22]. The assessment of TSH concentration in the umbilical cord's blood and possibly in the amniotic fluid might allow for a prenatal diagnosis in risk cases [21].

Phenylketonuria

Phenylketonuria - when we examine its multiple symptoms - has an incidence of approximately 1:10,000 newborn (all over the world).

The classical form alone affects about half cases and only 2% derives from a pterin deficit.

Diagnosis is based on the finding of hyperphenylalaninemia associated with normal tyrosinemia.

An early diagnosis at birth is of clear and fundamental importance thanks to the possibility of ensuring treatment and control resorting to an adequate diet.

Phenylketonuria was one of the first diseases for which the concept of neonatal "screening"was implemented using the Guthrie test performed on the 4th-5th day of life.

Thanks to the metabolic control of the disease and consequently the lower incidence of the related side-effects, an ever increasing number of women with phenylketonuria can procreate. A retrospective analysis of 524 pregnancies in 155 women with phenylketonuria with serumal phenylalanine concentration exceeding 20 mg/d showed that 95% of mothers had at least one child with mental retardation [46]. Besides, maternal disease is associatd with microcephaly, congenital heart diseases, low birth weight as well as increased abortion rate [47]. Fetal brain damage seems to be correlated with maternal phenylalaninemia levels [46].

Cases of fetal neurological pathology occuring in the presence of low phenylalanine levels can be partially explained by the higher concentration gradient in the fetus, where the amino acid levels remain approximately 50% higher than in the mother. With regard to the teratogenic risk a higher incidence of microcephaly was noticed in infants born to mothers with phenylalaninemia exceeding 15 mg/dl and aspecific heart diseases (no pathognomonic lesion was found) at concentrations over 10 mg/dl [48].

Other structural defects can be identified, including esophageal atresia, that seems to occur more frequently [47]. Maternal diet control started after conception can improve fetal prognosis though not preventing the abnormalities that might have occurred during organogenesis [48]. The best results are obtained when treatment is started in preconceptional age, by keeping phenylalanine concentrations ranging between 4 mg/dl and 8 mg/dl. During pregnancy diet has anyway to be supplemented with proteins, vitamins and minerals intake, and accompanied by a strict monitoring of phenylalaninemia and tyrosinemia [48].

Fetal growth must be followed by monthly ultrasound examinations while paying great attention to biometric measurements of heart and cranial development [48].

The prevention of fetal abnormalities in mothers with phenylketonuria is based on treatment in preconceptional age and consequently on early diagnosis of the disease, that is now made possible by neonatal screening programs.

In case pregnancy starts without any dietary treatment, the patient should be informed of fetal risks and a therapeutical abortion can be considered.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) affects mainly female patients in fertile age with a woman-man ratio of 9:1. The prevalence of the disease in women in reproductive age ranges between 1:250 and 1:700 [49]. The disease entails a rise in reproductive failures with a high risk of abortions and intrauterine deaths [50]. The phenomenon is related to the presence of antiphospholipid and/or anticardiolipin antibodies, that can often be found even in clinically silent forms [51].

Fetal prognosis depends on the degree of activity of the disease and in particular on the degree of maternal renal insufficiency. 18-25% of pregnancies in patients with SLE is complicated by preeclampsia [51]. There is also a teratogenic risk asociated with SLE. In 15-20% of cases, congenital heart diseases were found, such as persistence of the Botallo's duct, endocardial fibroelastosis, mitral insufficiency, transposition of the great vessels and conduction system abnormalities, such as atrioventricular congenital block that can be lethal in 15% of cases, while in 20% of them it requires the implant of a pace-maker [52, 53]. The abnormalities are probably due to the transplacental passage of immune complexes or maternal antigens that stimulate the fetal immune system to form pathogenetic complexes especially during organogenesis [51]. Congenital AVB is related to the presence of antinucleus-extractable antibodies (anti-Ro-SSA, anti-La-SSB) that are not exclusively to be found in SLE (30% of cases), but also in Sjogren syndrome (60% of cases) and arthritis rheumatoid [21, 52].

