# A CONCEPTUAL MODEL OF FETO-INFANT MORTALITY IN LATE AND LOW FERTILITY CONTEXT[1]

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## 1 Introduction

Many researches have been undertaken in order to detect the influence of social and biological factors on feto-infant mortality. The epidemiological and medical literature focuses more on the biological factors while the demographic literature focuses on social factors. The awareness by social scientists of the importance of linking both types of factors in order to understand the feto-infant mortality process is not new however (*e.g.* Gortmaker (1979), Mosley and Chen (1984), Cramer (1987)). In other words, authors generally recognise that the search for the determinants of feto-infant mortality has to pass through a conceptual framework, namely a comprehension of the direct and indirect mechanisms leading to feto-infant death. Simplifying the pathway, socio-economic factors influence biological factors which ultimately play a role on feto-infant mortality. The general idea behind the construction of a conceptual framework is to highlight the causal mechanisms leading to a particular event, in this present case to feto-infant death. Based on a conceptual framework, any relation has to be interpreted from a causal point of view rather than a simple association between two or more variables.

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In the context of the developed countries, some studies set up their empirical model of the determinants of infant mortality on a conceptual model. Due to the huge number of socio-economic factors affecting infant mortality and the risk of detecting spurious association (due to the high correlation between potential social factors), Cramer (1987) has developed a conceptual model of infant mortality. Based on this conceptual model, his objective is to use a causal modelling approach in order to detect direct and indirect effects of the socio-economic factors. Hopeless Cramer limited his conceptual framework on the indicators he has access to (birth and infant death records from single livebirths in California - 1978). More precisely he considers that maternal age, marital status, race and education (socio-economic factors) influence birth order, birthweight and prenatal care (intervening variables which finally influence the infant mortality). A statistical tool (hierarchical log-linear model) is applied in order to control for spurious association and to test interaction. Cramer does not at all control for the impact of the unobserved variables however. He can consequently not interpret his results from a causal perspective. Indeed, unobserved factors might again lead to spurious association. Sharma (1998) limits also his conceptual framework to the available variable of interests. His conceptual framework is composed of two social factors (maternal education and marital status) and several proximates determinants (health care, gestation duration, birthweight, maternal age, birth intervals and intergenerational risk). Based on this model, nested logistic regression is used to implement the causal structure proposed in the conceptual framework. Analysing infant survival in the Czech Republic, Rychtařýková and Demko (2001) highlight also the direct and indirect mechanisms through which socio-demographic factors (maternal age, birth order, marital status, maternal education and region of living) influence infant mortality. They consider only gestation duration and birthweight as proximate variables. The same comment as earlier can be made...the conceptual model is limited to available information! Before making use of any statistical tools, Matteson et al. (1998) think about a conceptual model of infant mortality independently of the indicators they are going to use in the empirical model. The framework is made of three main components: the proximates determinants (biological determinants), the background determinants (the mother's social, demographic and economic characteristics) and the community factors (the characteristics of the community in which the mother and the child live). The suggested model is however too broad and there is a lack of information on the different mechanisms through which each determinant influences directly or indirectly infant mortality. The concep-

tual model is consequently not useful to study the determinants of infant mortality from a causal point of view.

Known as high indicators of infant morbidity/mortality, numerous researches have been interested in the risk factors of preterm birth and of low birth weight. In such a context, some conceptual framework have also been proposed. For example, Misra et al. (2001) include three main concepts in the causal chain leading to preterm delivery. Social factors (such as socio-economic status and race) influence the psychosocial factors (stress, pregnancy locus of control, depression...) which ultimately influence biomedical factors (chronic diseases, complications of pregnancies and health behaviours). Finally, the biomedical factors influence the risk of preterm birth. Note that the authors include also a direct effect of the social factors on the biomedical factors. The impact of these factors on the risk of preterm birth is obtained using multiple logistic regression (sequential model building) and by comparing parameters of these regressions. Kramer et al. (2001) suggest also a causal pathway from socio-economic status to preterm birth. They emphasize two particular pathways. The first one going through chronic and acute stress factors, the second one through the combined effect of a genetic defect and low folate intake. Their model, while quite documented and well constructed, appears however too narrowly targeted to these two intermediary factors. Other important factors (such as prenatal care) are not integrated in the model, which can leads to spurious associations. Other researchers present conceptual model of preterm birth or of low birth weight but limit themselves to the impact of certain biological factors or of particular selected behaviours on the risk of preterm birth (*e.g.* Sheehan (1998): impact of stress on low birth weight).

These few examples show that the suggested conceptual models of feto-infant mortality or morbidity generally focus on specific variables of interests and, more damaging, are limited the available information, namely the indicators available from a particular database. This last argument makes it difficult to distinguish between the conceptual framework and the so-called operational framework, precludes interpretation in terms of causal effects and makes difficult the decomposition of the effects of the determinants of feto-infant mortality into direct and indirect effects. The objective of this paper is consequently to propose a conceptual framework of feto-infant mortality, in a late fertility context. The model must of course simplify the reality in order to highlight the main relevant causal mechanisms and make the model testable. It must also be independent upon the indicators which will be used later on in order to estimate causal effects. In such a way, it will become possible to detect the impact of the non ob-

served concepts on the causal interpretation. Being aware of the complete theoretical pathway allows to detect, in the estimation, the presence of spurious association due to non observed variables and to interpret the results consequently.

The set of causal pathways leading to feto-infant death is based on an review of the demographic, epidemiological and medical literature on the determinants of feto-infant mortality in late and low fertility countries. The intention is clearly not to make a meta-analysis of the determinants of feto-infant mortality but clearly to highlight the main causal mechanisms.

## 2 General pathway

Feto-infant death is always caused by failures of biological variables. Indeed, a fetus or a child is not dead because its parents have a specific occupation or because he lives in a polluted region. At most, the characteristics of the parent's occupation or of the region might influence the biological characteristics of the infant which, consequently, influence mortality. Figure 1 represents these mechanisms. Socio-economic variables (*e.g.* the occupation of the parents), behavioural variables (*e.g.* smoking or drinking habits) and environmental characteristics (*e.g.* region of living) might influence the biological variables of the fetus, the infant or the mother. Those biological variables will then influence the risk of feto-infant mortality. Note that the biological variables are called *proximate variables* because they have a direct effect on the risk of mortality. The relation between each variable is represented by an arrow indicating the causal relation between variables. Absence of directed arrows does not exclude association between characteristics but they exclude causal association. In Figure 1 feto-infant mortality is determined by five groups of variables: socio-economic characteristics, environmental characteristics, parental age, behavioural characteristics and biological characteristics. The highlighting of parental age is justified by the context of interest, namely late fertility.

