

Late Maternal Age and Risk of Congenital Malformation

Età della Madre al Parto e Rischio di Malformazioni Congenite

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Riassunto: In questo studio si considera una particolare implicazione della fecondità posticipata: il rischio di malformazioni congenite diagnosticate alla nascita. L'obiettivo principale è lo studio della relazione tra età al parto e rischio di malformazioni, al netto dell'effetto di fattori sociali, biologici e territoriali. I dati sono tratti dalle schede di nascita Istat D1 e D2 della regione Lombardia. Per stimare in maniera non parametrica l'effetto dell'età della madre si adotta un modello additivo generalizzato, con effetti casuali per tenere conto della correlazione tra le madri appartenenti allo stesso contesto territoriale. Il rischio che alla nascita un bambino sia malformato, al netto dei fattori di controllo, risulta particolarmente elevato prima dei 20 e dopo i 37 anni.

Keywords: maternal age, congenital malformation, general additive models, random effects.

1. Theoretical frame and aims

Age at childbirth has been rising in recent decades in many developed countries. Currently, Italy is among the countries in which this phenomenon has reached its highest levels. The trend is most pronounced in Northern Italy, where the birth of the first child is increasingly postponed. Among younger generations, almost 45% of women start bearing children after their 30s (Rosina, 2004). This makes the Italian case particularly interesting in the study of the implications of late fertility. While delayed childbirth is associated with some positive economic and psychological outcomes, the biological implications are generally negative (Tarin *et al.*, 1998). The negative outcomes concern medical complications during pregnancy and delivery, such as pre-term delivery, low birth weight, and the necessity of caesarean section (Gilbert *et al.* 1999), as well as maternal mortality, foetal and neonatal mortality, and long-term negative consequences for mothers and children (Alonzo, 2002). In this study, we shall consider a specific late fertility implication: the risk of congenital malformation (CM). In particular, we would like to estimate the extent of the increase in the incidence of CM with age (particularly after 35 years old), controlling for both biological and social variables.

2. Data

We used data ($N = 73,997$) gathered from Istat D1 and D2 forms. More specifically, these data refer to all registered births (only single) from mothers resident in Lombardy during the 1996 year. We are aware of changing in the births survey rules since 1/1/1999 (Buratta *et al.*, 2003). Nevertheless we studied the topic with these data because the only one at disposal for the Lombardy, the most populous region of Northern Italy, protagonist of the postponement process. Among the six Italian population-based registries for the epidemiological surveillance of congenital anomalies currently operative as member of EUROCAT, Lombardy is, in fact, not included. The main information available are the following: the presence of CM, some relevant maternal characteristics (age at childbirth, education, place of residence, parental consanguinity) and pertinent information relating to the birth and the child (duration of gestation, birth weight, type of childbirth). The information on CM refers to all the congenital defects (with no specification regarding type) diagnosed at the time of birth. Therefore, we disregarded the CM (internal or insidious) manifesting themselves at a certain age after birth or even diagnosed during adulthood through clinical tests, which were not carried out during the neonatal period. The chief advantage of this dataset is the high number of cases observed, which allows for consistent estimates. This set also includes data for mothers at age 40 and older and provides a detailed geographical information (municipality).

3. Variables and hypothesis

We focus on the relationship between maternal age and negative birth outcome. Therefore in our model the dependent variable is the presence of CM and the main explanatory variable is age at childbirth. As control factors, among the available information (section 2), we include mother's education, consanguinity between parents, the father's age and territorial variables (such as the demographic size and the altitude of the municipality). Educational level has a substantial impact on both the age of the mother at childbirth (positive) and on the risk of malformation (negative: more educated women have in general better medical care and assistance and more healthy behaviour during pregnancy). Consanguinity too is considered as a control variable because it is strongly related to the dependent variable and it might be connected to the age of the mother (consanguinity is particularly common in the more isolated municipalities in the Alps, where also age at marriage is traditionally higher than elsewhere). To take into account the father's age and to avoid the problem of collinearity with the mother's age, we include the variable "age difference" between parents in the model. Lastly, we consider the territorial variables to estimate the mother's age effect on CM net of the unobserved contextual factors (such as the presence of specific sources of risk; particularly efficient health structures; and so on).

