Genetic Causes of Congenital Malformation

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INTRODUCTION

It is interesting to note that individual with genetic disorders are rare but collectively they comprise over 15,500 recognized genetic disorders. It has been reported that approximately 3-5% of all births result into congenital malformations (McKusick, 1998). 20-30% of all infant deaths are due to genetic disorders (OMIM, Online) 30-50% of post-neonatal deaths are due to congenital malformations. In developed countries11.1% of pediatric hospital admissions are for children with genetic disorders and 18.5% are children with other congenital malformations. However, there is no such type of statistics available from India. Further 12% of adult hospital admissions are for genetic causes. In Table 1 the background prevalence risk for every million pregnancy is shown.

All those parents and also the individuals who suffer from congenital malformations are under an emotional stress. If the genetic basis of congenital malformation is known a better genetic counseling can be provided which provides a option for the couples for the next pregnancy. Congenital malformations due to genetic causes are shown in Table 2.

Once there is a genetic disorder in the family. The child should undergo physical examination like: wide set eyes, cleft palate, Hirsutism, web neck, large tongue, flattened face, round vs. triangular face, coloboma (failure of Iris to close), cataracts, low set finger and thumb position, simian crease in palm, polydactylism wide gap between toes etc., club foot, rocker bottom feet, congenital heart defects, renal agenesis, polycystic kidneys etc, Small for gestational age or intrauterine growth retardation, mental retardation If the child is not meeting the developmental milestones he should be considered for the genetic testing. Most of the causes observed during the first year of life are enumerated in Table 3.

As discussed above not only the genetic factors are responsible for the congenital anomalies environment also contribute significantly. More than 50 teratogenic environmental drugs, chemicals, and physical agents have been described (Aase, 1990; Brent and Beckman, 1990, 1994, 1999a, b; Brent, 1993; Beckman et al., 1997; Heinonen et al., 1997.) using modern epidemiologic tools and the talents of clinical dysmorphologists (Brent, 1967, 1986; Carter, 1976; Fraser, 1976; Brent and Beckman,1991; Jones, 1994;

Table 1: Background reproductive risks per million pregnancies

Reproductive Risk	*Frequency*
Immunologically and clinically diagnosed spontaneous abortions per million conceptions	350 000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies	150 000
Genetic diseases per million births	110 000
Multifactorial or polygenic genetic environmental interactions) (eg, neural tube defects, cleft lip, hypospadius, hyperlipidemia, diabetes)	90 000
Dominantly inherited disease (eg, achondroplasia, Huntingtons chorea, neurofibromatosis)	10 000
Autosomal and sex-linked genetic disease (eg, cystic fibrosis, hemophilia, sickle-cell disease, thalassemia)	1200
Cytogenetic (chromosomal abnormalities) (eg, Down syndrome [Trisomy 21]; Trisomy 13, 18; Turner syndrome; 22q deletion)	5000
New mutations*	3000
Severe congenital malformations (as a result of all causes of birth defects: genetic, unknown, environmental per million births)	30 000
Prematurity/million births	40 000
Fetal growth retardation/million births	30 000
Stillbirths (>20 wk)/million births	2000–20 900
Infertility	7% of couples

*The mutation rate for many genetic diseases can be calculated. This can be readily performed with dominantly inherited diseases when offspring are born with a dominant genetic disease and neither parent has the disease (reference).
Congenital malformations have multiple causes, including a significant proportion that is genetic.

Table 2: Causes of genetic health problems

1. Inherited genetic diseases:	Caused by abnormal groups of genes passed down from one generation to the next. Ex. CF, Phenylketonuria, and muscular dystrophy. Spontaneous Genetic mutations are caused by an error in DNA replication leading to a base substitution or an insertion or deletion of one or two base pairs from the DNA.
2. Somatic genetic disease:	Caused by the sudden appearance of an abnormal form of a gene in one part of the body. eg. Cancer.
3. Chromosomal Aberrations:	Abnormalities of chromosomal structure. Ex. Down Syndrome.