## 3 Specific pathways

In this section, the potential relations between parental age, socio-economic variables, behavioural variables, biological variables, and feto-infant mortality are considered. With respect to the general pathway presented in section 2, biological characteristics are decomposed in three categories: maternal characteristics, fetal characteristics and obstetrical characteristics

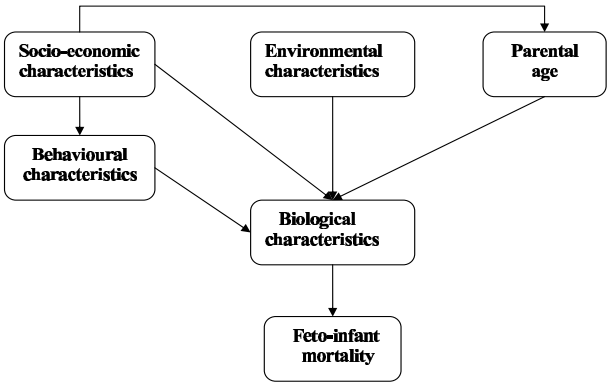


Figure 1: General pathway of feto-infant mortality

which are considered as the three main groups of causes of feto-infant mortality. Maternal age and paternal age are also represented by two distinct boxes. Indeed, (biological) mechanisms of ageing are not similar for men and for women. The different groups of determinants of feto-infant mortality are well-known concepts but include many potential indicators. They are consequently defined more precisely. The socio-economic characteristics of the parents include classical socio-economic variables such as income, marital status, education level or occupation of the parents. The behavioural characteristics combine several behaviours of the parents during pregnancy and after delivery: smoking and drinking habits, nutrition *etc.* They include also attendency of pre- and post-natal care consultations (frequency and calendar) . Environmental characteristics gather the characteristics of the region of living (or of working), such as housing conditions, pollution (around home or at work), climate *etc.* The concept of pollution is very large: it includes air, ground, water or food pollution. The maternal characteristics are grouped into two categories. The first one is the reproductive history of the mother which includes events such as the number of previous live births, the number of previous stillbirths or the number of previous spontaneous abortions. The general health state of the mother during pregnancy and (possible) breastfeeding is the second category. The fetal characteristics include all the characteristics describing the child at birth, *i.e.* weight, dysmaturity, gestation duration, potential presence of congenital anomalies, sex, parity... The obstetrical characteristics include all variables linked to complications occurring during the delivery and to

the conditions of the delivery. Finally, feto-infant mortality refers to deaths coming from clinically identified pregnancies until the first year of life of the infant (from birth)[3].

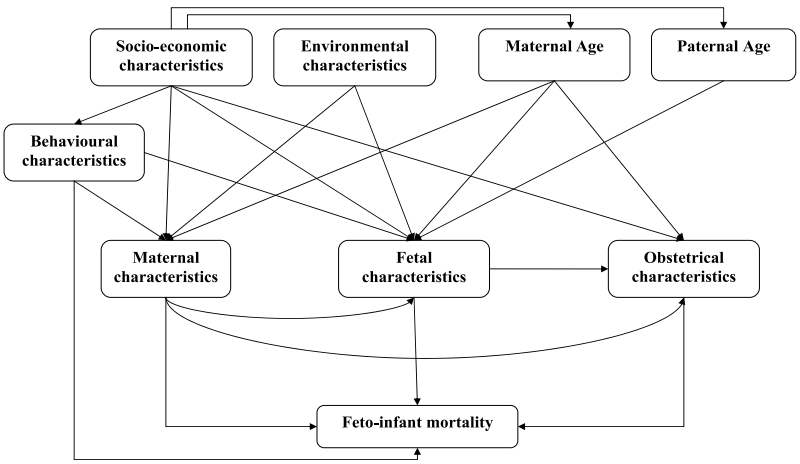


Figure 2: Conceptual framework

Figure 2 shows the causal pathways expressing all potential relations when decomposing the biological variables into the three categories presented above. At this stage attention should be given to some particular relations: the potential links between parental age, socio-economic variables and the three main biological variables. The socio-economic variables might have an effect on the behavioural characteristics, on the maternal characteristics, on the fetal characteristics and on the obstetrical characteristics. Paternal age seems to influence the fetal characteristics only. Maternal age influences the maternal characteristics, the obstetrical characteristics and the fetal characteristics. In this figure, the behavioural characteristics have a direct effect on mortality. This is justified in the next section.

Congenital anomalies[4] are one of the main causes of feto-infant mortal-

[3]The classical definition of feto-infant mortality includes only pregnancies from 20 weeks of gestation (or from 500gr.). In this conceptual framework, fetal mortality includes also miscarriages (spontanous expulsion of the baby before the $20^{th}$ week of gestation).

[4]Congenital anomaly is an *abnormality of structure, function or body metabolism that is present at birth (even if not diagnosed until later in life) and results in physical or mental disability, or is fatal* (March of Dimes Resource Center (1998)). Congenital anomalies can be caused by genetic factors, environmental factors or a combination of both. The genetic factor

ity. Statistics for Brussels (Belgium), for the period 1998-2002, show that 20% of feto-infant mortality is linked to congenital anomalies (Observatoire de la santé et du social, 2004). Furthermore, an important risk factor of congenital anomalies is maternal age. While, until recently, interest lies exclusively on maternal age, interest for paternal age as risk factor of congenital anomalies takes more and more interest. In order to take these facts into account, the fetal characteristics are decomposed into two groups of variables: the congenital anomalies and the physical characteristics of the newborn. The physical characteristics of the child at birth include ”observable” characteristics of the newborn, such as weight, sex, parity, multiple births or gestation duration, that are not associated to congenital anomalies.

*Remark*: Some of the congenital anomalies influence the weight at birth or the gestation duration, the two main physical characteristics of the newborn. It is consequently necessary to distinguish variation in birthweight or in gestation duration caused by the congenital anomalies from those caused by others determinants. In other words, if a child is born with a low birth weight due to a specific congenital anomaly, I consider its death will be classified, in this paper, within the congenital anomalies as cause of death and not in the category low birthweight.

# 4 Description of the mechanisms through a literature review

Figure 3 extends the causal diagram presented in Figure 2 by decomposing the fetal characteristics into the two variables presented above, namely congenital anomalies and the others biological characteristics of the child at birth. The conceptual model includes consequently nine determinants of feto-infant mortality which have either a direct either an indirect impact or both on feto-infant mortality. The presence of a direct arrow is justified by results found in the literature. At the opposite, the absence of a directed arrow means that, taking into account the actual knowledge in the field, no causal relation can be affirmed. The presence of a causal relation has to be justified by behavioural, cultural or biological mechanisms. A unique ‘*statistically significant*’ result cannot be used for considering a relation as

can be decomposed into abnormalities of the gene itself, or abnormalities in the structure or in the number of chromosomes. When the child inherits a genetic disease from one of its parents, this is called a dominant inheritance (the parent could still not present any anomalies). When both parents give the same abnormal gene to the child, this is called a recessive inheritance (again both parents could still not present any anomalies).

causal. Replication of identical statistical results might however lead to a presumption of causality.

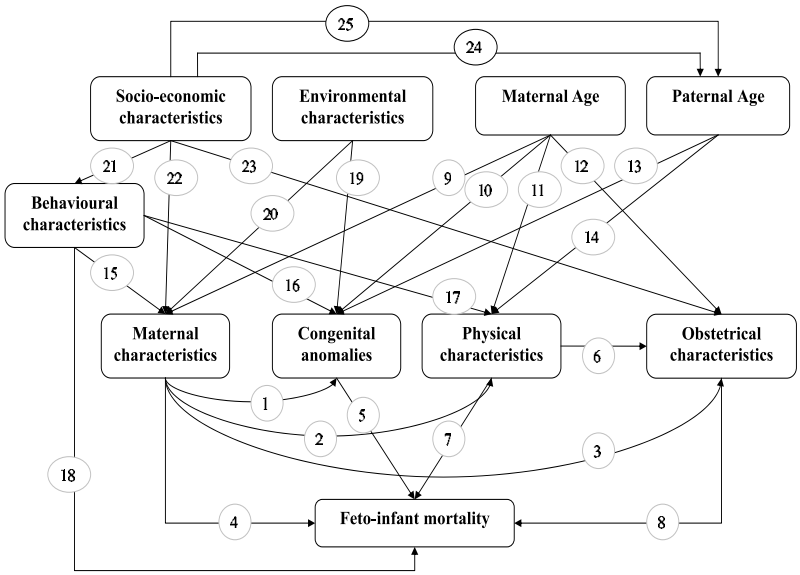


Figure 3: Conceptual schema: decomposition of the fetal characteristics

## 4.1 Maternal characteristics

The maternal characteristics include reproductive history but also the general health state of the mother. It seems that mother's health state has an impact on the risk of congenital anomalies. Past researches in medicine show that a deficiency in vitamins B-12, obesity or diabetes are risk factors of congenital anomalies. For example, Waller et al. (1994) found that obesity might be a risk factor of congenital anomalies and more particularly of neural tube defects. Their study is based on women living in California and Illinois; 1370 women participated in the survey (836 mothers having an offspring with congenital anomalies and 534 without). The effect is still present after controlling for maternal age, race, education and family income. Moore et al. (2000) found a significant relation between major non chromosomal congenital defects and obesity or diabetes. 22 951 pregnant women have been included in the sample (prospective cohort study). No covariates have however been introduced in the statistical model (logistic

