

Genetic Factors

Embryonic development is regulated by the genome of the fertilized egg. Modern genetic studies have identified numerous specific genes which direct normal development. Abnormalities in the genetic material can result in maldevelopment with congenital malformations as results. Abnormal genes can be inherited from one or both of the parents or may have been formed as mutations at the formation of sperm or egg cells. Mutations occurring in somatic cells during embryonic or fetal development are not likely to cause malformations but may cause tumors.

Little is known about factors which can increase the risk for a non-inherited chromosome anomaly with the exception of the increased risk with maternal age. Other factors have been discussed like high parity or paternal age but they are probably of less significance.

If we use Down syndrome as a model for trisomy, the presence of the extra chromosome 21 results in a large number of abnormalities in the infant, including mental retardation and deviations in facial and other structures. Major congenital malformations also occur at an increased risk, for instance, a large proportion of these infants have cardiovascular defects, and also other major malformations like duodenal atresia are common. Some studies have been made in order to identify non-genetic factors which could influence the occurrence of major malformations in Down syndrome children but with little success. One way of reasoning is that the presence of the extra chromosome is such a dominant cause of, for instance, the cardiac malformation that non-genetic factors play no observable role. Another way of reasoning is that the trisomic genotype could be especially sensitive to environmental factors and therefore could be used to identify such risk factors (Shapiro 2003). One example of this type of study is that by Torfs and Christianson (1999) who found an effect of maternal smoking on the occurrence of cardiac defects in infants with Down syndrome.

For the analysis of causes of specific malformations, cases with a known chromosome anomaly are usually

excluded. A corresponding situation will exist in conditions with a monogenic background – also here could non-genetic factors influence the phenotypic expression of the genes, for instance, in the form of malformations associated with the genetic syndrome. Obviously it is of interest to identify factors which can increase the risk for mutations but this is a difficult task due to the low frequency of conditions caused by new mutations. Mutations in sex cells can occur long before conception, notably in women. Factors causing mutations (mutagens) may differ from factors which directly disturb development (teratogens).

In analogy with what was said about chromosome anomalies, an exclusion of conditions which are monogenic can also be made but the number of such conditions is low and the exact identification of monogenic cases is often difficult at least in large epidemiological studies. This means that if some factor is identified which is associated with an increased occurrence of, for instance, microcephaly, the estimated risk will be too low because a substantial proportion of such cases are genetic.

A much more common problem is that there is a genetic component in the origin of a specific malformation; examples are orofacial clefts or hypospadias. The genetic risk is not as high as in the cases with monogenic conditions. It may either be a monogenic condition where the gene has a low penetrance or – more commonly – a polygenic situation when a number of genes contribute. In this situation, one often finds an excess of the malformation in question in the family tree but the recurrence risk in a sibship is usually moderate.

Should cases with a family history be removed in an analysis of non-genetic risk factors, alternatively, adjustment for family history be made? The answer to this question is not evident. On one side it can be argued that the presence of a genetic component, observed as a positive family history, may reduce the effect of a non-genetic causative factor which would argue for removal of such cases. On the other hand it is possible that the non-genetic factor acts together with the gene(s) and removal of cases with a known or suspected

genetic component would then reduce or even eliminate the effect of the non-genetic factor. Absence of a known family history does not exclude the presence of specific genes involved in the origin of the malformation. If the material is large enough and family histories are known well enough, a stratification into cases with and without family history can be made, but this is seldom possible. In some instances, specific genes of importance for a certain malformation have been identified and efforts have been made to study the effect of non-genetic factors in the presence or absence of these genes but numbers have been restricted and it has been difficult to draw any firm conclusions (Lammer et al. 2004; Chevrier et al. 2008).

Non-genetic Factors

Which non-genetic risk factors should be studied? Some are relatively easy to define and identify even in register studies, e.g., maternal age and parity, race or ethnicity, socioeconomic variables like education. Other factors necessitate more detailed data like maternal smoking, BMI or drug use but at least in some populations there are such data available, collected prospectively or available by record linkage. Some factors may be available in crude form like occupational exposures or ambient pollutant exposure. Information on occupation may be retrieved from various sources but is often so crude that it does not give adequate information on actual occupational exposure. For many other exposures the only reasonable way to get information is via interviews or questionnaires which means retrospective exposure ascertainment which will carry marked risks for bias as will be discussed in a later Chapter. Examples of such factors are nutrition, common virus infections, use of hot tub baths or sauna. It would be theoretically possible to build up data bases with such information collected prospectively during pregnancy and large enough to permit analyses of malformations but as far as I know there are none available.