Table 3: Cause of human congenital malformations observed during the first year of life

Suspected Cause	*% of Total*
Unknown	65–75
Polygenic	
Multifactorial (gene-environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	15–25
Autosomal and sex-linked inherited genetic disease	
Cytogenetic (chromosomal abnormalities)	
New mutations	
Environmental	10
Maternal conditions: alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking and nicotine, starvation, nutritional deficits	4
Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella zoster, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): amniotic band contrictions, umbilical cord constraint, disparity in uterine size and uterine contents	1–2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	<1

Graham et al., 1999). The basic science and clinical rules for evaluating teratogenic risks have been established (Brent, 1977, 1999). The development of the rubella vaccine and the recognition of the importance of adequate folic acid intake in women of reproductive age are forerunners for the prevention of birth defects from teratogenic infectious agents and nutritional components that are important for normal development. The completion of the first stage of the Human Genome Project in 2000 offers the geneticist and the teratologist, a large amount of information.

EMOTIONAL IMPACT OF CONGENITAL MALFORMATIONS

Reproductive problems encompass a multiplicity of diseases, including sterility, infertility, abortion (miscarriage), stillbirth, congenital malformations (as a result of environmental or hereditary causes), fetal growth retardation, and prematurity. These clinical problems occur commonly in the general population, and therefore environmental causes are not always easy to corroborat. Severe congenital malformations occur in 3% of births. According to the Centers for Disease Control and Prevention, severe congenital malformations include birth defects that cause death, hospitalization, mental retardation; necessitate significant or repeated surgical procedures; are disfiguring; or interfere with physical performance. That means that each year in the United States, 120 000 newborns are born with severe birth defects. Genetic diseases occur in approximately 11% of births. Spontaneous mutations account for <2% to 3% of genetic disease. Therefore, mutations induced from preconception exposures of environmental mutagens are difficult endpoints to document.

Along with cancer, psychiatric illness, and hereditary diseases, reproductive problems have been viewed throughout history as diseases of affliction. Inherent in the reactions of most cultures is that these diseases have been viewed as punishments for misdeeds (Hertig, 1967; Boue et al., 1975; Simpson, 1980; Sever, 1982; Brent and Holmes, 1988.). Regardless of the irrationality of this viewpoint, these feelings do exist. Ancient Babylonian writings recount tales of mothers being put to death because they delivered malformed infants. George Spencer was slain by the Puritans in New Haven in the 17th century, having been convicted of fathering a cyclopean pig, because the Puritans were unable to differentiate between George Spencer's cataract and the malformed pigs cloudy cornea (Boue et al., 1975). In modern times, some individuals with reproductive problems reverse the historical perspective and blame others for the occurrence of their congenital malformations, infertility, abortions, and hereditary diseases. They place the responsibility of their illness on environmental agents dispensed by their health care provider or used by their employer (Hertig, 1967; Boue et al., 1975).

Cause of Congenital Malformations

The cause of congenital malformations can be divided into 3 categories: unknown, genetic, and environmental. The cause of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown cause is likely to have an important genetic component. Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip, fit in the category of multifactorial disease as well as in the category of polygenic inherited disease (Brent and Holmes,1988; Brent, 1999). The multifactorial/ threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors.

Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. Spontaneous errors of development may indicate that we never achieve our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that the majority of all conceptions are lost before term, many within the first 3 weeks of development. The World Health Organization estimated that 15% of all clinically recognizable pregnancies end in a spontaneous abortion, 50% to 60% of which are attributable to chromosomal abnormalities (Simpson, 1980; Sever, 1982; Hook, 1992; Alwan and Modell, 1997). Finally, 3 to 6% of offspring are malformed, which represents the background risk for human maldevelopment.

Environmental Agents whose Exposure during Pregnancy has been Demonstrated to Result in Reproductive Toxicity

Environmental agents that have resulted in reproductive toxicity and or congenital malformations in human populations are shown in Table 4. The list cannot be used in isolation because so many other parameters must be used in any analysis of the risks in individual patients. Many of these agents represent a very small risk, whereas others may represent substantial risks. The risks will vary with the magnitude, timing, and length of exposure.

Once knowing the causes it is important to initiate a nationwide intervention programme for the control of any health problem, there are two prerequisites. The first is evidence that the magnitude of the problem is significant, and the second is an indication that prevention is both feasible and cost-effective. In a nation like India it is very important to have the prevention strategy. As we know carrier of thallasemia is quite high i.e 3-4% in India two carries marrying will result into thallasemic child which is a both familial and national burden. In India it is required to have the analysis of the available epidemiological data clearly indicates that hereditary disorders and congenital malformations. The health care need of our populations necessitate that this problem be addressed promptly. Moreover, great advances have been made in our knowledge of genetic disorders, and the principle of equity in health care demands that the gap between medical progress and health care services should be narrowed whenever possible.