regression). Garne (2004), in a short review of the literature on the link between maternal diabetes and congenital anomalies, mentions that *the risk of congenital malformations for diabetic pregnancies even with optimal metabolic control is at least twice as high as for non-diabetic pregnancies*. During pregnancy, some medications could increase the risk of congenital anomalies. For example, Robert (2004) mentions that the increasing risk of congenital anomalies with maternal epilepsy is *partly attributable to the teratogenicity of the drugs used to treat epilepsy*. These studies (and many others) suggest a directed arrow going from maternal characteristics to congenital anomalies (①).

Several maternal characteristics influence also the physical characteristics of the child (②). Berkowitz and Papiernik (1993), in their review of the literature on preterm birth, mention past obstetrical history and prenatal care as two important factors influencing preterm birth. The same study excludes, however, a causal relation between induced abortion and prematurity. This last relation is controversial. Indeed, recent studies have found a significant effect of past induced abortion on prematurity. For example, **?** argue for a higher risk of prematurity for women with at least one previous induced abortion. The authors mention that this significant effect might be due to a better declaration of induced abortion. Based on a review of the literature from 1966, Rooney and Calhoun (2003) conclude that past induced abortions are a risk factor of prematurity. Biological mechanisms linking induced abortions to preterm births are namely incompetency of the cervix[5], infections.... Basso et al. (1998) found previous spontaneous abortion being a risk factor of preterm delivery and growth retardation. The authors evaluate the risks by multivariate logistic regressions. The database is relatively important (55 201 observations from the National Board of Health and Statistics, Denmark). Different covariates were included in the regression: maternal age, social status and interpregnancy interval. Birthweight might also be influenced by the mother's weight and the last interpregnancy interval. Haram et al. (2002) mention that excessive maternal weight gain and obesity are two risk factors of fetal macrosomy [6]. In their review of low birth weight risk factors, Shiono and Behrman (1995) mention low maternal weight gain and low prepregnancy weight as two major risk factors of low birth weight and preterm birth. Concerning birth interval, Conde-Agudeli et al. (2006) did a meta-analysis (from 1966

[5]Cervix which is too weak to stay closed during a pregnancy.

[6]Large for gestational age fetuses, *i.e.* either a fetal weight of above 90th percentile, or a birth weight of above 4000 g or 4500 g, or a birth weight of greater than +2 standard deviations from the mean. (Haram et al. (2002)).

to 2006) on birth spacing and different risks of perinatal outcomes. They conclude that preterm birth, low birth weight and small for gestational age are dependent upon birth interval. Severe maternal fever during pregnancy might also shorten gestation duration.

Reproductive history of the mother influences both the conditions of delivery and potential complications. For example, the mode of delivery of the previous pregnancies influences the current pregnancy's mode of delivery. Maternal health status might also influence the delivery's condition. For example, obesity and gestational diabetes are risk factors of shoulder dystocia[7] (Haram et al. (2002)). Note that this relation could be partly due to an increasing risk of macrosomy with maternal obesity or diabetes but it seems however reasonable to introduce a causal relation between maternal characteristics and obstetrical characteristics (relation ③).

Reproductive history might also influence the feto-infant mortality (relation ④). Selvin and Garfinkel (1972) show that birth order has an impact on the risk of fetal loss. Their study is based on 1,5 million pregnancies occuring in the State of New York. Data were collected during 1959 and 1967. In order to avoid a spurious relationship[8], the authors include maternal age as well as paternal age in their model. Many studies have also concluded that longer births intervals decrease the risk of feto-infant death. The negative relation between short birth interval and mortality is often explained by two main hypotheses: maternal depletion [9] or sibling competition [10]. Note however that both hypotheses are more influential in the developing countries where the number of pregnancies is generally high. In the developed countries the mechanism of maternal depletion might still be considered but causes rather prematurity than mortality. However, as noted in Miller (1989), the mechanism of maternal depletion "*may be implausible in the context of developed countries, because inadequate nutritional intake during the reproductive period is not likley to affect the majority og women in those populations*". A direct link between birth interval and feto-infant mortality is consequently not considered in the present context. Note that from a methodological point of view, the causal impact of interpregancy interval on feto-infant morbidity/mortality is not easily detected due to the fact that interpregancy interval includes most of the time the con-

[7]The infant's shoulders get stuck after the head has already been delivered.

[8]The estimated parameters of a regression might not express a causal relationship. This might be due to a high correlation with a latent factor. This is called a spurious relationship.

[9]Mother with short birth interval does not have sufficient time for recovery - both physically and nutritionally.

[10]Sharing limited resources which do not increase with arrival of a new child.

ception interval and the length of gestation. Past fetal losses and past infant deaths might also explain part of the feto-infant mortality. The argument is linked to the reproductive capacity of women: the number of previous fetal and infant deaths might represent the observable events of a deficient biological mechanism of the reproductive capacity of the mother. Note that the direct impact of maternal characteristics on feto-infant mortality is considered as a direct pathway but it includes intermediary biological variables which are not represented for simplification concern.

## 4.2 Congenital anomalies

In the conceptual schema, the presence of congenital anomalies has only an influence on the feto-infant mortality (arrow ⑤). As stated in the definition of the concept, congenital anomalies lead also to physical disability or to mental disability but they are not of concern in the present context. Santé Canada (2002) mentions that the some severe congenital anomalies are close to 100% lethal. Concerning miscarriages, approximately 60% of them are due to chromosome abnormalities (Seller (2004)).

## 4.3 Physical characteristics of the child at birth

The physical characteristics of the child might have a causal impact on the obstetrical characteristics (arrow ⑥) and on feto-infant mortality (arrow ⑦). An important increase in weight of the child by the end of the pregnancy may influence the mode of delivery. In case of macrosomy, the risk of a difficult delivery or of a caesarean increases. As an exemple, Haram et al. (2002) analyse different problems linked to macrosomic fetusses (large for gestational age). The study is based on a review of the literature. They found that a delivery by caesarean section is more often applied in case of macrosomy. This avoids the complication due to a difficult shoulder delivery (shoulder dystocia). Multiple births also make the conditions during delivery more difficult (*e.g.* increasing risk of cord accidents or of malpresentation).