In the present text, analyses have been restricted to variables which have been collected prospectively in the Medical Birth Register. Table 2.1 summarizes these variables and give some background data. Table 2.2 presents total numbers in the various sub-groups with exception for drugs use which are listed in Table 2.3.

Data in MBR were obtained from copies of medical documents. Information on smoking in early pregnancy, pre-pregnancy weight and height (from which BMI was calculated), and family situation was obtained from midwife interviews that were made at the first antenatal care visit, usually during weeks 10–12. Also information on drug use was obtained from that interview – the drug names were written down in clear text and then transferred into ATC codes centrally. All medical documents in all hospitals in the country were identical.

There is a complex interaction between various variables. Figure 2.1 illustrates how maternal age and parity affect percentage of smokers (among women with known smoking habits). It shows both a distinct effect of maternal age within parity and of parity within age class. Similar graphs can be made for other exposures. Figure 2.2 illustrates use of antidepressants in early pregnancy. There is a clear increase in use with age but at the same age, parity 2 has a tendency to lie below other parities up to the highest age group.

In the analysis of drug effects a complication occurs because women using one type of drug may also use other drugs in excess as amply shown by analyses of concomitant drug use (Källén 2009). Thus for instance women who use antidepressants may also use mood stabilizers like anticonvulsants and if such drugs have a teratogenic effect, it may affect the risk estimated for antidepressants. Such an effect necessitates that there is an excess use of a drug with teratogenic effects linked to the drug under study. It is, however, also possible that two or more drug categories act synergistically as suggested by Oberlander et al. (2008) for antidepressants and benzodiazepines. Reis and Källén (2013) could, however, not verify this observation.

Table 2.1 Summary of variables used for risk analyses

Variable	Source	Categorization
Year of birth	MBR	One-year 1998–2010
Maternal age	MBR	<20, 20–24, 25–29, 30–34, 35–39, ≥40
Parity	MBR, SCB	1, 2, 3, ≥4
Smoking	MBR (midwife interview)	Unknown, no, <10 cigs/day, ≥10 cigs/day
BMI	MBR (midwife interview)	Unknown, <19.8, 19.8–24.9, 25–29.9, 30–34.9, 35–39.9, ≥40
Cohabitation	MBR (midwife interview)	Unknown, cohabiting, non-cohabiting
Mother born outside Sweden	SCB	Unknown, yes, no
Maternal drug use in early pregnancy	MBR (midwife interview)	Specified after 7-digit ATC code when possible, otherwise in clear text
Maternal pre-existing diabetes	MBR, ICD-10 code	Yes, no

MBR Medical Birth Register, *SCB* Statistics Sweden, *ATC* Anatomical Therapeutic Chemical classification, *ICD-10* International Statistical Classification of Diseases and Related Health Problems, 10th edition

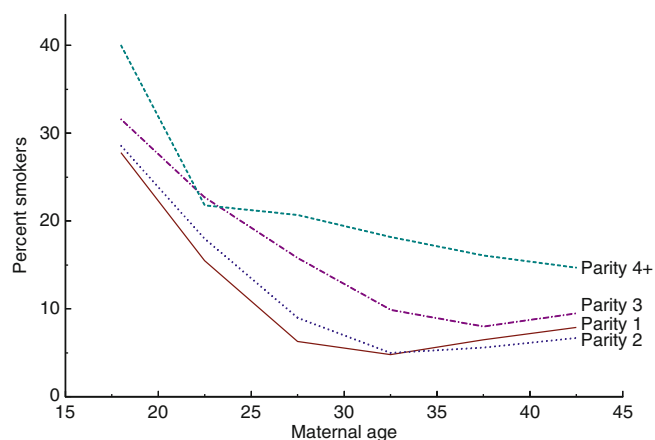
Table 2.2 Numbers in various subgroups in the population

