Time to pregnancy: methodological insights and new results

Extended abstract - Work in progress

Zsuzsanna Makay – Hungarian Demographic Research Institute. makay@demografia.hu
Laura Szabó - Hungarian Demographic Research Institute

Introduction

Postponement of childbirth is one of the main characteristics of the demographic changes that took place in the last decades in developed countries (Schmidt et al., 2012; Sobotka, 2004). Indeed, the mean age of mothers at the birth of the first child increased from 26.4 years in 2000 to 29.2 years in 2020 in the OECD countries and it is above 30 years in 10 out of 41 countries (OECD Family database). Besides, the mean age of fathers at childbirth has also increased. In the United States, mean paternal age was 27.4 years in 1972 and 30.9 in 2015 (Khandwala et al., 2017). In the case of fathers data are scarce in several countries since male fertility is less well documented than female fertility (Schoumaker, 2019).

An important consequence of delayed childbearing is the increase of subfertility (defined as any form of reduced fertility with prolonged time of unwanted non-conception) and infertility (or sterility, meaning only sporadically occurring spontaneous pregnancies) in both women and men (Gnoth et al., 2005). According to several previous studies, the probability of conceiving decreases with age, and so does the probability of live birth. Several studies have shown that, as a consequence, female fertility has a "best-before date" of 35 years, while men's is probably around 40 years (Balasch, 2010; Rochebrochard & Thonneau, 2003).

However, the results are not unanimous. Some studies don't show any effect of age on the probability of conception, while others point to important differences in the results according to the definition of the sample.

Thus, the aim of our study is to clarify the importance of sample definition showing that in a sample of pregnant women, who are asked about time to conception, results depend mainly on the time scale used in the definition of time to pregnancy (TTP) because of an important bias in the population. Indeed, several previous studies have omitted this issue and did not indicate the time at which age was determined (e.g. Gnoth et al., 2003; Rochebrochard & Thonneau, 2003; for an overview: (Jensen et al., 2000))

Theoretical background

Fertility, fecundity and fecundability

Fertility can be measured in different ways at different levels. In a population, biological fertility refers to the number of offsprings actually produced and is measured as the general fertility rate (the birth rate multiplied by the number of sexually productive women) or the total fertility rate (the average number of offspring per woman over her lifetime). The physiological ability to have children - which for women is roughly between menarche and menopause - is called fecundity, which is simply the biological ability to reproduce (Encyclopedia.com). In demography, fertility refers to the product or output of reproduction rather than the ability to have children (Frank 2023). In addition, demographers define a third, further aspect of reproduction - fecundability - which is the probability of becoming pregnant, or the likelihood of being exposed to this possibility, depending on patterns of sexual and pregnancy-preventing behaviour. In our study we refer to the demographic definition when talking about fertility and fecundability.

Measuring TTP

Time to pregnancy (TTP) measures how long a couple takes to conceive and it has been proven to be a good measure of biologic fertility and to give a good estimation of the true TTP (Baird et al., 1991; Joffe et al., 2005).

TTP can be defined as the length of time in either calendar months or menstrual cycles, with the option to collect data retrospectively or prospectively (Baird et al. 1991, Cooney et al. 2009). Both approaches have their advantages and limitations. The prospective cohort design is particularly useful as it allows for the monitoring and documentation of lifestyle changes during the pregnancy attempt period, as well as the recording of biochemical pregnancies and early terminations (Hong et al. 2022). The limitations include the expense of maintaining the cohort, the pressure of follow-up on participants, and potential influence of follow-up on the association between covariates and fecundability. A retrospective cohort study would involve surveying pregnant women about their experience and time to pregnancy with their most recent pregnancy. Although this form of measurement is more cost-effective than the prospective one, it is still subject to several biases. The recall bias is a potential issue with this method of measurement. Cooney et al. (2009) discovered that only 19% of women were able to accurately recall their TTP 10 years after giving birth. However, Jukic et al. (2016) has found that the recalled TTP was in good agreement with the prospective TTP. Another issue is selection bias. Couples who fail to conceive are not represented in the sample (Joffe et al. 2005, Hong et al. 2022). Temporal bias can also occur when variations in individuals' exposure to hazardous factors during different time periods are not considered. We should also take into account the potential bias resulting from changes in family planning policy during the study period, the potential bias towards subjects who are actively preparing for pregnancy, the possible bias due to medical interventions impacting lifestyle, health status and other indicators during pregnancy preparation as well as the potential effect of unhealthy workers (TTP studies show an increased duration and probability of remaining in the job for workers who have been preparing for pregnancy for a long time and are not pregnant, Hong et al. 2022).