In India, from some parts of the country, high degree of consanguinity is found for example in Muslims (all over India) and south Indian communities. India is a vast country and needs some of the disorders are prevented by basic public health measures and activities focusing primarily on education and approaches in primary health care that are applicable in most of the other countries. While basic genetic diagnostic facilities should be available in order to deal with all aspects of prevention and care, the establishment of such facilities, if they do not already exist, may not require the sophistication and high costs that many people think.

Action is therefore required to initiate activities to control genetic and congenital disorders in India. The nature and sophistication of such activities will vary from one country to another, but national programmes should be established to provide basic services covering prevention, health promotion and case management activities.

Strategies and Feasible Approaches

While the overall objective of a national programme is the prevention of genetic and congenital disorders in the community. The strategies adopted to achieve this objective should be carefully selected to match the unique

Table 4: Proven human teratogens or embryotoxins-drugs, chemicals, milieu and physical agents that have resulted in human congenital malformations

Reproductive Toxin	*Alleged Effects*
Aminopterin, Methotrexate	Growth retardation, microcephaly, meningomyelocele mental retardation, hydrocephalus, and cleft palate.
Androgens	Masculinization of the developing fetus can occur from androgens and high doses of some male derived progestins.
Angiotensin Converting Enzyme (ACE) Inhibitors	Fetal hypotension syndrome in 2nd and 3rd trimester resulting in fetal kidney hypoperfusion, and anuria, oligohydramnios, pulmonary hypoplasia and cranial bone hypoplasia. No effect in the first trimester.
Antituberculous Therapy	INH, PAS has an increased risk for some CNS abnormalities.
Caffeine	Moderate caffeine exposure is not associated with birth defects; high exposures are associated with an increased risk of abortion but the data is inconsistent.
Chorionic Villous Sampling (CVS)	Vascular disruption malformations, i.e., limb reduction defects.
Cobalt in hematemic multivitamins	Fetal goiter
Cocaine	Vascular disruptive type malformations in very low incidence, pregnancy loss.
Corticosteroids	High exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiological studies are not consistent.
Coumarin Derivatives	Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malformations can occur in late pregnancy exposure due to bleeding.
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive agents like cyclosporine or leflunomide	Many chemotherapeutic agents used to treat cancer have a theoretical risk for producing malformations in the fetus when administered to pregnant women, especially since most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword.
Diethylstilbestrol	Administration during pregnancy produces genital abnormalities, adenosis, clear cell adenocarcinoma of vagina in adolescents. The latter has a risk of 11000 to 1 10 000, but the other effects, such as adenosis can be quire high.
Ethyl Alcohol	Fetal Alcohol Syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.
Ionizing Radiation	The threshold is greater than 20 rad (0.2 Gy) can increased the risk for some fetal effects such as micocephaly or growth retardation, but the threshold for mental retardation is higher.
Insulin Shock Therapy	This therapeutic modality when administered to pregnant women resulted in microcephaly, mental retardation.
Lithium Therapy	Chronic sage for the treatment of manic depressive illness has an increased risk for Ebstein's Anomaly and other malformations, but the risk appears to be very low.
Minoxidil	The discovery of the growth promotion of hair was discovered for this drug because administration during pregnancy resulted in hirsutism in newborns.
Methimazole	Aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy*.
Methylene blue intramniotic instillation	Fetal intestinal atresia, hemolytic anemia and jaundice in neonatal period. This procedure is no longer utilized to identify one twin.
Misoprostol	A low incidence of vascular disruptive phenomenon, such as limb reduction defects and Mobius syndrome have been reported in pregnancies in which this drug was used to induce an abortion.
Penicillamine (D-penicillamine)	This drug results in the physical effects referred to as lathyrism, the results of poisoning by the seeds of the genus Lathyrus. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition appears to be reversible and the risk is low.
Progestin Therapy	Very high doses of androgen hormone derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of these drugs have the potential for producing non-genital malformations.
Propylthiouracil	This drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter.

Table 4: Contd....