4. Statistical model and results

An additive logistic model (Hastie and Tibshirani, 1990) is fitted to grasp the age effect in a more flexible way using a nonparametric regression framework. Congenital mal-

formations have a very low incidence on the population and, as a consequence of that, the estimates of a model obtained using all data will not be really efficient in particular if we are interested in the specific effect of the explanatory variables on the incidence of CM. With logistic regression, some theoretical results (Prentice and Pyke, 1979) show that the use of a strategy of random selecting a balanced sample from all data (obtaining a disproportionate stratified sample), and estimating the model on those data, raises to a biased estimation of the level, but give a more efficient estimate of the effects of the explanatory variables on the dependent one; the same reasoning can be followed also in the case of nonparametric models (Berry and Linoff, 2000). For our model we obtained a balanced sample of 620 births from data, with all the cases of CM (272 births) and approximately the same number (randomly selected) of normal cases. On this data we estimated a model trying to measure the effect of the parental age on the incidence of malformation net of some confounding factors. The additive model has been estimated by backfitting algorithm, where the smoother for the quantitative variables was the smoothing splines; for each smoother we selected the equivalent degrees of freedom empirically, considering different values and determining those which best seemed to describe the observed values. Some variables resulted not statistically significant and they have been discarded (altitude, total population of the municipality of residence and difference between the age of mother and the father). Table 1 shows the results of the final model.

Table 1. *Estimate of the parameters for the binomial additive model*

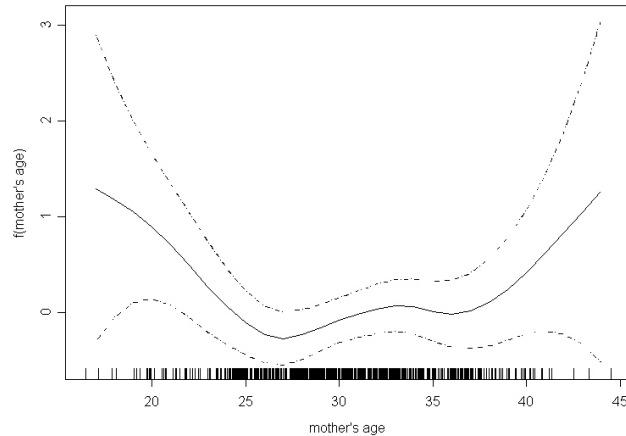
	Estimate	se	df*	Extra-deviance	p-value
<i>Mother's age</i>			5	12.45	0.0141
<i>Consanguinity</i>			2	-24.02	<0.0001
No	-0.1360	0.0467			
Yes	0.8163	0.4742			
<i>Place of Residence</i>			1	-0.6611	0.4165
Milan	-0.4152	0.2700			
Other	0.0437	0.0284			
<i>Mother's education</i>			3	-15.77	0.0013
University degree	0.0879	0.2912			
High school degree	0.0069	0.0987			
Middle school degree	-0.1734	0.0956			
Elementary school degree	1.6497	0.4824			
<i>Place of residence: Random effect</i>			10	20.20	0.0274

*For the variables with non parametric estimates it shows the *equivalent degree of freedom*

To evaluate the effect of the place of residence of the mother, we used first an indicator to get the specificity of the city of Milan, which is much bigger and different than all the others municipalities, then we fitted a random effect to allow for the variability between all the municipalities. We can observe that consanguinity between parents is very important, as expected, for the prediction of CM, but also the mother's education is a relevant variable dividing women with low level of education from the others. From Figure 1 it is clear that the probability to have a child with congenital malformation grows up with the age after 36-37 years. For women before 20 years old, the probability of malformation is also higher. The approximated 95% confidence bands are quite large when the estimate is bigger, and this is due to the really small amount of CM observed in that region, as we can see looking at the rugs presents on the x axis in the plot; however, the effect of the mother's age seems still to be statistically significant. Note that the variable indicating the differ-

ence in age from the father and the mother is not significant; that means that it seems not to be a specific effect of the age of the father other than the effect got from the mother's age variable.

Figure 1: Nonparametric estimate of the function that in the additive model relates the maternal age and the risk of CM, with 95% confidence bands.



5. Conclusions

The probability of giving birth to a child with a malformation proves to be relatively low (between 4 and 5 out of 1,000 births) for women between 25 and 37-38 years old. We have obtained a risk of CM which is particularly high for teenagers, and declines during the early 20s; confidence bands are quite large, but the difference between risks still seems slightly significant. Regarding the process of the continuous postponement of childbearing, it is interesting to note that the risk of malformation seems to rise dramatically only starting from the late 30s (reaching relatively high levels during the early 40s).

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