However, the meta-analysis conducted by Hong et al (2022:123) indicates that retrospective TTP studies may be prone to different biases, but these are not consistent across studies and the effects of interest are minimally impacted.

Age affecting TTP

Several studies have investigated TTP and its association with various demographic, health, and lifestyle factors (for a summary, see Axmon et al. 2006 and Hong et al. 2022). Age stands out as one of the most important and definitive factors influencing TTP (Hong et al. 2022). However, the findings appear inconsistent. According to Rothman et al (2013), women aged 35-40 have a significantly lower fecundability ratio (0.77; 95% CI: 0.62-0.97) compared to women aged 20-24. Conversely, Wesselink et al. (2017) stated that there is no optimal age group for female fertility since it decreases after the age of 20. According to their data (Wesselink et al. 2017:149), fecundability ratios for ages 25-27 were 0.91 (95% CI: 0.74-1.11), for ages 28-30 were 0.88 (95% CI: 0.72-1.08), for ages 31-33 were 0.87 (95% CI: 0.70-1.08), for ages 34-36 were 0.82 (95% CI: 0.64-1.05), for ages 37-39 were 0.60 (95% CI: 0.44-0.81), and for ages 40-45 were 0.40 (95% CI: 0.22-0.73) compared to the reference group (ages 21-24 years).

A retrospective study analysing TTP in Sweden, using an age/calendar-time model, found that subfertility increased between the ages of 20 and 30, and decreased significantly thereafter in women over the age of 35 (Scheike et al., 2009: 193). The paradoxical finding that older women have lower subfertility than younger women in this retrospective pregnancy sample design is explained by the authors by selection bias, as women who have given up trying to become pregnant are not included at all in the study.

Jensen et al (1999) presented rather similar results when they examined TTP among women with first and planned pregnancies in Denmark during 1972-1987. According to their results, the fecundability odds ratio - calculated as the odds of conception in one menstrual cycle among older women divided by the odds among women aged 15-24 years - was 1.12 (95% CI: 1.04-1.20) for women aged 25-29 years, 1.15 (95% CI: 1.01-1.30) for women aged 30-34 years, and 2.44 (95% CI: 1.84-3.22) for women aged 34 years and older, after adjustment for confounders. The authors point out that these results contradict those of previous studies and reiterate the selection bias of not including sterile women (Jensen et al 1999).

This selection bias in the sample of pregnant women is also convincingly presented by Juul et al (2000), who compare the results of an international retrospective cohort study (general population of women), in which fertility clearly decreases with age, with the results of a sample of women with a completed pregnancy, in which this effect disappears. The Kaplan-Meier curves for waiting time to pregnancy in the general population of women, stratified into three groups (25-29, 30-34, 35+) according to age at the start of attempt, show that the older the woman, the longer she waits, with relative hazards of 0.88 (95% CI: 0.79-0.97) and 0.62 (95% CI: 0.51-0.75) of becoming pregnant for the 30-34 and 35+ age groups, respectively, taking the 25-29 age group as the baseline (Juul et al. 2000:717). In contrast, looking at the results for women with completed pregnancies, the 25-29 and 30-34 age groups are almost identical, while there is a slight tendency for the 35+ age group to be initially above and then below the other two, with Cox regression's relative risks being of 0.98 (95% CI: 0.89-1.09) and 1.02 (95% CI: 0.85-1.22) for the 30-34 and 35+ age groups, taking the 25-29 age group as the baseline (Juul et al. 2000:718), indicating the absence of an age effect in the retrospectively collected data.