The "neonatal SLE syndrome" is characterized by hemolytic anemia, thrombocytopenia, leukopenia, face and chest erythema (that clears up spontaneously in about 1 year), cardiac malformations (including AVB) [53].

Pregnancy in patients with SLE should be planned after at least 6 months from the remission of the disease [21]. The most important laboratory data concerning disease activity is the levels of complementary fractions C3 and C4 [21]. In inactive SLE and in normal pregnancy C3 and C4 increase progressively although they remain within the normal range. When SLE is active there is a significant progressive decrease in complementary levels [51].

All pregnant women with SLE are faced with the problem of the pharmacological treatment, considering the absolute need for checking the disease upon conception.

The drugs to be used also in silent forms must anyway be molecules having a low known teratogenic risk.

The therapy of choice is based on antiinflammatories and steroids; among them fluorocortolone is the lowest risk drug, having a good placental metabolization and consequently a lower bioavailability in fetal compartment. Predinisone too is a low fetal risk steroid preparation. A long-term aspirin intake may entail a prolonged labour, a longer duration of gestation, an increased incidence of postmaturity, a higher blood loss upon delivery [21, 51, 54].

Obstetrical precautions in pregnancy associated with SLE are aimed to control the high risk of delayed growth. The control of the fetal heart-rate is also important; in case of atrioventricular block, rate is fixed at approximately 70-80 beats/minute. A fetal ecocardiography would exclude possible heart malformations.

SLE is not an indication to choose a cesarean section.

Moreover, a reduction in post partum exacerbations was reported with an increase in intra an post partum posology of steroid preparations.

In the cases that are not completely controlled by steroid therapy, an immunosuppressant can be added to reduce maternal and fetal risks due to hyperdosage of steroid preparations and combine the effects of the two drugs with different specific actions.

In some cases it might be necessary to resort to high doses of immunoglobulins i.v. or plasmapheresis [21, 51, 54].

Epilepsy and anticonvulsive drugs

Epilepsy affects approximately one per cent of women in fertile age. Half of them does not show any significant variation of the frequency of convulsions after the beginning of pregnancy, 25% improves and the remaining 25% worsens. The latter group includes women tending to have convulsions during the menstrual phase of cycle, probably responding to an unclear metabolic stimulus [55-57]. Moreover, pregnant women with a male fetus are doubly predisposed to have a worsening of symptoms to women with a female fetus [56]. Given that the clinical response of an epileptic woman to pregnancy varies considerably, it is necessary to carefully control her and possibly reassess her pharmacological therapy. The most critical periods for the reacutization of seizures are the first trimester and during labour.

Hyperemesis gravidarum, that is frequent in the first trimester may actually affect the assimilation of the customary dosage of anticonvulsive drugs. Hyperventilation and fatigue may be responsible for the reacutization of seizures during labour [55].

Most of the anticolvulsive drugs currently used have antagonist effects on folic acid [58]. Epileptic women may hance develop overt anemias in pregnancy. Some drugs (phenytoin) induce the production of enzymes that hydrolize and reactivate vitamin D [21], other drugs (phenytoin, phenobarbital) interfere with vitamine K metabolism, thereby increasing the risk of hemorrhagic feto-neonatal pathologies [59]. Therefore, all epileptic

women have to receive a vitamin supplement of folic acid, vitamin D and vitamin K, besides iron, during pregnancy [55].

Recent studies demonstrated that in epileptic women the risk of bearing a child with congenital anomalies increased 2-3 times compared to normal (6-10% *vs* 3%). The most frequent congenital abnormalities seem to be midline closure defects (harelip, cardiac malformations due to interatrial septum and intraventricular septum defect) [60-62]. Infants born to epileptic mothers frequently have minor dysmorphic abnormalities related to cranio-facial development (trigonocephaly), and of the phalanges and of metacarpus and metatarsus [60-62]. The direct cause of the increase of congenital anomalies is uncertain. Possible explanations include:

