Estimation of the frequency of involuntary infertility on a nation-wide basis

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1　**Estimation of the frequency of involuntary infertility on a nation-**

2　**wide basis**

3

4　Running title:

5　A nation-wide survey of couple fecundity

6

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24

25　Word count:

26　　　Abstract: 246

27　　　Text: 5323

28

1   ABSTRACT

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3   BACKGROUND: Assessing the couple fecundity on a nation-wide basis without excluding

4   couples who eventually remain infertile is challenging. Our aim was to describe the couple

5   fecundity (in terms of frequency of involuntary infertility) among the general population living

6   in France. METHODS: We used a current-duration design. A random sample of 64,262

7   households was selected in 2007-2008, allowing us to identify 15,810 women aged 18-44

8   years. Eligible women (n=1089) were those having regular sexual intercourse with a male

9   partner, not using any method of contraception and not having delivered in the previous 3

10 months. These women reported information on the current duration of unprotected

11 intercourse (CDUI, the time elapsed between the start of the period of unprotected

12 intercourse and the time of inclusion in the study). The CDUI distribution was used to

13 estimate the frequency of involuntary infertility, using a newly developed statistical technique

14 that does not require couples to be followed-up until the end of the period of unprotected

15 intercourse. RESULTS: CDUI was defined for 867 women. An estimated 46% of couples had

16 no detected pregnancy conceived during the first 6 months of unprotected intercourse (95%

17 confidence interval, 36-56%). The proportions of couples with no detected pregnancy within

18 12 and 24 months were 24% (19-30%) and 11% (8-14%), respectively. CONCLUSIONS:

19 These results constitute one of the few descriptions of the fecundity of a nation-wide

20 representative sample of couples from the general population, not limited to couples who

21 eventually conceived or to those resorting to medical help.

22

23 Key words: Fecundability; Fecundity; Infertility; Involuntary infertility; Pregnancy;

24

1   INTRODUCTION

2   Few descriptions of the couples' ability to conceive a pregnancy (fecundity) exist in non-

3   selected groups of the general population. Fertility, the actual number of children per woman,

4   is monitored in most countries and is statistically associated with having a time to pregnancy

5   longer than 12 months (Joffe, et al., 2009). However, outside the specific context of

6   populations not using contraceptive methods (Larsen and Vaupel, 1993), it constitutes a very

7   indirect and probably not very sensitive indicator of the occurrence of impaired fecundity.

8   Data on the use of assisted reproduction technologies (ART) are widely available (de

9   Mouzon, et al., 2010, de Mouzon, et al., 2009), but information on the number of couples

10   resorting to ART is difficult to interpret without knowledge of the population at risk (those

11   trying to become pregnant), and because involuntarily infertile couples seek for medical help

12   after variable durations of unprotected intercourse (Moreau, et al., 2010) and do not always

13   resort to ART.

14   Fecundity studies relying on a pregnancy-based design have been conducted in several

15   countries (Jensen, et al., 2001, Juul, et al., 1999, Muller, et al., 2006) (reviewed by Leridon,

16   2007), but this design excludes couples who do not conceive finally, thus overestimating the

17   fecundity level. Few surveys including couples who remain infertile have been conducted.

18   The European Studies of Infertility and Subfecundity (Karmaus, et al., 1999), a set of

19   retrospective studies conducted in Denmark, Germany, Poland, Italy and Spain in 1991-93,

20   considered unsuccessful attempts at pregnancy. Some cohort studies of pregnancy planners

21   have been conducted, but generally for etiologic or biologic purposes rather than to describe

22   fecundity at the population level, and in selected populations (Bonde, et al., 1998, Buck, et

23   al., 2004, reviewed by Guzick and Swan, 2006, Tietze, 1968, Weinberg, et al., 1994, Wilcox,

24   et al., 1988, Zinaman, et al., 2000). Demographers have also studied perceived fecundity or

25   impaired fecundity in the general population, for example in France (Leridon, 1992, Leridon,

26   2007) or in the US National Survey of Family Growth (Stephen and Chandra, 2006); these

27   studies, usually relying on large and well-defined population based samples are difficult to

28   compare to the above-mentioned "time to pregnancy" studies, either because they did not

1   use an objective cut-off (e.g., 12 or 24 months) to define involuntary infertility (Leridon, 1992)

2   or, in the case of the National Survey of Family Growth, because the number of cases of

3   (current) 12-month infertility is not divided by the number of couples (currently) at risk of

4   pregnancy, but by the size of the (larger) group of married women, regardless of whether

5   they were "at risk" of pregnancy, leading to a much lower rate of involuntary infertility than in

6   other studies (Guzick and Swan, 2006).