A fetus needs 37 weeks of gestation for being fully developed. Consequently, the infant mortality (and early neonatal mortality more particularly) decreases with gestation duration. A minimal gestation duration is required for the fetus to be considered viable at birth. Similarly, infant mortality decreases with weight at birth, and a minimal condition is also required for viability at birth. It is extremely difficult to find a compromise on the precise limits of viability, either in terms of gestation duration or in

terms of weight at birth. A birthweight of at at least 500 gr. or a gestation duration of at least 22 weeks are the minimal thresholds recommended for declaration by the World Health Organization (see Gourbin and Masuy-Stroobat (1995)). However, the definition of viability might also influence the minimal requirements: do we consider that the child at birth should be viable independently of medical technology or not? In the first case, the conditions of viability will depend upon the medical progress. Birthweight and gestation duration seem to be the most important direct determinants of infant death. Shiono and Behrman (1995) note that, currently, most infants born at 24 or more weeks of gestational age survive but that very few infants survive below this gestation duration. Tough et al. (2002) mention that low birth weight (LBW) *contributes to approximately 65 % to 75 % of neonatal deaths*. Gestational age and birthweight are highly associated however. The notions of Intra Uterine Growth Retardation (IUGR) or of Small for Gestational Age (SGA) have been consequently used in order to study the impact of weight independently of the gestation duration. In this perspective, Wilcox and Skjaerven (1992) have shown that gestational age and relative weight at each gestational age are related to perinatal mortality.

## 4.4 Obstetrical characteristics

Complication during delivery and the conditions of delivery might both lead to feto-infant death (arrow ⑧). With congenital anomalies and preterm births, maternal complications during the delivery is a leading cause of infant death and particularly of the neonatal death.

## 4.5 Maternal age

Biological ageing of the mother has an impact on the maternal characteristics (arrow ⑨). Indeed, the general health status of the mother is influenced by her age. For example, older women ($> 35$) have a higher risk of hypertension or diabetes. In a late fertility context, an older mother could also envisage to reduce birth interval in order to attain the desired number of children. However, the impact of maternal age is more important on the risk of congenital anomalies (arrow ⑩). This increasing risk has been well documented (*e.g.* Boue et al. (1975); Naeye (1983); Cowchock et al. (1993); Spira et al. (1993); Eurocat (1995); Foix-L'Hélias and Blondel (2000)). Down's syndrome is the most famous congenital anomaly linked to maternal age (*e.g.* De Michelena et al. (1993)). Harper (1998) notes that maternal age might also affect the risk of congenital heart defects. A huge

number of references can be given to assess the link between congenital anomalies and maternal age, but this is not the purpose of this section. We will only here mention that a higher maternal age affect the genetic capital of the child by increasing the risk of genetic diseases leading to congenital anomalies.

Several studies have shown an increasing risk of feto-infant mortality with maternal age. These studies are often concentrated on the risk of spontaneous abortion: older women are more at risk of fetal deaths (*e.g.* Dominguez et al. (1991); Spira et al. (1993); Nybo Anderson et al. (2000); Osborn et al. (2000); de La Rochebrochard and Thonneau (2002)). Based on a prospective study of 634 272 women in Denmark (from 1978 to 1992), Nybo Anderson et al. (2000) try to isolate the impact of maternal age (at conception) on the risk of fetal death (including spontaneous abortion, ectopic pregnancy and stillbirth). The statistical model controls for the reproductive history (complete information on previous pregnancies). The study shows an increasing risk of fetal loss with maternal age (from 30 years old). The chance of a successful pregnancy outcome for a mother older than 40 is quite low. Osborn et al. (2000) study the impact of maternal age on the risk of spontaneous abortion. Contrary to Nybo Anderson et al. (2000) they include some socio-economic variables in the model: marital status and education level. Gravidity is the only variable representing reproductive history. The negative impact of maternal age on the risk of spontaneous abortion appears from 35 years of age. Some studies have also found that maternal age is a risk factor of infant mortality (*e.g.* Cramer (1987); Friede et al. (1988)). After huge theoretical considerations and references on the structure of the determinants of infant mortality, Cramer (1987) estimates the risk of infant mortality with respect to maternal age and other socio-economic variables (marital status, race and education level). Aware that some biological and behavioural factors are crucial in the analysis of infant mortality, Cramer takes also into account the weight at birth, prenatal care and parity. Whatever the level of the other explanatory variables, the study shows that maternal age becomes damaging to infant survival from 35 years of age. The database includes 289 232 single livebirths in California (1 % of the sample did not survive until 1 year). Including only birthweight as control variable, Friede et al. (1988) found also that mothers older than 35 are at higher risk of infant mortality. However, all those findings do not justify a direct link between maternal age and feto-infant mortality. The mechanism leading to feto-infant death goes through a biological variable which is affected by maternal age. Maternal age increases the risk of genetic diseases. The presence of genetic diseases leads then to

spontaneous abortions, fetal death or infant death. For fetal deaths, Nybo Anderson *et al*. mention that *a major reason for the association between maternal age and fetal loss is an increased risk of aneuploid* [11] *conceptions with increasing maternal age and the fact that auneuploid are more likely to results in a fetal loss*. These results reinforce consequently the causal effect of maternal age on congenital anomalies.

Several characteristics of the baby might also be influenced by maternal age (arrow (1)). For example l'Observatoire de la santé et du social (2004) indicates that the frequency of macrosomy (birth weight $> 4$ kg) increases with maternal age. Spira et al. (1993) or Foix-L'Hélias and Blondel (2000) found that older women are more at risk of pre-term babies. Martius et al. (1998) found also that young mothers ($<$18 years) as well as older mothers ($>$40 years) are at higher risk of preterm birth ($<$32 and $<$37 weeks of gestation). However, although these authors take some confounding variables into account, it is not evident to differentiate the biological (causal) mechanism linked to ageing of the mother from the behavioural mechanism. The latter is rarely integrated as confounding variables. An increasing risk of low birth weight has also been observed for younger or older women. This might again be explained by behavioural factors such as alcohol or smoking habits (due to the presence of financial problems, especially for younger women, or the presence of stress due to difficult work situation or familial situation). Similarly, general health status of the mother decreases with age (large number of chronic diseases such as hypertension or diabetes) which may lead to an increasing risk of preterm birth (Martius et al. (1998)). This general health status might explain part of the relation between maternal age and the characteristics of the child at birth. A direct link between maternal age and preterm birth or lower birthweight should consequently not be excluded but be interpreted with care. Maternal age has also been detected as a risk factor of multiple birth. Pison (2000) mentions that the proportion of fraternal twins increases with maternal age until 37 years, followed by a decrease. According to the same author, the risk of identical twins is independent of maternal age. Up to 37 years (of maternal age) the risk of producing multiple eggs in a same cycle increases (a cause of fraternal twins[12]). A more detailed explanation of the biological mechanisms linking maternal age to multiple birth can be found in Beemsterboer et al. (2006). However they do not agree on a decreasing risk of multiple births from 40 years of age of the mother. The biological mechanism described is similar across both studies however.

[11] Abnormal number of chromosomes

[12] Identical twins come from the division of one fertilised egg into two babies.

Finally, maternal age can also influence the obstetrical characteristics (arrow ⑫). Potential relations between maternal age and the obstetrical characteristics might often be explained by confounding factors. In a review of the literature on the clinical aspects of pregnancy after 35 years, van Katwijk and Peeters (1998) mention that *the probability of delivering vaginally decreases with advancing age*. They put forward two explanations. The increasing part of cesarean delivery due to age-related confounders such as multiple birth (multiple ovulation with medically assisted reproduction) or macrosomia (gestational diabetes) is the first one. The increase in biological weaknesses directly related to maternal age such as loss of elasticity of the pelvic joints (which increases the resistance of the birth canal during the second stage of the labour) or a reduction of the expulsion force is the second one. This last argument justifies a direct link between maternal age and obstetrical characteristics.