1) the teratogenic action of anticonvulsive drugs. It depends on type and dose, whether they are taken alone or in association with others (in this case risks increase). Valproic acid is surely teratogenic; in about 1% of cases it can cause neural tube defects (spina bifida, myelomeningocele). These defects can however be diagnosed early in the uterus (ultrasound - alphaFP dosage in the amniotic fluid). Phenytoin and carbamazepine are likely to be teratogenic. Phenobarbital does not seem to be free of malformation risk either [62-67];

2) during epileptic convulsive attacks there may be breathing disorders up to apnea and cardiac output alterations that, in pregnancy, may affect fetal well-being, especially in case of frequent attacks [61];

3) the possible link - still to be demonstrated - between genetic predisposition to contracting epilepsy and a possible predisposition to bear abnormal children.

Even if anticonvulsive drugs seem to be the main factor favouring the onset of congenital anomalies, they shall not be suspended during pregnancy. It is advisable to monitor drug blood rates, to ensure a satisfactory control of maternal disease with the lowest risk for the fetus. A single-therapy is preferrable, to avoid biochemical and metabolic interactions among the different anticonvulsive drugs [66, 67].

Phenobarbital is considered as the drug of choice, whenever the disease permits its use and if it is efficient in keeping the woman free of any symptoms. Neonatal hemorrhagic pathology can be prevented by sypplements of vitamin K to the mother during the last gestational months [68, 69].

Submitted on invitation.
Accepted on 25 September 1992.

REFERENCES

1. GABBE, S.G., MESTMAN, J.H., FREEMAN, R.K., GOEBELSMANN, U., LOWENSOHN, R.I. & CETRULO, C. 1977. Management and outcome of diabetes mellitus classes B throught R. *Am. J. Obstet. Gynecol.* **129**: 723-732.

2. O'SULLIVAN, M.J., SKYLER, J.S., RAINER, K.A. & ABU-AMAD, A. 1992. Diabetes and pregnancy. In: *Principles and practice of medical therapy in pregnancy*. M. Gleicher (Ed.). Appleton & Lange, Norwalk. pp. 357-378.

3. KUCERA, J. 1971. Rate and type of congenital anomalies among offsprings of diabetic women. *J. Reprod. Med.* **7**: 61-70.

4. VAN ASSCHE, F.A., AERTS, L. & HOLEMANS, K. 1991. The effects of maternal diabetes on the offspring. *Baillieres Clin. Obstet. Gynecol.* **5**: 485-492.

5. FRANCE STUDY GROUP. 1991. Multicenter survey of diabetic pregrancy in France. *Diabetes Care* **14**: 994-1000.

6. HOD, M., MERLOB, P., FRIEDMANS, S., RUSECKI, Y. & OVADIA, J. 1991. Prevalence of congenital anomalies and neonatal complications in the offspring of diabetic mothers in Israel. *Isr. J. Med. Sci.* **27**: 498-502.

7. HOD, M., MERLOB, P., FRIEDMAN, S., SCHOENFELD, A. & OVADIA, J. 1991. Gestational diabetes mellitus. A Survey of perinatal complications in the 1980's. *Diabetes* **40** (Suppl. 2): 74-78.

8. PEDERSEN, L.M., TYGSTRUP, I. & PEDERSEN, J. 1964. Congenital malformations in new-born infants of diabetic women: correlations with maternal diabetic vascular complications. *Lancet* **1**: 1124-1126.

9. SADLER, T.W. 1980. Effects of maternal diabetes on early embyiogenesis. I. The teratogenetic potential of diabetic serum. *Teratology* **21**: 339-347.

10. LANGER, O., BRUSTMAN, L., ANYAEGBUNAM, A. & MAZZE, R. 1987. The significance of an abnormal glucose tolerance test value on adverse outcome in pregnancy. *Am. J. Obstet. Gynecol.* **157**: 758-763.

11. MENON, R.K. 1990. Transplacental passage of insulin in pregnant woman with insulin dependent diabetes mellitus. *N. Engl. J. Med.* **323**: 309-315.