7   Our aim was to describe the frequency of involuntary infertility among the general population

8   of France without excluding couples involuntarily infertile. In terms of approach and study

9   design, the need to efficiently include infertile couples (Olsen and Rachootin, 2003, Sallmen,

10 et al., 2000, Slama, et al., 2004) implied the exclusion of retrospective designs. Among

11 prospective designs, the main options are the incident cohort design (Bonde, et al., 1998),

12 the prevalent cohort design (Keiding, 1992, Wise, et al., 2010), and the current duration

13 approach (Keiding, et al., 2002, Slama, et al., 2006). The very low eligibility rate of the

14 incident cohort design –probably around 1% of women of reproductive age (Bonde, et al.,

15 1998, Slama, et al., 2006) – made it in our eyes little suited for descriptive studies. The first

16 stage of the prevalent cohort design requires one to recruit a cross-sectional sample of

17 couples not using contraception and to collect the time elapsed since the start of the period

18 at risk of pregnancy to account for left-censoring in the analysis; this first stage also

19 corresponds to a current duration approach, which is therefore embedded into the prevalent

20 cohort design. We have recently demonstrated the feasibility of this design (Slama, et al.,

21 2006). For these reasons, we chose to use a current duration approach (Keiding, et al.,

22 2002, Slama, et al., 2006, Weinberg and Gladen, 1986).

23

1   METHODS

2   The study, termed the Observatory of Fecundity in France (Obseff), aims is to describe the

3   fecundity of couples from the general population at the nation-wide level, to describe

4   characteristics of menstrual cycle function using urinary biomarkers and to characterize the

5   influence of environmental factors (in particular atmospheric pollutants) on fecundity; only the

6   first aim is presented here. Our study follows the methodology of our feasibility study on the

7   current duration approach (Slama, et al., 2006), with slight modifications.

8

9   Population sample

10   Our approach was a two-stage stratified sampling (Slama, et al., 2006). At the first stage, a

11   random probability sample of households was selected using a stratified random sample of

12   all landline phones in mainland France (86% of households had a landline phone at the time

13   of the survey). Subjects who only had a mobile phone or no phone were not included in the

14   sample. Households in areas corresponding to urban areas of more than 100,000 inhabitants

15   were over-sampled and corresponded to about 61% of the random list of phone numbers

16   (compared to 46% in the whole French population), a feature taken into account in the

17   analysis by a reweighing approach (see below).

18   *Eligibility criteria*

19   Eligible households were those which were the main residence of a woman aged 18 to 44

20   years; if several women in this age range lived in the selected household, we randomly drew

21   one, without selecting another one if she turned out not to be eligible. Women aged 18 to 44

22   years (i.e. between their 18th and 45th birthdays) answered an eligibility questionnaire lasting

23   about 4 minutes. Eligible women were those living with a male partner or engaged in a

24   regular relationship with a male partner, who were not regularly using any method to avoid

25   pregnancy (nor was their partner) at the time of the study. The interviewer asked questions

26   about all types of methods to avoid pregnancy, enumerating all of them. Couples sporadically

27   using contraception were not considered to be eligible, unless they simultaneously declared

28   that they were trying to become pregnant. Women who did not have sexual intercourse in the

5

1 month prior to interview, and women who had delivered in the 3 months prior to interview

2 were excluded. Women were asked if they were currently trying to become pregnant, but this

3 was not an eligibility criterion. Indeed, following the logic of a previous study (Karmaus, et al.,

4 1999), our aim was to capture the whole population theoretically at risk of pregnancy,

5 whatever their fecundity level, without excluding those who are subfertile or may consider

6 themselves sterile after some duration of involuntary infertility. For the same reason, we did

7 not exclude from the main analysis women with irregular menstrual periods or couples in

8 which a male fertility disorder (e.g., low sperm count) had been diagnosed. Sensitivity

9 analyses excluding "non-planners" (defined with respect to the start of the period of

10 unprotected intercourse) and women without menstrual bleeding in the last 12 months are

11 provided (see below).

12 *Correction for population sampling and selection bias*

13 We used a weighting approach to correct for possible differences between the women who

14 accepted to reply to the eligibility questionnaire and women from the general population, and

15 to correct for the over-sampling of subjects living in urban areas of more than 100,000

16 inhabitants. First, a weight correcting for the over-sampling of large urban areas was defined;

17 a weight correcting for the lower probability of inclusion of women who were not the only

18 woman aged 18 to 44 years in the home was then generated. Finally a weight allowing the

19 recruited population of women aged 18 to 44 years who answered the eligibility criteria to be

20 more similar to the general population of women in this age range (based on the distributions

21 of age, marital life, number of children, age at the end of studies observed in the national

22 census) was created. The estimation of this last weight was based on a generalized raking

23 procedure (Deville, et al., 1993) and was implemented using CALMAR macro implemented

24 on SAS statistical software (INSEE). Finally, these weights were multiplied, and the

25 corresponding final weight was used in all analyses.

26

27 Current duration of unprotected intercourse

1   The main outcome was the rates of 6-month (respectively 12- and 24-month) involuntary

2   infertility, defined as the proportion of couples without a recognized pregnancy within 6

3   months (respectively, 12 or 24 months) of unprotected intercourse (although the term

4   *involuntary* tends to assume that couples wished to become pregnant -at least at the start of

5   the period of unprotected intercourse- we also used it in analyses including all periods of

6   unprotected intercourse, even those started in the absence of a pregnancy wish). These

7   outcomes were derived from the current duration of unprotected intercourse (CDUI), using an

8   approach outlined below. CDUI corresponds to the time elapsed between the start of the

9   period of unprotected intercourse and the interview. Women were also asked to provide the

10   duration elapsed since they last used a method to avoid pregnancy (in weeks, months and

11   years), if any, which was used if the date was missing. The starting date of the period of

12   unprotected intercourse was determined in three different ways. For the majority of women

13   (63%), it corresponded to the date of discontinuation of use of the last contraceptive method,