## 4.6 Paternal age

An important medical literature links paternal age to the quality or the quantity of spermatozoa. For example, Sartorrelli et al. (2001) show a higher frequency of sperm chromosome aberrations in older men. Rosenbusch and Sterzik (1991) mention that chromosomal abnormalities are partly due to paternal genetic factors. In particular, paternal ageing leads to new dominant autosomic mutations[13] causing congenital anomalies, such as achondroplasia, Marfan syndrome, etc (Murdoch et al. (1972); Friedman (1981); Lian et al. (1986); Risch et al. (1987); Bordson and Sears Leonardo (1991); Gavrilov and Gavrilova (1997) and (2001)). Briefly, these references suggest that paternal age also influences the genetic capital of the offspring: there is an increasing risk of genetic diseases with higher paternal age, and as a consequence, an increasing risk of congenital anomalies (arrow ⑬).

The few studies including paternal age as a risk factor of feto-infant mortality show that the age of the father seems to play a significant effect on this issue. Rychtařýková et al. (2004) found a significant effect (by logistic regression) of paternal age on stillbirths, controlling for the age of the mother, the education of father and mother, sex of the child, prematurity and biological parity. A potential confounding effect linked to multiple births is controlled by analyzing singletons only (data from the Czech

[13] A mutation occurs when a DNA gene is damaged or changed in such a way as to alter the genetic message carried by that gene. Source: http://www.brooklyn.cuny.edu/bc/ahp/BioInfo/MUT/Mut.Definition.html

Republic for the years 1986 to 1990). de La Rochebrochard and Thonneau (2002) found that *the risk of an adverse pregnancy outcome is highest if both partners are advanced in age*. The database includes 3174 last planned pregnancies (1991 and 1993) from a population-based study on women aged 25-44 years in Denmark, Germany, Italy and Spain. Parental age is represented by a unique combined variable (no separate variables for maternal age and paternal age). Different confounding factors are included in the statistical model (logistic regression): the time to pregnancy, smoking habits of the parents and past reproductive history of the mother. Slama et al. (2003) found also an increasing risk of spontaneous abortions for fathers older than 35 years. Nybo Anderson et al. (2000) have found that the risk of fetal death increases when the father is aged 44+. Wunsch and Gourbin (2002) study the impact of parental age on infant survival. A logistic regression is applied for early neonatal, neonatal and post-neonatal mortality. The database is composed of individual registration forms for livebirths and infant deaths collected in Hungary (from 1984 to 1988). In addition to parental age, the number of previous livebirths, the number of previous induced abortions, the number of previous fetal deaths, the activity of the mother and the education of the parents are considered. These variables have been included in the statistical model as covariates. The study concludes that paternal age and maternal age have both a significant effect on early neonatal and neonatal mortality (older parents increase the risk of mortality), but slighter than the other biological variables such as the number of previous livebirths, the number of previous fetal deaths and the number of previous induced abortions (see also Gourbin and Wunsch (1999)). However, the authors of all those studies highlight that the association is probably due to intermediate variables, such as the *increase in genetic damage of spermatozoa with higher paternal age* (Rychtařýková et al. (2004)). As mentioned by Nybo Anderson et al. (2000), the association between paternal age and fetal death is due to mutations of paternal origin. Those mutations lead to genetic diseases, revealed by congenital anomalies which may lead to feto-infant death. Consequently, with the same reasoning as maternal age, paternal age influences feto-infant mortality through biological variables such as genetic diseases. There should not be a direct effect of paternal age on feto-infant mortality.

The effect of paternal age on the physical characteristics of the child at birth is less documented and controversial. We found only one study in favour of a significant single impact of paternal age on birthweight. Taking into account maternal age and birth order, Selvin and Garfinkel (1972) show that older ages of fathers are a risk factor of low birth weight. 1

515 443 birth certificates from the State of New York have been analysed. More recent studies did not find a significant impact however (*e.g.* Tough et al. (2003)). While some authors found a significant impact of paternal age on gestation duration (Zhu et al. (2005)), others studies do no confirm these results (*e.g.* Tough et al. (2003)). Based on Italian data (from 1990 to 1998) Astolfi et al. (2006) and (2005) found a significant impact of paternal age on the risk of preterm birth (<37 and <32 weeks of gestation). Astolfi and her colleagues mention that *among the older (> 40 years) fathers, age-dependent alterations in reproductive functions, semen quality and fertility might contribute to the steeper increase in the relative risk* (of premature birth). This is a potential biological mechanism explaining the relation between paternal ageing and prematurity. Tough et al. (2003) mention however that it is extremely difficult to control for all potential risk factors, which explains the presence of controversial results. Although results are controversial, a causal effect justified by the potential effect of the alterations of the reproductive functions is still introduced in the conceptual framework (arrow ⑭).

## 4.7 Behavioural characteristics

Maternal health status is influenced by the smoking or alcohol habits of the couple, nutrition, hygiene or stress. Haas et al. (2005) found that *women who reported a history of alcohol dependence were more likely to report depressive symptoms*. Prenatal consultations might also influence maternal health states. One of the objectives of prenatal care is to prevent and detect major complications. This is done by managing, among others, maternal hypertension and diabetes. Maternal health status might consequently be better when attending prenatal clinics. It *can play an important role in assisting women to maintain healthful lifestyles* (Shiono and Behrman (1995)). These arguments suggest a causal relation between the behavioural characteristics and maternal health status (arrow ⑮). Behavioural characteristics influence also the risk of congenital anomalies (arrow ⑯). Alcohol habits, smoking habits or exposition to chemical environment are often cited as risk factors of congenital anomalies. For example, maternal smoking has been detected as risk factor for limb reduction defects (Wasserman et al. (1996); Czeisel et al. (1994)). In his report on congenital anomalies, the Canadian Minister of Public Works and Government Services notes that congenital heart defects might be affected by

alcohol abuse and that smoking habits influence oral facial clefts [14](Santé Canada (2002)).

It is also well-known that behavioural characteristics of the parents influence child's characteristics at birth (arrow ⑰). Several researches mention the smoking habits of the mother as a risk factor for low birthweight. Jadsri and Jadsri (1995) analyse the factors which determine birthweight, and low birthweight in particular. The explanatory variables included in the analysis are sex of the newborn, parental smoking habits, coffee intake, gestation duration and birth order. They found that maternal smoking as well as paternal smoking increase the risk of low birthweight. Coffee intake has no significant effect. Shiono and Behrman (1995) mention that, in the United-States, cigarette smoking during pregnancy causes close to one-fifth of all low birth weight births. Exposure to environmental cigarette smoke (such as smoking habits of the father) might also influence birthweight (Martin and Bracken (1986)). Note however that maternal smoking causes a significant decrease of the weight at birth independently of the gestation duration. Kramer et al. (2000) present two interesting graphical representations of the determinants of preterm birth and of intra uterine growth retardation (IUGR). Cigarette smoking appears to be the most important factor associated to IUGR; alcohol and drugs are also present, but with less importance. For preterm birth, the impact of cigarette smoking is not dominant, though still important. Alcohol has also been detected as risk factor for low birthweight (*e.g.* Little (1997)). The well-known Fetal Alcohol Syndrome (FAS) affects the characteristics of the child: low birth weight and low birth height. Stress has also been detected as a risk factor of preterm birth. Copper et al. (1996) analyse the impact of stress and anxiety on spontaneous preterm birth, fetal growth restriction and low birth weight. The database includes 2593 women (from 1992 to 1994) where the level of stress and anxiety were evaluated at 25 to 29 weeks of gestation. The statistical model (logistic regression) includes different covariates representing obstetrical history and socio-demographic conditions (alcohol, drug, race, income, education, marital status and maternal age). The results of this research show that stress is associated with spontaneous preterm delivery and low birth weight, even after adjustment for the socio-demographic variables. Cocaine abuse is also cited as a risk factor of low birth weight (*e.g.* Bateman et al. (1993)). Concerning prenatal care several researches have shown that the number of prenatal consultations is favourable to the child's development, particularly in terms of birthweight (*e.g.* Gortmaker

[14]includes cleft lip and cleft palate

(1979)). However, some researches have highlighted that two type of pregnancies are to be considered: the 'normal' and the 'complicated' ones. The argument is as follows: *complicated pregnancies typically entail a large number of prenatal care visits, but yield poorer outcomes* (Conway and Deb (2005)). Without integrating those two types of pregnancies, the causal relation between prenatal care and birthweight might be biased. Furthermore, it has already been mentioned that the gestation duration at first consultation is even more important that the number of consultations itself.