12. VIGNALI, M. & CASTIGLIONI, M.T. 1992. Malattie della ghiandole endocrine. In: *La clinica ostetrica e ginecologica*. G.B. Candiani, V. Danesino & A. Gastaldi (Ed.). Masson, Milano. Vol. 2. pp. 335-359.

13. MILLER, E., HARE, J.W.T. & CLOHERTY, J.P. 1981. Elevated maternal haemoglobin A1c in early pregnancy and major congenital anomalies in infant of diabetic mother. *N. Engl. J. Med.* **304**: 1331-1334.

14. YLINEN, K., AULA, P., STENMAN, U.H. & KESANIEMI-KUOKKANEM, T. 1984. Risk of minor and major fetal malformations in diabetics with high haemoglobin A1c values in early pregnancy. *Br. Med. J. Cl. Res.* **289**: 345-346.

15. MIODOVNIK, M., SKILLMAN, C., HOLROYDE, J.C., BUTLER, J. B., WENDEL, J.S. & SIDDIQI, T.A. 1985. Elevated maternal glycohaemoglobin in early pregnancy and spontaneous abortion among insulin-dependent diabetic women. *Am. J. Obstet. Gynecol.* **153**: 439-442.

16. OATS, J.N. 1991. Obstetrical management of patients with diabetes in pregnancy. *Baillieres Clin. Obstet. Gynecol.* **5**: 395-411.

17. KAPPY, M.S. 1991. Diabetes in pregnancy: rationale and guidelines for care. *Compr. Ther.* **17**: 50-56.

18. STEWART, J.M. & STOLL, S. 1979. Familial caudal regression anomalad and maternal diabetes. *J. Med. Genet.* **16**: 17-20.

19. LANDON, M.B. & GABBE, S.G. 1991. Fetal surveillance in the pregnancy complicated by diabetes mellitus. *Clin. Obstet. Gynecol.* **34**: 535-543.

20. MARRERO, D.G., MOORE, P., LANGENFELD, C.D., GOLICHOWSKI, A. & CLARK C.M. 1992. Care of diabetic pregnant women by primary-care physicians. Reported strategies for managing pregestational and gestational diabetes. *Diabetes Care* **15**: 101-107.

21. KAPLAN, M.M. 1992. Thyroid disease. In: *Principles and practice of medical therapy in pregnancy*. N. Gleicher (Ed.). Appleton & Lange Norwalk, Connecticut. pp. 321-338.

22. BURROW, G.N. 1988. Thyroid disease. In: *Medical complication during pregnancy*. G.N. Burrow & T.F. Ferris (Eds). W.B. Saunders Company, Philadelphia. pp. 187-203.

23. BURROW, G.N. 1985. The management of thyrotoxicosis in pregnancy. *N. Engl. J. Med.* **313**: 562-565.

24. VAN DER SPUY, Z.M. & JACOBS, H.S. 1984. Management of endocrine disorders in pregnancy. Part I. Thyroid and parathyroid disease. *Postgrad. Med. J.* **60**: 245-252.

25. AMINO, N.M, TANIZAWA, O., MORI, H. *et al.* 1982. Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. *J. Clin. Endocrinol. Metab.* **55**: 108-112.

26. MCDOUGALL, I. R. 1989. Hyperthyroidism and maternal-fetal thyroid hormone metabolism. In: *Endocrine disorders in pregnancy*. S.A. Brody & K. Ucland (Eds). Appelton & Lange, Norwalk. p. 151-164.

27. MATSUURA, N., KONISHI J., FUJEDA, K., KASAGI, K., IIDA, Y., MAGISAWA, M. & FUJIMOTO, S. 1988. TSH-receptor antibodies in mothers with Graves' disease and outcome in their offspring. *Lancet* **1**(8575): 14-17.

28. DAVIS, L.E., LUCAS, N.J. HANKINS, G.D.V., ROARK, M.L. & CUNNINGHAM, F.G. 1989. Thyrotoxicosis complicating pregnancy. *Am J. Obstet. Gynecol.* **160**: 63-70.