14   as declared by the woman. Women were asked if, upon discontinuing use of contraception,

15   they had waited for 1, 2 or 3 cycles before actively trying to become pregnant; if this was the

16   case then 28, 56 or 84 days, respectively, were subtracted from CDUI. We also checked that

17   no pregnancy declared by the woman had occurred since this date, and corrected the

18   starting date accordingly if this was not the case. If the couple had not used any method to

19   avoid pregnancy since the last pregnancy (32% of women), then the starting date was

20   defined as the end of the last pregnancy, plus three months in case of a live or stillbirth; if the

21   resulting assumed starting date was after the date of interview (*e.g.*, for women who

22   delivered a live newborn in the previous 3 months), then the couple was not considered to be

23   eligible. For couples who had never used any method to avoid pregnancy and in which the

24   woman had never been pregnant (5% of women), the starting date was that of the start of the

25   relationship.

26

27   Estimation of the probability of pregnancy

1　The principle of the current duration approach is to infer the underlying distribution (or

2　survival function) corresponding to an unobserved time interval until a given event, from the

3　distribution of the so far elapsed part of this time interval (Keiding, et al., 2002, van Es, et al.,

4　2000, Weinberg and Gladen, 1986, Yamaguchi, 2003). Here, we are interested in total time

5　interval of unprotected intercourse before a pregnancy (if any), but we only observe couples

6　not using contraception at a certain time period (the time of interview), without following them

7　up like in a cohort study. More precisely, the end of the period of unprotected intercourse, in

8　addition to successful conception, may also happen because the couple gives up (resumes

9　contraception because the couple considers it is not anymore a good time to become

10　pregnant, e.g. as a result of a change in their financial situation, or because the couple splits,

11　becomes too old, die). The possible onset of fertility treatment can also be considered as the

12　end of the period of unprotected intercourse, but another interpretation is possible. Indeed, it

13　is possible to argue *either* that fertility treatments change to some extent the probability of

14　conception away from the primary interest, so that the relevant time is unprotected

15　intercourse before onset of medical infertility treatment; in other words, we then consider

16　start of fertility treatment as another way of giving up trying. Alternatively, one may consider

17　that the couple is still trying to become pregnant during fertility treatment, if our focus is the

18　actual fecundity in today's society as it is (in which case onset of such treatments can be

19　ignored in analyses). We present both results here since each one has its logic. Note that

20　this way of handling a competing risk is necessary in the current duration approach in order

21　to avoid complex hypotheses on the transition rate to infertility treatments, and that it differs

22　from classical prospective (e.g., Cox) survival modelling, in which fertility treatments can be

23　handled by censoring or as competing risks. Infertility treatments were assessed by asking

24　specifically if each type of medical infertility treatment (drugs, artificial insemination, in vitro

25　fertilization, intra-cytoplasmic sperm injection) had been used by the woman or her partner,

26　and when.

27　The survival function corresponding to this underlying distribution has been estimated using

28　a parametric approach assuming a generalized gamma distribution (Keiding, et al., 2002,

1   Yamaguchi, 2003). Confidence intervals were built using a bootstrap approach. The

2   estimations were repeated restricting the population to women declaring that they were

3   currently trying to become pregnant or that they had stopped using a contraceptive method

4   because they wished to become pregnant (thereafter called "pregnancy planners"). A

5   modification of the approach initially proposed (Keiding, et al., 2002, Slama, et al., 2006)

6   regards very long current durations of unprotected intercourse. Many of these long durations

7   most probably concern couples who are aware of strong subfertility or even sterility, and

8   since our interest is in the shape of the distribution of time to pregnancy for the very first

9   years, we based the estimation on all durations shorter than 36 months and replaced

10   (without excluding them) those reported as being longer than 36 months by the information

11   that they were longer than 36 months.

12   The resulting estimated survival function can be interpreted as an estimate of the proportion

13   of couples who, after a given number of months, still have unprotected intercourse (that is,

14   they did not give up the period of unprotected intercourse) and did not obtain a clinically

15   detected pregnancy. In the case where couples with infertility treatments are excluded, it is

16   an estimate of an alternative fecundity measure, namely the proportion of couples who, after

17   a given number of months, still have unprotected intercourse and have neither obtained a

18   clinically detected pregnancy nor started fertility treatment.

19

20   Sensitivity analyses

21   We repeated the estimation of the proportion of couples who still have unprotected

22   intercourse in various subgroups or imposing alternative sets of assumptions: 1) assuming

23   that couples who had not resumed contraception since their last pregnancy had a duration of

24   post-partum infertility of 6 months (instead of 3 in the main analysis); 2) excluding women

25   who declared not to have had menstrual cycles in the last 12 months; 3) excluding couples

26   who declared that they had used contraception sporadically (included in the main analysis if

27   they declared to be currently trying to become pregnant) and 4) including couples with

28   sporadic contraception mentioned in 3) above, but assigning them a reduced CDUI, to

10

1   account for the fact that they were not exposed to pregnancy risk during all months since the

2   start of the pregnancy attempt; in practice, we arbitrarily halved their CDUI.