Behavioural characteristics influence the maternal, fetal characteristics and obstetrical characteristics. However, a direct relation between behavioural characteristics and mortality may be considered (arrow ⑱), more particularly for post-neonatal mortality. For example, the smoking habits of the parents is cited as the main factor of Sudden Infant Death Syndrome (SIDS). In their meta-analysis of the epidemiological evidence relating parental smoking and SIDS, Anderson and Cook (1997) concludes that maternal smoking (during pregnancy) doubles the risk of SIDS and that environmental tobacco smoke (post-natal exposure to tobacco) influences also the risk of SID. Venners et al. (2004) shows that paternal smoking might also cause an increasing risk of miscarriage. The authors could not identify the biological mechanisms however. They mention that these mechanisms are linked either to paternal or maternal pathways: paternal pathway includes the impact of paternal smoking on chromosomal damage in sperm while maternal pathways include the impact of passive smoking (such as reduced placental blood flow due to nicotine). Infant mortality, and post-neonatal mortality more particularly, are also affected by potential adverse behaviours of the parents. This might lead to accidental death or malnutrition leading to death.

## 4.8 Environmental factors

Environmental factors might cause congenital anomalies (arrow ⑲). In a special report, the European Surveillance of Congenital Anomalies (Eurocat (2004)) reviews the environmental risk factors for congenital anomalies, including among others the chemical factors and occupational exposures. Doyle (2004) gives many references showing the increasing risk of genetic diseases with ionising radiation (IR) exposures. Risks linked to high exposure to such substances have not to be proved anymore. *Large doses of IR were used to induce therapeutic abortion in the 1920's and 1930's and the high exposures received by pregnant Japanese women as a result of atomic bombs resulted in a variety of adverse pregnancy outcomes*

(Doyle (2004)). The effect of low exposures to IR on congenital anomalies are less known and controversial. Dolk and Vrijheid (2003) reviews the literature dealing with chemical exposures as a risk factor of congenital anomalies. They limit the chemical exposures to environmental pollution such as drinking water contamination, waste disposal, pesticides in agricultural areas, air and industrial pollution and food contamination. The authors conclude that few environmental pollution exposures significantly influence the risk of congenital anomalies. Note that the analysis of the determinants of congenital anomalies is far from being easy. Indeed, *major congenital anomalies are diagnosed in 2-4% of births* (Dolk and Vrijheid (2003)). It is consequently important to possess a substantiel database for detecting a significant impact, which is not always possible. The region of living or of working might also influence maternal health status (arrow 20). Polluted areas (such as living in a large city) might be harmful for the mother. Similarly, the work environment (such as chemical environment) might have some consequences on the biological characteristics of the mother.

## 4.9 Socio-Economic characteristics

The conceptual framework (Figure 3) does not show a direct link between the socio-economic variables and the physical characteristics of the infant at birth. As mentioned in Kramer et al. (2000), poor socio-economic conditions *lead to unhealthy behaviours, exposure to stress and psychological reaction to stress* which might consequently affect the child's characteristics at birth (preterm delivery, low birth weight...). Kramer et al. (2000) explain that women with a low socio-economic status are more exposed, not only to acute (life events) and chronic (difficult life conditions) stressors but also to less social support. These elements influence the mother's health status and of the newborn's health. For example a higher degree of education allows for a better knowledge of health practices, for a better comprehension of the advices given by the medical staff and make parents aware of the importance of the medical follow-up. Socio-economic characteristics influence also the timing and frequency of prenatal consultations. Financial access to prenatal care is more easy for couples with a certain level of income. The access to adequate medical care during and after the pregnancy might depend on couple's income. Lifestyle (*e.g.* stress at work or at home, poverty...) might influence the consumption of alcohol and tobacco. These effects justify a causal relation between the behavioural characteristics and the socio-economic characteristics (arrow 21 ).

The socio-economic characteristics of the parents might also influence directly the maternal characteristics (arrow 22). Mozurkewich et al. (2000), in a meta analysis on the consequences of working conditions on adverse pregnancy outcome, give several references (*e.g.* Wergeland and Strand (1989), Saurel-Cubizolles et al. (1991), Luke et al. (1995) and Spinillo et al. (1995)) suggesting an increasing risk of preeclampsia and hypertension with characteristics of the work such as long working hours, strenuous physical activity or heavy work. Haas et al. (2005) found that women who do not have enough money for food or housing are more at risk of depressive symptoms or poor physical functioning. We consequently have substantial arguments to approve that socio-economic characteristics have not only an impact on the behavioural characteristics but also on the maternal characteristics, especially on the health status of the mother.

The conditions of delivery might also be influenced by the socio-economic status of the parents (arrow 23). Parents with a higher level of education and with a good financial status are certainly those who are more likely to attend optimal health services and to receive better care in case of (expected or unexpected) complications.

Finally, maternal education is seen as an important determinant of maternal age at conception (Beets (2004)). Mothers with higher education levels delay their time to conception for different reasons: difficulties of combining family and education, longer absence of income (during education), desire to benefit from time spent to education through a remunerated work (desire of working is greater than the desire for children)... Actual economic situation of the parents as well as beliefs on future earning (*e.g.* situation of the market labour at the individual and macro level) influence also parental age at conception. Occupational status of the parents is also one of the determinants of fertility. Unemployed parents have more financial difficulties but can spend more time to children and the opportunity cost of a child is lower. The desire for children can consequently be more important in such a situation, which decreases consequently the age at conception. Difficulty to combine work and family might also be in favour of delayed fertility decision. Several arguments explain the causal impact of socio-economic conditions on age at conception. This can consequently not be neglected in the conceptual schema (arrows 24 and 25).

# 5 Conclusion

This note presents a conceptual model of feto-infant mortality which has been constructed step by step according to the context of interest, namely the delayed fertility observed in numerous developed countries. The construction of this conceptual schema has been based on 5 criteria which are presented by way of conclusion. First, the conceptual model is based on a *review of the literature* gathering the actual theoretical knowledge of the process and past empirical results. A conceptual framework can definitely not be restricted to the available data. Secondly, the conceptual framework *simplifies reality*. All concepts and their multiple interactions cannot be inserted, at the risk of becoming untestable. It is consequently necessary to select the most relevant (groups of) variables and their relationships. Thirdly, the framework is adapted to the context. As example, the problematic of feto-infant mortality is not identical in the developed and developing countries. Some concepts are highlighted according to the context. In the present context, namely late and low fertility, both parental ages and congenital anomalies have been underlined. Fourthly, a conceptual framework should be *falsifiable*, namely confrontable with reality. This confrontation is of course restricted to the available data. The empirical (or operational) model should consequently take this limitation into account but in any case the conceptual schema should restrict oneself to the available data (indicators from the database). Finally, the fifth criteria is the *interpretation of the mechanisms* presented in the model. The assumptions on the mechanisms should be given a priori and then tested with an empirical model. Interpretations should not be given a posteriori according to the results of the empirical model. The construction of this conceptual schema is the first necessary condition for analysing the determinants of feto-infant mortality from a causal point of view, with the distinction between direct and indirect effects.