There has been much less analysis of the optimal age for male fertility. Rothman et al (2013) reported that the age of the male partner followed the same pattern as for women, but there was no significant difference in the fecundability ratio for males in different age groups compared to those aged 20-24 (Rothman et al 2013:15). Similarly, in the findings of Wesselink et al (2015:14), there was no significant difference in fecundability ratio for males from different age groups as compared to those aged 21-24. As with female age, increasing male age was associated with significantly increasing TTP and decreasing conception rates. There was a fivefold increase in TTP for men aged >45 years. Compared with men aged <25 years, those aged >45 years were 4.6 and 12.5 times more likely to have a TTP of >1 or >2 years. Restricting the analysis to partners of young women showed similar effects of increasing male age. Women aged >35 years were 2.2 times more likely to be subfertile than women aged <25 years (Hassan et al. 2003).

Data

The data source is the nationally representative longitudinal birth cohort study Cohort '18 Growing Up in Hungary, launched by the Hungarian Demographic Research Institute (HDRI) in 2017 (Veroszta (ed.). 2018, 2019; Szabó et al., 2021; Veroszta et al., 2022). The primary sampling units were the territorial health visitor districts (628 health visitor districts randomly selected on the basis of several variables characterising each health visitor district, Kapitány 2018), and all pregnant women whose due date fell between 1 April 2018 and 30 April 2019 in the selected health visitor districts were included in the sample. During the longitudinal survey, women were interviewed in the antenatal wave, when their children were 6 months old, when their children were 18 months old, and when their children were 3 years old. Due to the very high coverage of the Hungarian antenatal care system by health visitors - in 2017 there were approximately 4000 health visitor districts in Hungary, and 98% of pregnant women have access to this service - and the relatively low rate of late foetal mortality, the sample covers almost 10% of all children born in Hungary during this period.

The size of the target population was about 90,000 and the number of final birth cohort samples was 8600. 8287 women completed the questionnaire in the antenatal wave. (There are 383 retrospective responses in the second, 6-month pregnancy wave where women were unable to respond in the antenatal wave and their responses are also included in the analysis). Health visitors interviewed the mothers who responded to our invitation. The sample of pregnant women was adjusted by a cell weighting procedure according to maternal educational attainment, parity, official marital status and maternal age at birth (based on HCSO vital statistics and population event statistics), and also according to the economic development of the mother's place of residence based on GDP (Kapitány, 2018). Data is representative of annual childbirth in Hungary (Szabó, 2021; Veroszta (ed.), 2019).

Participation was voluntary. All participants gave written informed consent to HDRI. The reference number of the ethical approval of the Ethical Committee for the Cohort '18 Growing Up in Hungary Study is 2022/1, the date of approval is 15 November 2022. The research methodology was also in accordance with the Declaration of Helsinki and the Code of Ethics of the Hungarian Psychological Association.

Methods

The first wave of data collection took place around the 7th month of pregnancy among 8,287 women. The questionnaire included several questions about birth-planning and the circumstances of the conception of the child to be born were included in the questionnaire as well as detailed information about the father. At this point of the survey there was no data collection among the partners (the upcoming fathers) so all information was provided by the women.

We analyse TTP which is only a meaningful concept for planned pregnancies. Therefore our sample consists only of women in this situation. Two questions in the questionnaire measured this.

1) *Before you got pregnant now, did you wish to have a child at some time?*
   Only respondents answering “Yes” are included in the present study.
2) *Did your <u>current pregnancy</u> happen sooner than you wished, later, or right on time? 1* – Earlier 2- Later 3- At the right time 4- Don’t know.
   Only respondents answering “Later” and “At the right time” are included.

After applying these criteria, 2/3 of the respondents remained in the sample. Among them 2% reported using some form of contraception, and were therefore excluded, as the definition of TTP implies that only unprotected intercourses are studied. We do not have information about the frequency of sexual intercourse, which is thought to be an important factor of TTP (Stanford & Dunson, 2007; Wilcox et al., 1995).

Time to conceive is measured with the following question, suggested by previous studies (Joffe et al., 2005) :

In case of your <u>current pregnancy</u>, how long did it take for you to get pregnant? If you had a miscarriage, calculate that time period as well!

___ years and _____ months

Data were collected at the 7th month of pregnancy, and even if at this time we have no information about the outcome of the pregnancy, there is solid evidence that the majority of these pregnancies will end in a livebirth. Therefore, the recommendation given to respondents to include previous miscarriages in the timeframe means that the time to a 'successful' pregnancy resulting in a live birth is taken into account We use survival analysis to estimate the effect of age and various background variables on TTP. We control for highest level of education, type of union (married or other, which are mainly cohabiting unions), subjective income, smoking before pregnancy, body mass index, previous miscarriage or an induced abortion. The characteristics of the sample are shown in the appendix.