Reproductive Toxin	*Alleged Effects*
Radioactive Isotopes	Tissue- and organ-specific damage is dependent on the radioisotope element and distribution, i.e. high doses of ^{131}I administered to a pregnant woman can cause fetal thyroid hypoplasia after the 8th week of development.
Retinoids (Acutane)	Systemic retinoic acid, isotretinoin, Etretinate can cause increased risk of central nervous system, cardio-aortic, ear and clefting defects. Microtia, anotia, thymic aplasia and other branchial arch, aortic arch abnormalities and certain congenital heart malformations.
Retinoids, topical	Topical administration is very unlikely to have teratogenic potential because one cannot attain a teratogenic serum level from topical exposure to retinoids.
Streptomycin	Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low risk phenomenon. Even children are less sensitive to the ototoxic effects of these drugs when compared to adults.
Sulfa drug and Vitamin K	These drugs can produce hemolysis in some subpopulations of fetuses.
Tetracycline	This drug produces bone and teeth staining, No other malformations are at increased risk.
Thalidomide	This drug results in an increased incidence of deafness, anotia, preaxial limb reduction defects, phocomelia, ventricular septal defects and GI atresias. The susceptible period is from the 22nd to the 36th day postconception.
Trimethorpin	This drug was frequently used to treat urinary tract infections and has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels. This has resulted in neurological symptoms in adults taking this drug.
Vitamin A	The same malformations that have been reported with the retinoids have been reported with very high doses of vitamin A (retinol). Dosages to produce birth defects would have to be in excess of 25 000 to 50 000 units per day.
Vitamin D*	Large doses given in vitamin D prophylaxis are possibly involved in the etiology of supravalvular aortic stenosis, elfin faces, and mental retardation.
Warfarin (Coumarin)	Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malformations can occur in late pregnancy exposure due to bleeding.
Diphenylhydantoin	Treatment of convulsive disorders increases the risk of the Fetal Hydantoin Syndrome**,** consisting of facial dysmorphology, cleft palate, VSD, growth and mental retardation
Trimethadione and Paramethadione	Treatment of convulsive disorders increases the risk of characteristic facial dysmorphology, mental retardation, V-shaped eye brows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay.
Valproic Acid	Treatment of convulsive disorders increases the risk of spina bifida, facial dysmorphology and autism.
Carbamazepine	Treatment of convulsive disorders increases the risk facial dysmorphology.
Chemicals	
Carbon Monoxide Poisoning	CNS Damage has been reported with very high exposures, but the risk appears to be low*.
Lead	Very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 ugm% in the serum of pregnant mothers.
Gasoline Addiction Embryopathy	Facial dysmorphology, mental retardation.
Methyl Mercury	Minamata disease consists of cerebral palsy, microcephaly, mental retardation, blindness, cerebellum hypoplasia. Other endemics have occurred from adulteration of wheat with mercury containing chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely to represent a teratogenic risk, but reducing or limiting the consumption of carnivorous fish has been suggested in order not to exceed the EPA's MPE (maximum permissible exposure), which is far below the toxic effects of mercury.

Table 4: Contd....

Reproductive Toxin	*Alleged Effects:*
Polychlorinated Biphenyls	Poisoning has occurred from adulteration of food products (Cola-colored babies, CNS effects, pigmentation of gums, nails, teeth and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures.
Toluene Addiction Embryopathy	Facial dysmorphology, mental retardation.
Embryonic and Fetal Infections	
Cytomegalovirus Infection	Retinopathy, CNS calcification, microcephaly, mental retardation.
Rubella	Deafness, congenital heart disease, microcephaly, cataracts, mental retardation).
Herpes Simplex	Fetal infection, liver disease, death.
Human Immunodeficiency Virus	Perinatal HIV infection.
Parvovirus Infection, B 19	Stillbirth, hydrops.
Syphilis	Maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis.
Toxoplasmosis	Hydrocephaly, microphthalmia, chorioretinitis, mental retardation.
Varicella –Zoster	Skin and muscle defects; intrauterine growth retardation; limb reduction defects, CNS damage (very low increase risk).
Venezuelan Equine Encephalitis	Hydranencephaly; microphthalmia; central nervous system destructive lesions; luxation of hip.
Maternal Disease States	
Corticosteroid Secreting Endocrinopathy	Mothers with Cushings Disease can have infants with hyperadrenocortism, but anatomical malfromations do not appear to be increased.
Iodine Deficiency	Can result in embryonic goiter and mental retardation.
Intrauterine Problems of Constraint and Vascular disruption	These types of defects are more common in multiple-birth pregnancies, pregnancies with anatomical defects of the uterus, placental emboli, amniotic bands; birth defects such as club feet, limb reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia, limb reduction defects, cleft lip, omphalocele, encephalocele).
Maternal Androgen Endocrinopathy (Adrenal tumors)	Masculinization.
Maternal Diabetes	Caudal and femoral hypoplasia, transposition of great vessels.
Maternal Folic Acid in reduced amounts	An increased incidence of neural tube defects (NTDs).
Maternal Phenylketonuria	Abortion, microcephaly, and mental retardation. Very high risk in untreated patients.
Maternal Starvation	IUGR, abortion, NTDs.
Tobacco Smoking	Abortion, IUGR, and stillbirth.
Zinc Deficiency*	Neural Tube Defects*