# References

Anderson, H. and Cook, D. (1997). Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. *Thorax*, 52:10003–1009.

Astolfi, P., De Pasquale, A., and Zonta, L. (2005). Late childbearing and its impact on adverse pregnancy outcome: stillbirth, preterm delivery and

low birth weight. *Revue Epidémiologique de santé publique*, 53:2s97–2s105.

Astolfi, P., De PAsquale, A., and Zonta, L. (2006). Paternal age and preterm birth in Italy, 1990 to 1998. *Epidemiology*, 17(2):218–221.

Basso, O., Olsen, J., and Christensen, K. (1998). Risk of preterm delivery, low birth weight and growth retardation following spontaneous abortion: a registry-based study in danemark. *International Journal of Epidemiology*, 27(4):642–646.

Bateman, D., Hansen, S., and Heagarty, M. (1993). The effects of intrauterine cocaine exposure in newborns. *American Journal of Public Health*, 83(2):190–193.

Beemsterboer, S., Homburg, R., Gorter, N., et al. (2006). The paradox of declining fertility but increasing twinning rates with advanced maternal age. *Human Reproduction*, 23:1–2.

Beets, G. (2004). De timing van het eerste kind: een overzicht. *Bevolking en Gezin*, 1:115–142.

Berkowitz, G. and Papiernik, E. (1993). Epidemiology of preterm birth. *Epidemiologic Review*, 15:414–443.

Bordson, B. and Sears Leonardo, V. (1991). The appropriate upper age limit for semen donors: a review of the genetic effects of paternal age. *Fertility and Sterility*, 3:397–401.

Boue, J., Boue, A., and Lazar, P. (1975). Retrospective and prospective epidemiological studies of 1500 kartotyped spontaneous human abortions. *Teratology*, 12:11–29.

Conde-Agudeli, A., Rosas-Bermùdes, A., and Kafury-Goeta, A. C. (2006). Birth spacing and risk of adverse perinatal outcomes. a meta-analysis. *Journal of American Medical Association*, 295(15):1809–1823.

Conway, K. S. and Deb, P. (2005). Is prenatal care really ineffective? or, is the 'devil' in the distribution? *Journal of Health Economics*, 24(3):489–513.

Copper, R., Goldenber, A. D., Elder, N., Swain, M., Norman, G., Ramsey, R., Cotroneo, P., Collins, B., Johnson, F., Jones, P., Meir, A., the National Insitute of Child Health, and Network, H. D. M.-F. M. U. (1996).

The preterm prediction study: Maternal stress is associated with spontaneous preterm birth at less than thirty five weeks gestation. *American Journal of Obstetrics and Gynecology*, 175(5):1286–1292.

Cowchock, F., Gibas, Z., and Jackson, L. (1993). Chromosome errors as a cause of spontaneous abortion: the relative importance of maternal age and obstetric history. *Fertility and Sterility*, 59:1011–1014.

Cramer, J. (1987). Social factors and infant mortality: identifying high-risk groups and proximate causes. *Demography*, 24(3):299–322.

Czeisel, A., Kodaf, I., and Lenz, W. (1994). Smoking during pregancy and congenital limb deficiency. *British Medical Journal*, 308:1473–1477.

de La Rochebrochard, E. and Thonneau, P. (2002). Paternal age and maternal age are risk factors for miscarriage; results of a multicenter european study. *Human Reproduction*, 17(6):1649–1656.

De Michelena, M., Brustain, E., Lala, J., and Vasquez, J. (1993). Paternal age as a risk for down syndrome. *American Journal of Medical Genetics*, 45:679–682.

Dolk, H. and Vrijheid, M. (2003). The impact of environmental pollution on congenital anomalies. *British Medical Bulletin*, 68:25–45.

Dominguez, V., Calle, E., Ortega, P., et al. (1991). Adjusting risk factors in spontaneous abortion by multiple logistic regression. *European Journal of Epidemiology*, 7:171–174.

Doyle, P. (2004). Ionising radiation. In *EUROCAT Special Report: A review of environment risk factors for congenital anomalies [www.eurocat.ulster.ac.uk]*.

Eurocat (1995). *Report 6 - Surveillance of congenital anomalies in Europe, 1980-1992*.

Eurocat (2004). *A Review of Environmental Risk Factors for Congenital Anomalies*.

Foix-L'Hélias, L. and Blondel, B. (2000). Changes in risk factors of preterm delivery in France between 1981 and 1995. *Paediatric and Perinatal Epidemiology*, 14(4):314–323.

Friede, A., Baldwain, W., Rhodes, P., Buehler, J., and Strauss, L. (1988). Older maternal age and infant mortality in the United States. *Obstetrics and Gynecology*, 72(2):152–157.

Friedman, J. (1981). Genetic disease in the offsrping of older fathers. *Obstetric and Gynecology*, 57(6):745–749.

Garne, E. (2004). Maternal diabetes. In *EUROCAT Special Report. A review of the environmental risk factors for congenital anomalies [www.eurocat.ulster.ac.uk]*, pages 94–97.

Gavrilov, L. and Gavrilova, N. (1997). Parental age at conception and offspring longetivity. *Reviews in Clinical Gerontology*, 7:5–12.

Gortmaker, S. L. (1979). Poverty and infant mortality in the united states. *American Sociological Review*, 44(2):280–297.

Gourbin, C. and Masuy-Stroobat, G. (1995). Registration of vital data: are live births and stillbirths comparable all over europe? *Bulletin of the World Health Organization*, 73(4):449–460.

Gourbin, C. and Wunsch, G. (1999). Paternal age and infant mortality. *Genius*, LV:61–72.

Haas, J. S., Jackson, R. A., Fuentes-Afflick, E., Stewart, Anita, L., Dean, Mitzi, L., Brawarsky, P., and Escobar, G. J. (2005). Changes in the health status of women during and after pregnancy. *Journal of General Internal Medicine*, 20(1):45–51.

Haram, K., Pirhonen, J., and Bergsjø(2002). Suspected big baby: a difficult clinical problem in obstetrics. *Acta Obstetricia et Gynecologica Scandinavica*, 81:185–194.

Harper, P. (1998). *Practicle Genetic Counselling*. Butterworth Heinemann, Boston.

Jadsri, S. and Jadsri, C. (1995). Parental smoking habits and infant birth weight. *Asia Pacific Journal of Public Health*, 8(2):134–137.

Kramer, M., Goulet, L., Lydon, J., et al. (2001). Socio-economic disparities in preterm birth: causal pathways and mechanisms. *Paediatric and Perinatal Epidemiology*, 15(suppl.2):104–132.

Kramer, M., Séguin, L., Lydon, J., and Goulet, L. (2000). Socio-economic disparities in pregancy outcome: Why do the poor so poor? *Paediatric and Perinatal Epidemiology*, 14(3):194–210.

Lian, Z., Zack, M., and Erickson, J. (1986). Paternal age and the occurence of birth defects. *American Journal of Human Genetics*, 39:648–660.

Little, R. (1997). Moderate alcohol use during pregnancy and decreased infant birth weight. *American Journal of Public Health*, 67(12):1154–1156.

Luke, B., Mamelle, N., Keith, L., Munoz, F., Minogue, J., and Papiernik, E. (1995). The association between occupational factors and preterm birth: A united states nurses' study. *American Journal of Obstetrics and Gynecology*, 173:849–862.