Before building the models we tested the proportionality assumption behind the Cox model. We had two variables for which we had to reject the proportionality assumption: diseases of the thyroid gland and having had an abortion. We stratified on these to variables in the models.

Preliminary results

Time to pregnancy and age at interview

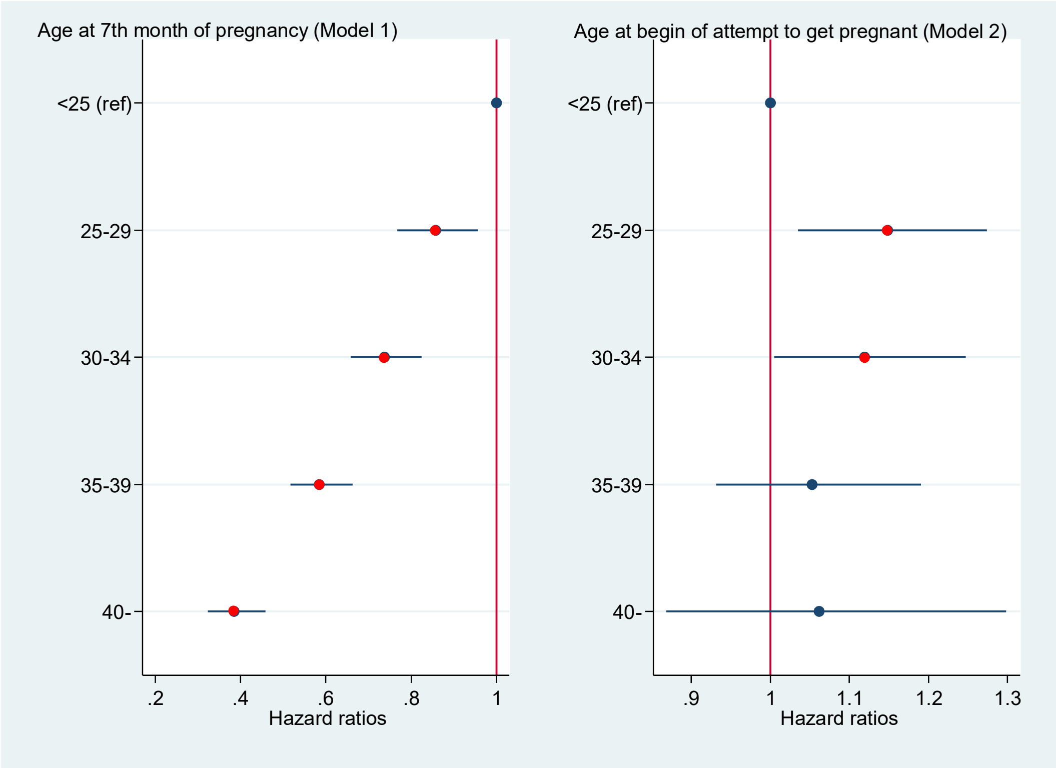
First we ran Cox regression models and defined the mothers' age at the time of interview, that is, in the 7th month of pregnancy. We controlled for the background variables described earlier.

Results show a significant decrease of the hazard ratios with age and this from a very young age (Figure 1, left panel). Compared to women below 25 years, those between 25 and 29 has a hazard ration which is decreased by 15% ($p < 0.028$). Among women who are between 30 and 34 years old, HR is 0.66 ($p<0.000$) while it is 0.51 in the next age group and 0.42 among women aged 40 and older. So, we see a significant and important decrease in the intensity of getting pregnant, and therefore an important increase in the time to pregnancy with age.

Time to pregnancy and age at the begin of attempt to get pregnant

The picture is different when our age variable is not age at the 7th month of pregnancy but age at the time women began their attempt of getting pregnant. In this case the earlier results disappear and we either get no significant results, or they point in the opposite direction (Figure 1, right panel). Hazard rate of women aged 25 to 29 is thus increased compared to women below 25 and the same stands for women aged 30 to 34.