demographic, cultural and religious characteristics of the population and should take into consideration the priorities set and the resources available. In all countries, irrespective of the resources available, certain public health measures capable of reducing the burden of genetic and congenital disorders can be feasibly implemented without major resource implications. These primary prevention measures, which should be integrated into primary health care, include the following:

- ❖ reducing genetic disorders related to advanced parental age, such as Down syndrome and autosomal dominant conditions due to new mutations, as part of the family planning services;
- ❖ reducing the occurrence of congenital abnormalities such as neural tube defects, and avoiding the sequelae of micronutrient deficiencies such as mental retardation due to iodine deficiency by promoting healthy nutrition for women;
- ❖ preventing congenital rubella syndrome by immunizing against rubella infection;
- ❖ reducing mortality and chronic handicap due to rhesus haemolytic disease through routine prenatal screening;
- ❖ reducing congenital abnormalities and stillbirths by better control of maternal diabetes prior to and during pregnancy;
- ❖ reducing the risk of miscarriage, congenital abnormality and fetal growth retardation through avoidance of smoking and alcohol intake during pregnancy;

- ❖ avoiding congenital abnormalities caused by certain infections such as syphilis by prevention, early detection and prompt treatment;
- ❖ reducing the occurrence of hereditary disorders in high-risk families through genetic counselling;
- ❖ providing information on the implications and availability of carrier testing for common disorders such as the haemoglobinopathies and G6PD deficiency.

Secondary prevention entails either the prevention of the birth of affected babies through prenatal diagnosis and selective abortion, or prevention of the full expression of the condition by proper early management aimed at minimizing the clinical features of the disease. In some communities selective abortion is generally unacceptable and secondary prevention will, in this case, refer to efforts to minimize the adverse clinical manifestations of these disorders through early detection and proper management.

To initiate interventions for the control of genetic and congenital disorders at the national level, the establishment of a vertical programme for genetics is not necessary. The strategies and public health approaches previously mentioned can be incorporated into the existing health care system. Integration into reproductive health programmes is probably the most appropriate way to achieve this objective. A multitude of prevention approaches can be feasibly integrated, at the primary health care level, within the reproductive health programmes already operating in the country, such as the maternal and child health care clinics and family planning clinics. Although some additional training and resources will be required, the potential benefit is considerable in terms of reduction of suffering as well as reduction of the health and economic burden related to the care of patients with genetic and congenital disorders.

The interventions that need to be integrated can be applied: a) before and during pregnancy and b) after delivery for the neonate.

Before and During Pregnancy

Preconception information and services for family planning can help to reduce the number of high-risk pregnancies related to increased parental age. Advice should be given to couples to complete their intended family size preferably before the age of 35 years for women.

The incidence of chromosomal disorders and spontaneous abortion rises rapidly with maternal age after the age of 35 years (Modell et al., 1992). Disorders due to new dominant mutations increase with advanced paternal age. Families should be informed of these risks. When family planning is generally available and couples are aware of the genetic risks associated with advanced parental age, they tend to curtail reproduction once they have reached the desired number of children. This leads to a selective fall in births to older parents. In western Europe, for example, the percentage of children born to women over 35 years fell from more than 20% to about 6% between 1950 and 1975 (Wald et al., 1988).

Miscarriage is strongly associated with maternal age: after the age of 40 years, over one-third of recognized pregnancies miscarry (Modell et al.,1992). Miscarriage is a common cause of maternal morbidity, with associated blood loss and risk of anaemia and folate deficiency. In addition, between the ages of 40 and 47 years, the risk in each pregnancy of a liveborn child with a serious chromosomal disorder rises from 1.5% to 8%. A relatively large proportion of children are now born to older mothers (16%-19% to mothers over 35 years, 3%-7% to mothers over 40 years).

It is also worth noting that a reduction in the proportion of older fathers reduces the rate at which new mutations enter the population, and this initiates a gradual long-term decrease in the frequency of inherited disease. Family planning, when widely available, is used preferentially by older couples and can reduce the prevalence of genetic problems related to parental age.