1   RESULTS

2   Population sample

3   We drew a random sample of 64,262 households, 19,121 of which were the main residence

4   of an 18-44 year old woman; 15,810 of these women accepted to reply to the eligibility

5   questionnaire (Figure I). Among women aged 18-44 years, 4.8% were pregnant at the time of

6   the eligibility questionnaire; 5.5% reported that they were currently trying to become pregnant

7   and 4.4% declared that they planned to try to become pregnant within the next 12 months

8   (Table I). Half of the women (48%) reported that they had no intention to try to become

9   pregnant in the future.

10

11   Estimation of the frequency of infertility

12   Among the women who answered the eligibility questionnaire, 1089 (6.9%) were eligible; that

13   is, they were not using any birth control method, had a male partner and had been sexually

14   active in the previous month. Out of these, 943 accepted to participate. The estimated overall

15   participation rate was 63% (Figure I). The current duration of unprotected intercourse (CDUI)

16   could be defined for 867 participating women. The characteristics of women with a defined

17   CDUI are shown in Table II. The median duration of CDUI, which has no direct interpretation,

18   was 13.2 months, with 25-75th percentiles equal to 3.7-41.8 months. From CDUI, we

19   estimated the underlying "survival" function, corresponding to the time to conception or end

20   of the period of unprotected intercourse for the source population (Figure IIA). The estimated

21   proportion of couples who would still not have conceived and would still be having

22   unprotected intercourse 6 months after the start of the interval of unprotected intercourse

23   was 46% (95% confidence interval, CI, 36-56%); it was 24% (95% CI, 19-30%) and 11%

24   (95% CI, 8-14%) within 12 and 24 months after the start of the period of unprotected

25   intercourse, respectively. Values were very slightly lower after restriction to the 708 couples

26   who declared that they had stopped using birth control methods in order to obtain a

27   pregnancy: rates were 45% (95% CI, 34-55%), 23% (18-28%) and 10% (8-12%) at 6, 12 and

28   24 months, respectively. After restriction to nulliparous couples, the proportions of couples

1   who had not conceived and were still having unprotected intercourse at 6, 12 and 24 months

2   after the start of the period of unprotected intercourse were 47% (95% CI, 26-68%), 26% (15-

3   36%) and 11% (7-16%), respectively (Figure IIB). In the analysis based on the alternative

4   fecundity measure (excluding from the initial population couples who had resorted to infertility

5   treatments, in order to estimate the proportion of couples who had not conceived nor started

6   infertility treatment and were still having unprotected intercourse), the rates at 6, 12 and 24

7   months after the start of the period of unprotected intercourse were 43% (95% CI, 34-53%),

8   20% (95% CI, 16-25%) and 8% (95% CI, 6-10%), respectively (Figure IIA).

9

10 Sensitivity analyses

11 Assuming a duration of 6 months of post-partum infertility instead of 3 led to the exclusion of

12 9 couples but had no impact on our estimates. Twelve women declared not to have had

13 menstrual cycles over the last 12 months before inclusion, and, again, excluding them had

14 no impact either on our results. Excluding couples who declared that they were trying to

15 become pregnant and that they were using contraception sporadically (n=113) yielded very

16 slightly increased rates of involuntary infertility (47%, 26% and 12% at 6, 12 and 24 months,

17 respectively). Including these couples with a halved current duration decreased the rates of

18 involuntary infertility to 37% (95% CI, 28-47%), 20% (15-25%) and 9% (7-11%) at 6, 12 and

19 24 months, respectively.

20

1   DISCUSSION

2

3   Comparison with former studies

4   To our knowledge, our study is one of the first to estimate the frequency of involuntary

5   infertility in a nation wide representative population sample and not relying on a retrospective

6   study design.

7   Several studies using other designs have provided descriptions of the couple fecundity (e.g.

8   Bonde, et al., 1998, Jensen, et al., 2001, Joffe, 2000, Karmaus, et al., 1999, Muller, et al.,

9   2006, Scheike, et al., 2008, Slama, et al., 2008). Most of these studies relied on

10   retrospectively collected information in women or men asked to describe earlier pregnancy

11   attempts, using either *pregnancy-based* (Jensen, et al., 2001, Joffe, et al., 2005, Scheike, et

12   al., 2008) or *historically prospective* (Karmaus, et al., 1999, Slama, et al., 2008) designs (the

13   former design is restricted to pregnancy attempts ending in a pregnancy, while the latter also

14   includes those ending with no pregnancy). In a historically prospective study, 932 couples

15   from Denmark, Germany, Poland, Italy and Spain described their periods of unprotected

16   intercourse resulting or not in a pregnancy, provided they had started less than 5 years prior

17   to the interview (Karmaus, et al., 1999). When the analysis was restricted to the first period of

18   unprotected intercourse, 23% of women had not conceived within the first 12 months of

19   attempt (varying from 33% in Poland down to 15% in South Italy); when the most recent time

20   of unprotected intercourse was considered (including current attempts started not more than

21   5 years before interview), the proportion of women who had not conceived within 12 months

22   of unprotected intercourse was 29% (Karmaus, et al., 1999). In a historically prospective

23   study in two French rural areas conducted in 2000 that considered pregnancy attempts

24   started between 1985 and 2000, Slama et al. (2008) reported a rate of 12-month involuntary

25   infertility of 16%. In a prospective study among Danish first pregnancy planners followed-up

26   for six months, 256 couples out of 430 conceived (Bonde, et al., 1998), which, after taking