29. BURROW, G.N. 1985. The management of thyrotoxicosis in pregnancy. *N. Engl. J. Med.* **313**: 562-565.

30. STEPHAN, M.J., SMITH, D.W., PONZI, J.W. & ALDEN, E.R. 1982. Origin of scalp vertex aplasia cutis. *J. Pediatr.* **101**: 850-853.

31. POTTER, J.D. 1980. Hypothyroidism and reproductive failure. *Surg. Gynecol. Obstet.* **150**: 251-255.

32. CUCKLE, H., WALD, N., STONE, R., DENSEN, J., HADDOW, J. & KNIGHT, G. 1988. Maternal serum thyroid antibodies in early pregnancy and fetal Down's syndrome. *Prenat. Diagnosis* **8**: 439-445.

33. FIALKOW, P.J. 1986. Autoimmunity and chromosomal aberrations. *Am. J. Hum. Genet.* **18**: 93-96.

34. BOYLAND, P. & DRURI, M.I. 1979. Pregnancy and untreated hypothyroidism. *Ir. J. Med. Sci.* **148**: 10-15.

35. KENNEDY, A.L. & MONTGOMERY, D.A.D. 1978. Hypothyroidism in pregnancy. *Br. J. Obstet. Gynecol.* **85**: 225-230.

36. LAO, T.T., CHIN, R.K.H. & SWAMINATHAN, R. 1988. Thyroid function in pre-eclampsia. *Br. J. Obstet. Gynecol.* **95**: 880-883.

37. EKINS, R. 1985. Roles of serum thyroxine-binding proteins and maternal thyroid hormones in fetal development. *Lancet* **i**: 1129-1132.

38. HARAKAWA, S., AZAKAWA, M., HASHIMOTO, M., YAMASHITA, S., IZUMI, M. & NAGATAKI, S. 1989. Changes of serum thyroid hormone levels induce malformations on early embryogenesis in rats. *Acta Endocrinol.* **121**: 739-743.

39. PHAROAH, P.O.D., BUTTFIELD, I.A. & HETREL, B.S. 1971. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. *Lancet* **i**: 308-310.

40. CAMARGO, C.A. 1989. Hypothyroidism and goiter during pregnancy. In: *Endocrine disorders in pregnancy*. S.A. Brody & K. Ucland (Eds). Appleton & Lange, Norwalk. pp. 165-176.

41. FOLEY, TP. jr. 1991. Maternally trasferred thyroid disease in the infant: recognition and treatment. *Adv. Exp. Med. Biol.* **229**: 209-226.

42. LAZANUS, J.H., & OTHMAN, S. 1991. Thyroid disease in relation to pregnancy. *Clin. Endocrinol.* **34**: 91-98.

43. BECKS, G.P. & BURROW, G.N. 1991. Thyroid disease and pregnancy. *Med. Clin. North Am.* **75**: 121-150.

44. SMITH, J.E. 1990. Pregnancy complicated by thyroid disease. *J. Nurse Midwifery* **35**: 143-149.

45. BALLABIO, M., NICOLINI U. & JOWETT, T. 1989. Maturation of thyroid function in normal human foetuses. *Clin. Endocrinol. Oxf.* **31**: 565-571.

46. SCRIVER, C.R., KAUFMAN, S. & WOO, SLC. 1989. The hyperphenylalaninemias. In: *The metabolic basis of inherited disease*. C.R. Scriver, A.L. Beaudet, W.S. Sly & D. Walle (Eds). Mc Graw-Hill. p. 495-501.

47. LENKE, RR. & LEVY, H.L. 1980. Maternal phenylketonuria and hyperphenylalaninema. *N. Engl. J. Med.* **303**: 1202-1208.

48. LENKE, RR. & LEVY H.L. 1982. Maternal phenylketonuria results of dietary therapy. *Am. J. Obstet. Gynecol.* **142**: 548-553.

49. HOUSER , M.T., FISH. A.J., TAGATZ, G.E., WILLIAMS, P.P. & MICHEAL, A. 1980. Pregnancy and systemic lupus erythematosus. *Am. J. Obstet. Gynecol.* **138**: 409-413.