Variable	Subgroup	Number of women	%	Number of children	Variable	Subgroup	Number of women	%	Number of children
Year of birth	1998	84,369	6.7	85,803	Smoking	Unknown	83,153	6.6	84,804
	1999	84,652	6.7	86,048		No	1,072,755	84.9	1,088,600
	2000	87,935	7.0	89,274		<10 cigs/day	78,334	6.2	79,422
	2001	89,067	7.0	90,494		≥10 cigs/day	29,544	2.3	30,033
	2002	92,108	7.3	93,537	BMI	Unknown	158,579	12.5	161,420
	2003	95,818	7.6	97,433		<19.8	94,544	7.5	95,664
	2004	98,570	7.8	99,972		19.8–24.9	612,470	48.5	621,353
	2005	98,514	7.8	99,889		25–29.9	275,253	21.8	279,542
	2006	102,780	8.1	104,248		30–34.9	87,390	6.9	88,738
	2007	104,065	8.2	105,522		35–39.9	26,324	2.1	26,767
	2008	105,696	8.4	107,224		≥40	9,226	0.7	9,375
Maternal age	2009	107,362	8.5	108,921	Family situation	Unknown	76,370	6.0	77,887
	2010	112,850	8.9	114,494		Cohabiting	1,120,476	88.7	1,137,135
	<20	22,468	1.8	22,622		Non-cohabiting	66,940	5.3	67,873
	20–24	164,861	13.0	166,344	Mother born outside Sweden	Unknown	13,575	1.1	13,892
	25–29	389,110	30.8	394,094		Yes	244,502	79.6	247,845
	30–34	439,284	34.8	446,588	Pre-existing diabetes	No	1,005,709	19.3	1,021,122
Parity	35–39	207,450	16.4	211,739		Yes	2,403	0.2	2,448
	≥40	40,613	3.2	41,472		No	1,261,383	99.8	1,280,411
	1	564,520	44.7	564,834					
	2	455,149	36.0	463,969					
	3	169,841	13.4	176,238					
	≥4	74,275	5.9	77,817					

Percentages are calculated on total number of women (1,263,786). Number of children: 1,282,859

Table 2.3 Drug groups reported by the women in early pregnancy

Drug group	ATC codes	Number
Drugs against GERD	A02B	11,259
Aminosalicylic acid	A07EC	3,138
Multivitamins	A11A	75,021
Vitamin B12	B03BA	5,956
Folic acid	B03BB01	73,992
Antihypertensives	C02, C07-C09	4,635
Oral contraceptives	G03A	3,714
Gestagens	G03D	6,315
Ovarian stimulators	G03G	2,441
Systemic corticosteroids	H02AB	4,490
Thyroxine	H03A	20,356
Antibiotics	J01	35,568
Antifungal drugs	J02	770
Cytostatics	L01	116
Immunosuppressants	L04	986
NSAID	M01A	21,691
Opioids	N02A	6,745
Minor analgesics	N02B	93,023
Drugs for migraine	N02C	3,333
Anticonvulsants	N03	3,657
Neuroleptics	N05A	3,668
Sedatives/hypnotics	N05B, N05C	6,121
Antidepressants	N06A	20,382
Drugs for rhinitis	R01	15,692
Antiasthmatics	R03	37,929
Cough medicines	R05	5,547
Antihistamines	R06	74,137

**Fig. 2.1** Per cent women who smoke for each maternal age and parity class

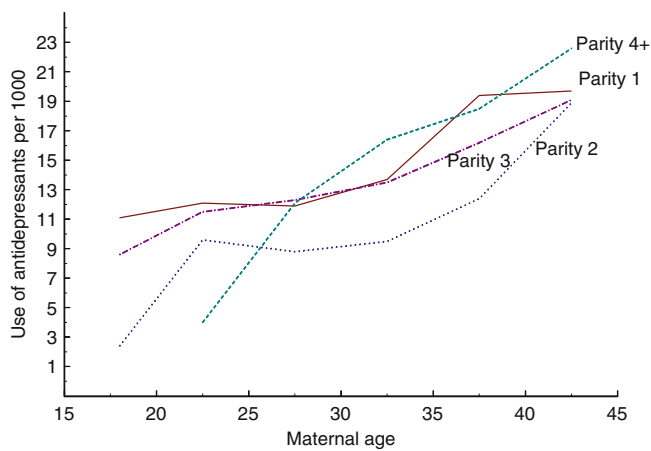


Fig. 2.2 Pro mille women who used antidepressants in early pregnancy for each age and parity class

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