27   into account censoring, corresponds to a 6-month involuntary infertility rate of 36%. In

28   another cohort of 221 women from America who volunteered in 1983-1985 as they were

1   planning to stop using birth-control methods in order to become pregnant, the 6-month

2   cumulative pregnancy rate was 78% (Wilcox, et al., 1988). Retrospective studies relying only

3   on periods of unprotected intercourse (or pregnancy attempts) leading to a live birth (the so-

4   called "pregnancy-based" design) yield lower rates of 12-month involuntary infertility: in

5   England, Joffe (2000) reported that 10% of couples whose first pregnancy attempt leading to

6   a live birth started in 1991-93 had needed more than 12 months to conceive. In another

7   pregnancy-based study in 4 European cities among couples who delivered in 1996-98, the

8   corresponding rate for couples recruited in Paris was 9.9% (Jensen, et al., 2001); it ranged

9   from 5 to 11% among fertile couples recruited using a similar design in four French cities in

10   2002-2003 (Muller, et al., 2006). In the *Enquête Nationale Périnatale*, a national sample

11   constituted of all women who delivered in all French maternity units in a given week in 2003

12   (Blondel, et al., 2006), time to pregnancy could be defined for 10,262 out of 14,482 live

13   births, and the rates of 6, 12 and 24-month infertility were 32% (95%, 31-33%), 18% (95%

14   CI, 17-19%) and 6% (95% CI, 5-6%), respectively (Slama, et al., (in press)). Although our

15   confidence intervals were relatively broad (19% to 30% for the estimated rate of 12-month

16   infertility), our estimate of the rate of 12-month involuntary infertility is somewhat higher than

17   the pregnancy-based values reported in the *Enquête Nationale Périnatale*. This is coherent

18   with what can expected from the facts that the latter study did not take couples remaining

19   infertile or giving up the pregnancy attempt into account and that couples fecund enough to

20   have many children are over-represented in such a pregnancy-based study.

21

22   Study population

23   Our study is based on a random sample from the general population. The estimated

24   participation rate of eligible couples was 63%, which offers potential for bias. Our population

25   was weighted to limit such bias. This weighing approach, consisting in making our population

26   more similar to the general population in terms of age and age at the end of studies, is

27   expected to correct efficiently for selection bias to the extent that factors associated with

28   participation and fecundity level are statistically linked with these sociodemographic

1   variables. Unlike some previous studies on time to pregnancy using a pregnancy-based

2   design, inclusion was not conditioned on couples having eventually obtained a pregnancy.

3   We tried to identify all couples possibly at risk of pregnancy, without excluding sterile or

4   subfertile couples. We chose not to condition inclusion on couples being currently trying to

5   become pregnant, because subfertile couples who had started a pregnancy attempt in order

6   to become pregnant may consider themselves subfertile or sterile after several months on

7   involuntary infertility, and may and consequently declare that they are not trying anymore to

8   become pregnant although they still have unprotected intercourse. We reported additional

9   results limited to couples who declared to have started the period of unprotected intercourse

10 in order to become pregnant so as to describe the fecundity of pregnancy planners, which

11 turned out to be very similar to that estimated without that exclusion.

12 Including parous women may induce bias or limit representativeness of the population

13 sample because previous reproductive history may impact persistency in trying to become

14 pregnant; this may also limit comparability with future studies because of possible temporal

15 changes in desired family size; for this reason, we also reported results restricted to

16 nulliparous women. These women had a very slightly higher rate of 12-month involuntary

17 infertility, compared to the overall population also including parous women.

18

19 Assumptions made by our design

20 Fecundity studies have several potential limitations. These relate in particular to the fact that

21 couples with unplanned or mistimed pregnancies usually have no defined duration of

22 unprotected intercourse; to variability in the delay before pregnancy detection, in access to

23 and use of contraception or in desired family size. These limitations however apply to most

24 other types of fecundity studies, and have been discussed at length elsewhere (see e.g.,

25 Joffe, et al., 2005, Key, et al., 2009, Slama, et al., 2006, Weinberg, et al., 1994); we will here

26 focus on sources of bias and assumptions specific to our study design. Our cross-sectional

27 design implies that couples who have had unprotected intercourse for a long time have a

28 higher probability of inclusion than couples with a shorter waiting time; however this length-

15

1   biased sampling is taken into account in the statistical analysis, which provides an unbiased

2   estimate under certain assumptions (Keiding, et al., 2002, Weinberg and Gladen, 1986). A

3   limitation of the design is that it does not allow one to distinguish couples who conceive a

4   pregnancy from those who abandon the pregnancy attempt, either because they split or

5   resume contraception before they conceive; that is, a period of involuntary infertility as

6   defined in our study corresponds to the time until pregnancy occurrence or end of

7   unprotected intercourse with no pregnancy. Data on the frequency of couples stopping a

8   period of unprotected intercourse before pregnancy occurrence are limited; persistency in

9   trying to become pregnant may vary according to mother's age at starting date, country

10 (Basso, et al., 2000), and probably other factors such as parity. The impact of such attempts

11 on the estimates from the current duration approach is expected to correspond to an

12 overestimation of the fecundity level, whose amplitude will depend on the frequency of these

13 attempts terminated because the couple split or resumed contraception. As forcefully pointed

14 out by Basso et al. (Basso, et al., 2000), these pregnancy attempts not ending in a