In the presence of a hereditary disorder in the family, taking a good family history will help to detect high-risk couples who can then be offered genetic counseling and referral to specialized canters if indicated.

When the couple is informed of the possibility that they are at an increased risk of having a genetically abnormal child, they can choose to plan conceptions according to medical advice and can make use of the genetic services available. Since primary prevention of genetic disorders depends largely on preconception information, screening and counseling, there is a strong case for including these approaches in primary health care services. Basic training and education of primary health care workers in the field of genetic counseling, detection and referral of high-risk

families can be integrated in their training courses. These courses should include following facts into consideration.

1. training in taking and recording a basic genetic family history, taking account of the complexities of large families with multiple consanguineous marriages;
2. guidelines on detecting possible genetic risks (e.g. history of previous stillbirth, neonatal death, congenital malformation, multiple abortion or hereditary blood disorder in the family);
3. guidelines on lines of referral and clear information on specialist services available;
4. training in the basic ethical principles and techniques of genetic counselling.
5. *Prevention and management of sexually transmitted diseases*. Some sexually transmitted diseases such as syphilis are teratogenic and their prevention and early treatment can prevent congenital malformations in the baby.
6. *Immunizing against rubella*. The possibility of rubella infection should be brought to the knowledge of women before conception. It may be desirable to test for immunity to rubella prior to pregnancy and to offer immunization to those who are seronegative.
7. *Screening for rhesus haemolytic disease*. It is essential to confirm that screening for rhesus blood group and antibodies is a routine component of pregnancy care and that adequate supplies of anti-D immunoglobulin are available.
8. *Treatment of existing conditions*. Women with insulin-dependent diabetes mellitus have about a 6% risk of having a seriously malformed child in each pregnancy. They can greatly reduce the risk by meticulous glycdemic control which must be started before pregnancy because major malformations are determined very early during embryonic development.
9. *Advice regarding nutrition and iron/folate supplementation*. Throughout the reproductive years, and particularly preconception, there is strong evidence that an optimal diet reduces the frequency of unsuccessful pregnancy outcomes and severe congenital malformations. Supple-menting women's diet with vitamins, including folate, prior to and in the first months after conception reduces the risk of fetal neural tube defect and also of some other congenital malformations (Czeizel, 1993). When fertility is high, as in India, it is not easy to identify a preconception period and it may be preferable to supplement women's diet throughout their reproductive span. Because of the high prevalence of iron deficiency anaemia and iodine deficiency, supplementation with iodine and iron may be considered. Information regarding the deleterious effects on the developing embryo of smoking, alcohol intake, unsupervised medication, exposure to X-rays and certain mutagens at the workplace should be made available to women prior to pregnancy.

Information on the availability and implications of carrier testing for specific genetic disorders common in the society, such as haemoglobin disorders and G6PD deficiency, should be provided to families at risk.

After Delivery for the Neonate

Neonatal screening programmes for some genetic disorders, where early diagnosis and management could ameliorate the clinical picture, are being implemented in several countries. These may include neonatal screening for phenylketonuria and other inborn errors of metabolism, for sickle-cell anaemia and G6PD deficiency and for congenital hypothyroidism. Midwives or nurses can take heel-prick blood samples and the drops of blood can be collected on to filter paper which is then posted to a neonatal screening laboratory. These programmes require specialized laboratory services, which already exist in many countries.

Training programmes for midwives can be conducted to facilitate the diagnosis of congenital abnormalities and prompt referral of affected neonates to appropriate centres.

CONCLUSIONS

The considerable challenge posed by genetic disorders and congenital abnormalities calls for the development of prevention programmes through the establishment of community genetics services. The strategies proposed in this article do not necessarily require sophisticated technical facilities but are primarily based on strengthening training of health professionals and public education. However, the molecular revolution that has characterized the past two decades has introduced into medical practice many procedures that help in the diagnosis and prevention of

genetic diseases, and it is important for countries like India to take account of these developments. Such technology can be introduced gradually into national prevention programmes.

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ABSTRACT There have been amazing advances in embryology, teratology, reproductive biology, genetics, and epidemiology in the past 50 years that have provided scientists and clinicians with a better perspective on the causes of congenital malformations. We still cannot provide the families of children with malformations a definitive

diagnosis and cause in every instance. The most common known cause is genetic, but the largest group, unfortunately, is unknown. In this review we have discussed the genetic causes for such malformations.

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