Figure 1: Hazard ratios for time to pregnancy with two different definitions of maternal age (with 95% CI)



Red dots mark significant effects (p<0.05).Source: Own calculations based on the Cohort'18 database. Results of the Cox models, controlled for highest level of education, type of, subjective income, smoking before pregnancy, body mass index, previous miscarriage or an induced abortion.

Wilcoxon Signed Rank Test

Since the two age variables (without recoding, in their continuous form) were not normally distributed, a Wilcoxon Signed Rank Test was performed to determine if there was a statistically significant difference between the two variables: age at the begin of attempt and age at 7th month of pregnancy.

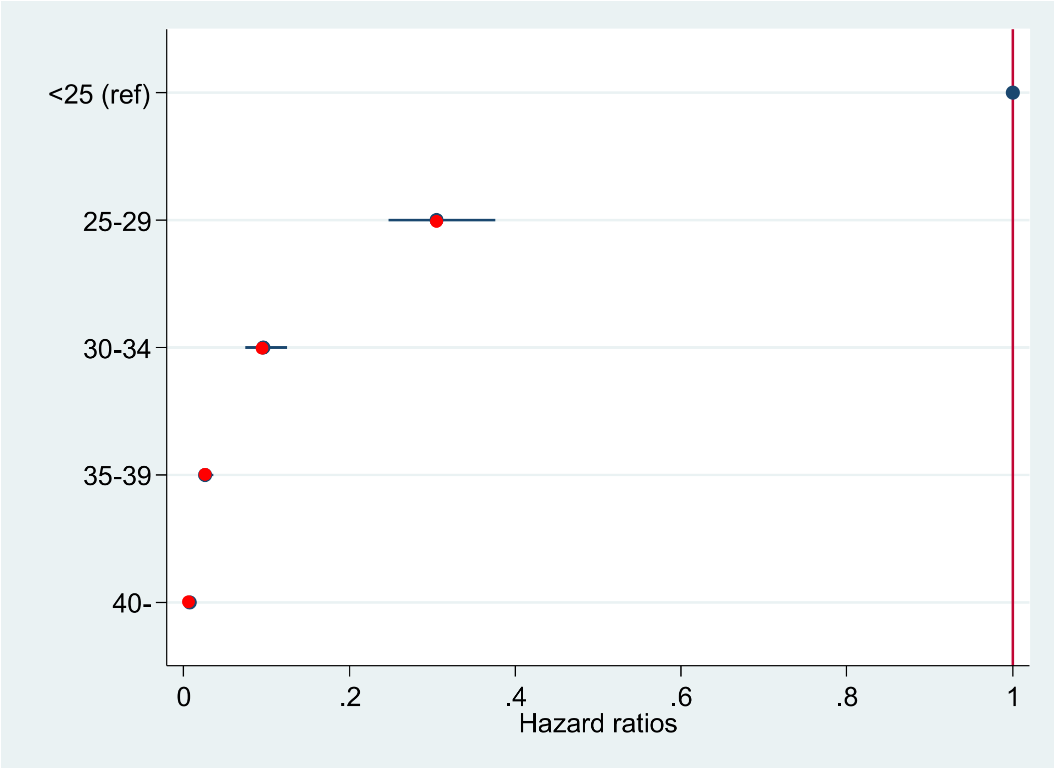
The test revealed that there was a statistically significant difference in mean between the two variables (z = 70.757, p = 0.0000) and that age at begin of attempt is statistically significantly lower than age at pregnancy.

Age at pregnancy with control for the begin of the attempt to get pregnant

In our final model we retain maternal age at the 7th month of pregnancy as the predictor variable, while controlling – among other background variables – for age at begin of the attempt to get pregnant.

Results show that age is an important predictor of time to pregnancy, and its effect is more important than in model 1, where we did not include age at attempts as control variable. In the final model, hazard ratios decrease in a drastic manner from the age of 25 suggesting a more important effect of age on fecundability, than found in in previous studies where the main benchmark was 30 years. Compared to women below 25, the hazard ration among those aged 25-29 is decreased by 70%. The effect is more pronounced in the older age groups, so that hazard rates of women over 40 only slightly pass 0 (Figure 2).

Figure 2: Hazard ratios for time to pregnancy with age at 7th month of pregnancy, controlled for age at begin of attempt (with 95% CI)



Red dots mark significant effects (p<0.10).Source: Own calculations based on the Cohort'18 database. Results of the Cox models, controlled for highest level of education, type of, subjective income, smoking before pregnancy, body mass index, previous miscarriage or induced abortion.