15 pregnancy also constitute a source of bias in the pregnancy-based design, which does not

16 allow including them either and in which the collected time to pregnancy is conditioned on

17 couples not giving up the period of unprotected intercourse; in that design also, their

18 exclusion leads to an overestimation of the fecundity level. In a prevalent cohort based on

19 couples recruited after less than 12 months of pregnancy attempt, the proportion of couples

20 who reported to discontinue trying to become pregnant during the following year was 5%

21 (Wise, et al., 2010). Compared to what had originally been suggested (Keiding, et al., 2002,

22 Slama, et al., 2006), we report here results including couples who had initiated an infertility

23 treatment since the start of the period of unprotected intercourse (as well as analyses

24 excluding these couples, corresponding to the approach used in our previous publication). If

25 these couples with infertility treatment are excluded, then the studied event is either

26 pregnancy, or end of the period of unprotected intercourse or start of a fertility treatment; if

27 these couples with infertility treatment are included, then the event is simply either pregnancy

28 or end of the period of unprotected intercourse; both estimates are worth reporting.

16

1   Coherently, including these couples yielded a somewhat higher frequency of 12-month

2   involuntary infertility (24%, compared to 20% if couples with a treatment are excluded),

3   corresponding to a longer time to event.

4

5   Relevance of the current duration approach to describe fecundity

6   Describing and possibly monitoring couple fecundity takes on importance in the context of

7   increasing use of ART and of the possible deterioration of male reproductive health. Indeed,

8   several studies have described temporal decreases in sperm concentration and motility in

9   specific areas of industrialised countries over the last decades (Auger, et al., 1995, Carlsen,

10   et al., 1992, Nelson and Bunge, 1974, Swan, et al., 2000). These decreases cannot be

11   considered as certain, in particular because studies reporting temporal trends in semen

12   quality are often based on self-selected subjects, not allowing quantification of participation

13   rates and description of possible selection bias (Cohn, et al., 2002, Eustache, et al., 2004,

14   Hauser, et al., 2005, Muller, et al., 2004). If true, such a decline might have had an impact on

15   fecundability, the cycle-specific probability of pregnancy among non-contracepting couples,

16   as indicated by a simulation study (Slama, et al., 2004). This decline in fecundability may not

17   imply strong changes in the average number of children per couple, but could entail

18   increases in the proportion of couples subject to 1- to 5-year involuntary infertility (Leridon

19   and Slama, 2008).

20   Very few studies directly tried to assess temporal trends in fecundability or involuntary

21   infertility of populations (Jensen, et al., 2005, Joffe, 2000, 2008). These studies generally do

22   not cover areas where temporal declines in semen quality have been reported. Results do

23   not show decreases in couple fecundity. Their pregnancy-based design excludes couples

24   who remain involuntarily infertile, therefore limiting the statistical power of analyses trying to

25   highlight changes in fecundity, and possibly biasing the comparison towards absence of

26   change in fecundity (Slama, et al., 2004). Additionally, it has been argued that temporal

27   trends in the proportion of unwanted pregnancies and abortion rates may make it difficult to

28   describe time trends in fecundity (Sallmen, et al., 2005). Several approaches can be used to

17

1   correct for these potential biases (Joffe, et al., 2006, Joffe, et al., 2005, Key, et al., 2009) but

2   the efficiency of these approaches may in practice be limited in the context of a retrospective

3   survey design (Sallmen, et al., 2006). For these reasons, alternatives to a retrospective

4   design are worth investigating. These include the (incident) cohort design (Bonde, et al.,

5   1998), the prevalent cohort design (Keiding, 1992, Wise, et al., 2010) and the current

6   duration approach. Other designs have been suggested (Olsen and Andersen, 1999) but not

7   applied to our knowledge.

8   The eligibility rate in the current duration approach is relatively low; we had to survey 15,810

9   couples in order to recruit 867 couples (5.5%) with a defined current duration of unprotected

10   intercourse. This eligibility rate is higher than that of the main other prospective design, the

11   (classical) cohort design, in which couples are recruited before the start of the period of

12   unprotected intercourse. Indeed, less than 2% of women aged 18-44 years contacted

13   indicated that they planned to start a pregnancy attempt within the next 6 months, out of

14   which probably not all will do so within this duration. Conversely, some couples may start a

15   pregnancy attempt in the same time period without having planned it long in advance, and

16   these would be hard to identify and include in an incident cohort. These study designs are

17   actually not incompatible one with the other; indeed, couples who plan to start a pregnancy

18   attempt soon (eligible in an incident or prevalent cohort on fecundity) can also be identified

19   from the eligibility questionnaire of a current-duration study such as ours, and these can be

20   followed-up, together with couples eligible for the current duration design at the time of

21   interview. If repeated at regular time intervals, such a design could be used to prospectively

22   monitor time trends in fecundity. This could be seen as a parallel to the studies monitoring

23   semen quality in young men in Scandinavian countries (Jorgensen, et al., 2006); as

24   suggested by Olsen and Rachootin (2003), a system monitoring fecundity should monitor

25   semen quality in parallel to a measure of the couple fecundity such as involuntary infertility.