50. FINE, L.G., BARNETT E.V. DANOVITCH, G.M. *et al.* 1981. Systemic lupus erythematosus in pregnancy. *Ann. Int. Med.* **94**: 667-677.

51. BURKETT, G. 1985. Lupus nephropathy and pregnancy. *Clin. Obstet. Gynecol.* **28**(2): 310-323.

52. CHAMEIDES L., TRUEX, R., VETTER, V.M. *et al.* 1977. Association of maternal systemic lupus erythematosus with congenital complete heart block. *N. Engl. J. Med.* **297**: 1204-1209.

53. DRAZNIN, T.H., ESTERLY, N.B., FUREU, N. & DEBOTSKHY, E. 1979. Neonatal lupus erythematosus. *J. Am. Acad. Dermatol.* **1**: 437-439.

54. ZURIER, R.B. 1987. Systemic lupus erythematosus and pregnancy. In: *Systemic lupus erythematosus*. R.G. Lahita (Ed.). John Wiley & Sons, New York. pp. 545-550.

55. SHARONY, R. & GRAHAM, J.M. Jr. 1991. Identification of fetal problems associated with anticonvulsant use and maternal epilepsy. *Obstet. Gynecol. Clin. North Am.* **18**: 933-951.

56. DANSKY, L.V. & FINNEL, R.H. 1991. Parental epilepsy, anticonvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades. II. Human studies. *Reprod. Toxicol.* **5**: 301-335.

57. FINNEL, R.H. & DANSKY, L.V. 1991. Parental epilepsy, anticolvulsant drugs, and reproductive outcome: epidemiologic and experimental findings spanning three decades. I. Animal studies. *Reprod. Toxicol.* **5**: 281-299.

58. OGAWA, Y., KANEKO, S., OTANI, K. & FUKUSHIMA, Y. 1991. Serum folic acid levels in epileptic mothers and their relatioship to congenital malformations. *Epilepsy Res.* **8**: 75-78.

59. MOSLET, U. & HANSEN, E.S. 1992. A review of vitamin K, epilespy and pregnancy. *Acta Neurol. Scand.* **85**: 39-43.

60. KANEKO, S., OTANI, R., HIRANO, T., KONDO, T. & FUKUSHIMA, Y. 1991. Teratogenicity of antiepileptic drugs: is the prevention possible? *Jpn. J. Psychiatry Neurol.* **45**: 478-481.

61. YERBY, M.S. 1991. Pregnancy and epilepsy. *Epilepsia* **32**(Suppl. 6): 51-59.

62. SHAKIR, R.A. & ABDULWAHAB, B. 1991. Congenital malformations before and after the onset of maternal epilepsy. *Acta Neurol. Scand.* **84**: 153-156.

63. ORRELL, R.W. 1991. Sodium valproate in pregnancy. *Brit. Med. J.* **303**: 56-57.

64. BOLOGA, M., TANG, B.M., KLEIN, J., TESORO, A. & KOREN, G. 1991. Pregnancy-induced changes in drug metabolism in epileptic women. *J. Pharmacol. Exp. Ther.* **257**: 735-740.

65. D'SOUZA, S.W., ROBERTSON, I.G., DONNAI, D. & MAWER, G. 1991. Fetal phenytoin exposure, hypoplastic nails, and jaundice. *Arch. Dis. Child.* **66**: 320-324.

66. LANDER, C.M. & EADIE, M.J. 1991. Plasma antiepileptic drug concentrations during pregnancy. *Epilepsia* **32**: 257-266.

67. KILPATRICK, C.J. & MOULDS, R.F. 1991. Anticonvulsants in pregnancy. *Med. J. Aust.* **154**: 199-202.

68. LANDER, C.M. & EADIE, M.J. 1990. Antiepileptic drug intake during pregnancy and malformed offspring. *Epilepsy Res.* **7**: 77-82.

69. BRODIE, M.J. 1990. Management of epilepsy during pregnancy and lactation. *Lancet* **336**: 426-427.