March of Dimes Resource Center (1998). Birth defects [http://www.modimes.org].

Martin, T. and Bracken, M. (1986). Association of low birth weight with passive smoke exposure in pregnancy. *American Journal of Epidemiology*, 124:633–642.

Martius, J., Steck, T., Oehler, M., and K-H., W. (1998). Risk factors associated with preterm (<37weeks) and early preterm (<32 weeks): univariate and multi-variate analysis of 106,345 singleton births from 1994 statewide perinatal survey of bavaria. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 80:183–189.

Matteson, D., Burr, J., and Marshall, J. (1998). Infant mortliaty: a multilevel analysis of individual and commnunity risk factors. *Social Science and Medicine*, 47(11):1841–1854.

Miller, J. E. (1989). Is the relationship between birth intervals and perinatal mortality spurious? evidence from hungary and sweden. *Population Studies*, 43(3):479–495.

Misra, D., O'Campo, P., and Strobino, D. (2001). Testing a sociomedical model for preterm delivery. *Paediatric and Perinatal Epidemiology*, 15:110–122.

Moore, L., Singer, M., Bradlee, M., Rothman, K., and Milunsky, A. (2000). A prospective study of the risk of congenital defects associated with maternal obesity and diabetes mellitus. *Epidemiology*, 11:689–694.

Mosley, H. W. and Chen, L. C. (1984). An analytical framework for the study of child survival in developing countries. *Population and Development Review*, 10, Supplements: Child Survivial: Strategies for Research:25–45.

Mozurkewich, E. L., Luke, B., Avni, M., and Wolf, F. M. (2000). Working conditions and adverse pregnancy outcome: a meta-analysis. *Obstetrics and Gynecology*, 95(4):623635.

Murdoch, J., Walker, B., and McKusick, V. (1972). Parental age effects on the occurence of new mutations for the marfan syndrom. *Annals of Human Genetics*, 35:331–336.

Naeye, R. (1983). Maternal age, obstetric complications, and the outcome of pregnancy. *Obstetrics and Gynecology*, 61(2):210–2106.

Nybo Anderson, A., Wohlfahrt, J., Christens, P., et al. (2000). Maternal age and fetal loss: population based register linkage study. *British Medicine Journal*, 320:1708–1712.

Observatoire de la santé et du social (2004). *Tableau de bord de la santé - Région de Bruxelles Capitale*.

Osborn, J., Cattaruzza, M., and Spinelli, A. (2000). Risk of spontaneous abortion in italy, 1978-1995, and the effect of maternal age, gravidity, marital status, and education. *American Journal of Epidemiology*, 151:98–105.

Pison, G. (2000). Près de la moitié des jumeaux naissent en Afrique. *Population & Sociétés*, 360.

Risch, N., Reich, E., Wishnick, M., and McCarthy, J. (1987). Spontaneous mutation and parental age in humans. *American Journal of Human Genetics*, 41:218–248.

Robert, E. (2004). Maternal epilepsy. In *Eurocat Special Report: A review of environmental risk factors for congenital anomalies [www.eurocat.ulster.ac.uk]*, pages 98–101.

Rooney, B. and Calhoun, B. C. (2003). Induced abortion and risk of later premature births. *Journal of American Physicians and Surgeons*, 8(2):46–49.

Rosenbusch, B. and Sterzik, K. (1991). Sperm chromosomes and habitual abortion. *Fertility and Sterility*, 56(2):370–372.

Rychtařýková, J. and Demko, G. (2001). Inequalities in infant survival: An analysis of czech linked records. *European Journal of Population*, 17(4):232–342.

Rychtařýková, J., Gourbin, C., and Wunsch, G. (2004). Paternal age and child death: The stillbirth case. *European Journal of Population*, 20:23–33.

Santé Canada (2002). Congenital anomalies in canada - a perinatal health report, 2002. Technical report.

Sartorrelli, E., Mazzucatto, L., and De Pina-Neto, J. (2001). Effect of paternal age on human sperm chromosomes. *Fertility and Sterility*, 76:1119–1123.

Saurel-Cubizolles, M., Kaminski, M., Du Mazaubrun, C., Llado, J., and Estryn-Behar, M. (1991). High blood pressure during pregnancy and working conditions among hospital personnel. *European Journal of Obstetrics, Gynecology and Reproductive Biology*, 40:29–34.

Seller, M. (2004). Genetic causes of congenital anomalies and their interaction with environmental factors. In *EUROCAT Special Report: A review of environment risk factors for congenital anomalies [www.eurocat.ulster.ac.uk]*.

Selvin, S. and Garfinkel, J. (1972). The relationship between parental age and birth order with the percentage of low birth-weight infants. *Human Biology*, 44:501–510.

Sharma, R. K. (1998). Causal pathways to infant mortality: Linking social variables to infant mortality through intermediate variables. *Journal of Health and Social Policy*, 9(3):15–28.

Sheehan, T. (1998). Stress and low birth weight: a structural modeling approach using real life stressors. *Social Science and Medicine*, 47(10):1503–1512.

Shiono, P. and Behrman, R. (1995). Low birth weight: Analysis and recommendations. *Future of Children*, 5(1):4–18.

Slama, R. et al. (2003). Does male age affect the risk of spontaneous abortion? an approach using semiparametric regression. *American Journal of Epidemiology*, 157(9):815–824.

Spinillo, A., Capuzzo, E., Colonna, L., Piazzi, G., Nicola, S., and Baltaro, F. (1995). The effect of work activity in pregnancy on the risk of severe preeclampsia. *Australian and New Zealand Journal of Obstetrics and Gynecology*, 35:380–385.

Spira, A. et al. (1993). Conception probability and pregnancy outcome in relation to age, cycle regularity, and timing of intercourse. In Gray, R., Leridon, H., and Spira, A., editors, *Biomedical and Demographic Determinants of Reproduction*, pages 271–274. Clarendon Press, Oxford, UK.

Tough, S., Faber, A., Svenson, L., and Johnston, D. (2003). Is paternal age associated with an increased risk of low birthweight, preterm delivery, and multiple birth? *Canadian Journal of Public Health*, 94(2):88–92.

Tough, S. C., Newburn-Cook, C., W., J. D., Svenson, L. W., Rose, S., and Belik, J. (2002). Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. *Paediatrics*, 109(3):399–403.

van Katwijk, C. and Peeters, L. (1998). Clinical aspects of pregnancy after the age of 35 years: A review of the literature. *Human Reproduction Update*, 4(2):185–194.

Venners, S., Wang, X., Chen, C., et al. (2004). Paternal smoking and pregnancy loss: A propsective study using a biomarker of pregnancy. *American Journal of Epidemiology*, 159(10):993–1001.

Waller, D., Mills, J., Simpson, J., et al. (1994). Are obese women at higher risk for producing malformed offspring. *American Journal of Obstetrical Gynecology*, 170:541–548.

Wasserman, C., Shaw, G., O'Malley, C., et al. (1996). Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology*, 53:261–267.

Wergeland, E. and Strand, K. (1989). Working conditions and prevalence of pre-eclampsia, norway 1989. *International Journal of Gynaecology and Obstetrics*, 58:189–196.

Wilcox, A. and Skjaerven, R. (1992). Birth weight and perinatal mortality: The effect of gestation age. *American Jounal of Public Health*, 82(3):378–382.

Wunsch, G. and Gourbin, C. (2002). Parent's age at birth of their offspring and child survival. *Social Biology*, 49(3-4):174–184.

Zhu, J., Madsen, K. M., Vestergaard, M., Basso, O., and Olsen, J. (2005). Paternal age and preterm birth. *Epidemiology*, 16:259–262.