26

27   In conclusion, our study provides an estimate of the frequency of involuntary infertility in the

28   general population showing that about one in four to five couples have not conceived a

19

1   detected pregnancy and are still having unprotected intercourse 12 month after having

2   stopped using a contraceptive method, and that about one couple out of ten may still be

3   unsuccessful in conceiving after 2 years of unprotected intercourse.

4

1   AUTHORS' ROLES

2   RS and JB initiated the study. RS, BD, NK, AB and JB designed the study and

3   questionnaires; AB, BD, JB and RS supervised data collection. AB, BD and RS cleaned and

4   prepared data. The statistical analyses were planned and supervised by RS and NK and

5   carried out by OH, DS and LGA. RS drafted the first version of the manuscript. BD, LGA,

6   MJCE, LR, JCT, NK and JB critically reviewed the manuscript.

7

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3

4

1   TABLES

2   Table I: Characteristics of the women who replied to the eligibility questionnaire.

Characteristic	Whole population (n=15,810)		Current duration group			
			Yes (n=867)		No (n=14,943)	
	n	Weighted %[a]	n	Weighted %[a]	n	%[a]
Age at interview (years)						
18-24	2,756	22.8	53	9.4	2,703	23.5
25-29	2,601	17.1	193	25.0	2,408	16.7
30-34	3,048	19.2	254	30.4	2,794	18.6
35-39	3,836	20.5	222	21.0	3,614	20.4
40-44	3,569	20.5	145	14.2	3,424	20.8
Currently has a male partner						
Yes	12,178	66.9	867	100	11,311	65.1
No	3,632	33.1	0	0	3,632	34.9
Number of children						
0	5,420	38.7	360	42.3	5,060	38.5
1	3,016	20.4	281	32.9	2,735	19.7
2	4,693	24.8	159	15.2	4,534	25.3
3 and more	2,681	16.2	67	9.6	2,614	16.5
Current contraception						
Yes, systematically used	13,105	82.0	0	0	13,105	86.5
Yes, sporadically used	136	0.9	113	13.1	23	0.2
No method to avoid pregnancy [b]	2,150	14.3	754	86.9	1,396	10.4
Surgical sterilisation [c]	406	2.8	0	0	406	2.9
Do not know	13	0.1	0	0	13	0.1
Defined CDUI						
Yes	867	5.2	867	100	0	0
No	14,943	94.9	0	0	14,943	100
Planning to try to become pregnant [d]						
Yes, currently trying	859	5.5	655	75.6	204	1.5
Yes, will start within 1 or 2 months	27	0.1	3	0.3	24	0.1
Yes, in about 3 months	60	0.4	2	0.1	58	0.4
Yes, within 4-6 months	181	0.9	1	0.03	180	1.0
Yes, within 7-12 months	511	3.0	12	1.7	499	3.1
Yes, in more than a year	1,789	12.0	17	2.2	1,772	12.5
Yes, but not planned when	3,460	24.9	32	4.0	3,428	26.1
No	7,700	48.1	139	15.6	7,561	49.9
Does not know	57	0.4	6	0.5	51	0.4
Currently pregnant	751	4.8	0	0	751	5.0

3
4   CDUI: Current duration of unprotected intercourse.
5   [a] Percentages were corrected for possible selection bias and over-representation of urban compared to rural
6   areas.
7   [b] Including pregnant women.
8   [c] Surgical sterilisation corresponded to tubal ligation, vasectomy or hysterectomy.
9   [d] Women with surgical sterilisation have not been asked about pregnancy planning.
10
11

12

1   Table II: Characteristics of the 867 women with defined current duration of unprotected

2   intercourse.

Characteristic	n	Weighted %[a]
Age at interview		
18-24 years	53	9.4
25-29 years	193	24.9
30-34 years	254	30.4
35-39 years	222	21.0
40-44 years	145	14.2
Age at start of period of unprotected intercourse		
18-24 years	101	16.2
25-29 years	263	32.7
30-34 years	293	30.1
35-39 years	175	17.6
40-44 years	35	3.3
Number of children		
0	360	42.3
1	281	32.9
2	159	15.2
3 and more	67	9.6
Frequency of sexual intercourse		
1-3 per month	165	18.0
1-2 per week	418	47.5
>2 per week	269	34.6
Duration of menstrual cycle		
<27 days	161	24.2
27-29 days	356	42.4
>29 days	273	33.5
Medical treatment for infertility since start of the PUI		
No	708	83.4
Yes	159	16.6
Started the PUI to obtain a pregnancy		
Yes	708	80.8
No	159	19.3
Currently trying to become pregnant		
Yes	655	75.6
No	212	24.4
Smoking at the start of the PUI		
No	580	62.0
Yes	279	38.0
Body mass index (kg/m^2)		
<18.5	78	10.9
18.5-19.9	132	12.9
20-22.4	248	25.4
22.5-24.9	163	20.0
25-29.9	151	18.8
≥ 30	82	12.0
Current duration of unprotected intercourse [b]		
<3 months	182	20.2
3-5.9 months	113	12.9
6-11.9 months	118	13.2
12-23.9 months	130	16.2
24-35.9 months	75	8.9
≥ 36 months	249	28.6