Cox regression with controls (Model 3)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf. Interval]	
AGE at 7th month of pregnancy						
<25	1	(base)				
25-29	**.3051358**	.0326225	-11.10	0.000	.2474514	.3762672
30-34	**.096545**	.0126722	-17.81	0.000	.0746456	.1248692
35-39	**.026219**	.0042149	-22.65	0.000	.0191328	.0359297
40=<	**.0070842**	.0014355	-24.43	0.000	.0047622	.0105384
EDUCATION						
Low	.89692	.066049	-1.48	0.140	.7763748	1.036182
Low vocational	1	(base)				
Middle	**1.158222**	.0659328	2.58	0.010	1.035945	1.294933
High	**1.250606**	.0769169	3.64	0.000	1.108584	1.410823
SMOKING BEFORE PREGANCY						
No	1	(base)				
Yes	**.9306423**	.0345247	-1.94	0.053	.8653766	1.00083
BODY MASS INDEX						

Underweight	.9771078	.0590181	-0.38	0.701	.868019	1.099906
Healthy weight	1	(base)				
Overweight	.9472447	.036056	-1.42	0.154	.879148	1.020616
Obesity	**.8803302**	.039547	-2.84	0.005	.8061338	.9613556
NUMBER OF PREVIOUS LIVEBIRTHS						
0	1	(base)				
1+	**1.269056**	.041407	7.30	0.000	1.190441	1.352864

Source: Own calculations based on the Cohort'18 database. Results of the Cox models, controlled for: age at begin of attempt, marital status, age at menarche, subjective income. Stratified for having had an abortion and for the diseases of the thyroid gland.

Conclusion

Our results raise important methodological issues in the study of time to pregnancy while confirming previous findings concerning the important effect of womens' age on TTP.

In a sample of pregnant women TTP has a different meaning than in the general population because important subjects are excluded from the analyses: sterile couples and couples who have given up trying to become pregnant (Olsen et al., 1998). Our sample is in addition a pregnant women cohort including women who became gravid at a same period (in 2018) while having had very different life histories behind. All of them are fertile women and even those with a longer TTP finally succeeded in achieving a pregnancy; while those who didn't, are excluded from the analyses. Older couples may by the way give up their attempt more quickly which by definition excludes them from the pregnant sample.

This explains to a large extent why our results were contradictory when we only looked at age at 7th month of pregnancy. This age variable showed much less variation than the age at the begin of the attempt to get pregnant, which was significantly lower. We therefore decided to control for age at begin of attempt in the final model, while presenting results for the effect of age at pregnancy. We were able to show that, in contrast to previous results which showed a cut-off age of 35 (Rochebrochard & Thonneau, 2003), in our sample women aged 25 and over already had a longer time to pregnancy than women under this age.

The effect of lifestyle factors such as smoking and body mass index, as shown in previous studies is besides confirmed (Axmon et al., 2006; Wesselink et al., 2019) as is the fact that having already had a child makes the arrival of a new pregnancy less problematic.

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Annexe: Description of the study population

Table 1. Description of the study population (n=4739)

		%
Maternal age at childbirth		
	< 30	41.3
	30-34	35.28
	35-39	18.97
	40=<	4.49
Paternal age at childbirth		
	< 35	53.41
	35-39	26.37
	40-44	15.43
	45=<	4.8
Highest level of education (mother)		
	Very low	9.2
	Low	9.0
	Middle	42.9
	High	39.0
Highest level of education (father)		
	Very low	7.4
	Low	24.0
	Middle	38.0
	High	30.6
Partnership (type)		
	Married	64.7
	Other	35.3
Subjective wellbeing		
	Difficult	3.9
	Middle	69.2
	Good	26.9
Female smoking during pregnancy		
	No	74.4
	Yes	25.6
Previous livebirth (mother)		
	No	50.96
	Yes	49.04
Previous livebirth (father)		
	No	50.46
	Yes	49.54
Previous miscarriage		

No	82.2
Yes	17.8
Previous induced abortion	
No	89.8
Yes	10.2

Source: Cohort'18. HDRI. Own calculations.