3   PUI: Period of Unprotected Intercourse
4   [a] Percentages were corrected for possible selection bias and over-representation of urban compared to rural
5   areas by a reweighting approach. This explains why the variables relative to medical treatment and to whether
6   couples started the PUI to obtain a pregnancy have different weighted percentages although the number of
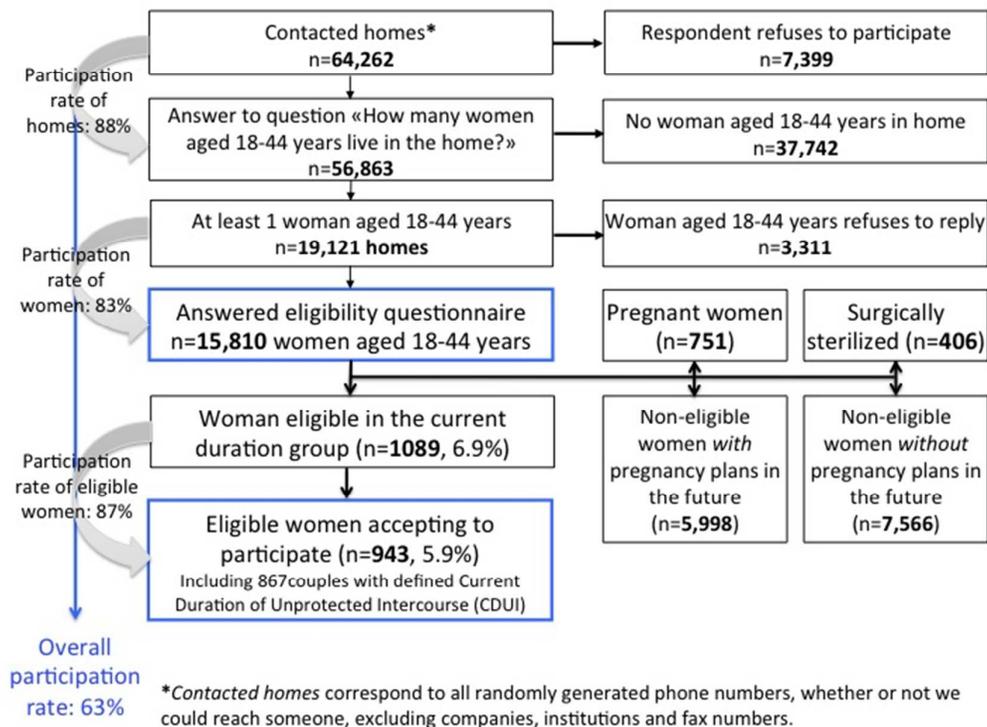7   subjects in each "Yes" and "No" categories, and hence the unweighted percentages, are the same.
8   [b] The distribution of the current duration of unprotected intercourse declared by couples has no direct
9   interpretation due to the length-biased sampling and should therefore not be interpreted as an estimate of the
10   frequency of involuntary infertility (given in Figure II).

1   FIGURES

2

3   Figure I: Flow chart of study population.

4

```
                    ┌─────────────────────────┐              ┌─────────────────────────────┐
                    │   Contacted homes*       │─────────────▶│ Respondent refuses to        │
Participation       │   n=64,262               │              │ participate  n=7,399         │
rate of             └─────────────────────────┘              └─────────────────────────────┘
homes: 88%          ┌─────────────────────────┐              ┌─────────────────────────────┐
                    │ Answer to question «How  │─────────────▶│ No woman aged 18-44 years in │
                    │ many women aged 18-44    │              │ home  n=37,742               │
                    │ years live in the home?» │              └─────────────────────────────┘
                    │ n=56,863                 │
                    └─────────────────────────┘
                    ┌─────────────────────────┐              ┌─────────────────────────────┐
Participation       │ At least 1 woman aged    │─────────────▶│ Woman aged 18-44 years       │
rate of             │ 18-44 years              │              │ refuses to reply  n=3,311    │
women: 83%          │ n=19,121 homes           │              └─────────────────────────────┘
                    └─────────────────────────┘
```

Contacted homes* n=64,262

Participation rate of homes: 88%

Answer to question «How many women aged 18-44 years live in the home?» n=56,863

Respondent refuses to participate n=7,399

No woman aged 18-44 years in home n=37,742

At least 1 woman aged 18-44 years n=19,121 homes

Participation rate of women: 83%

Woman aged 18-44 years refuses to reply n=3,311

Answered eligibility questionnaire n=15,810 women aged 18-44 years

Pregnant women (n=751)

Surgically sterilized (n=406)

Woman eligible in the current duration group (n=1089, 6.9%)

Participation rate of eligible women: 87%

Non-eligible women *with* pregnancy plans in the future (n=5,998)

Non-eligible women *without* pregnancy plans in the future (n=7,566)

Eligible women accepting to participate (n=943, 5.9%)
Including 867 couples with defined Current Duration of Unprotected Intercourse (CDUI)

Overall participation rate: 63%

*Contacted homes correspond to all randomly generated phone numbers, whether or not we could reach someone, excluding companies, institutions and fax numbers.

5

29

Figure II: Estimation of the proportion of sexually active couples still without detected pregnancy and still not using contraception, as a function of the number of months elapsed since the start of the period of unprotected intercourse. The usual clinical definitions of infertility would correspond to the values at 12 and 24 months. **A)** Whole eligible population (n=867, and n=708 after restriction to non treated couples); **B)** nulliparous couples only (n=360 and n=277 after restriction to non treated couples).

A) Whole population

B) Nulliparous couples
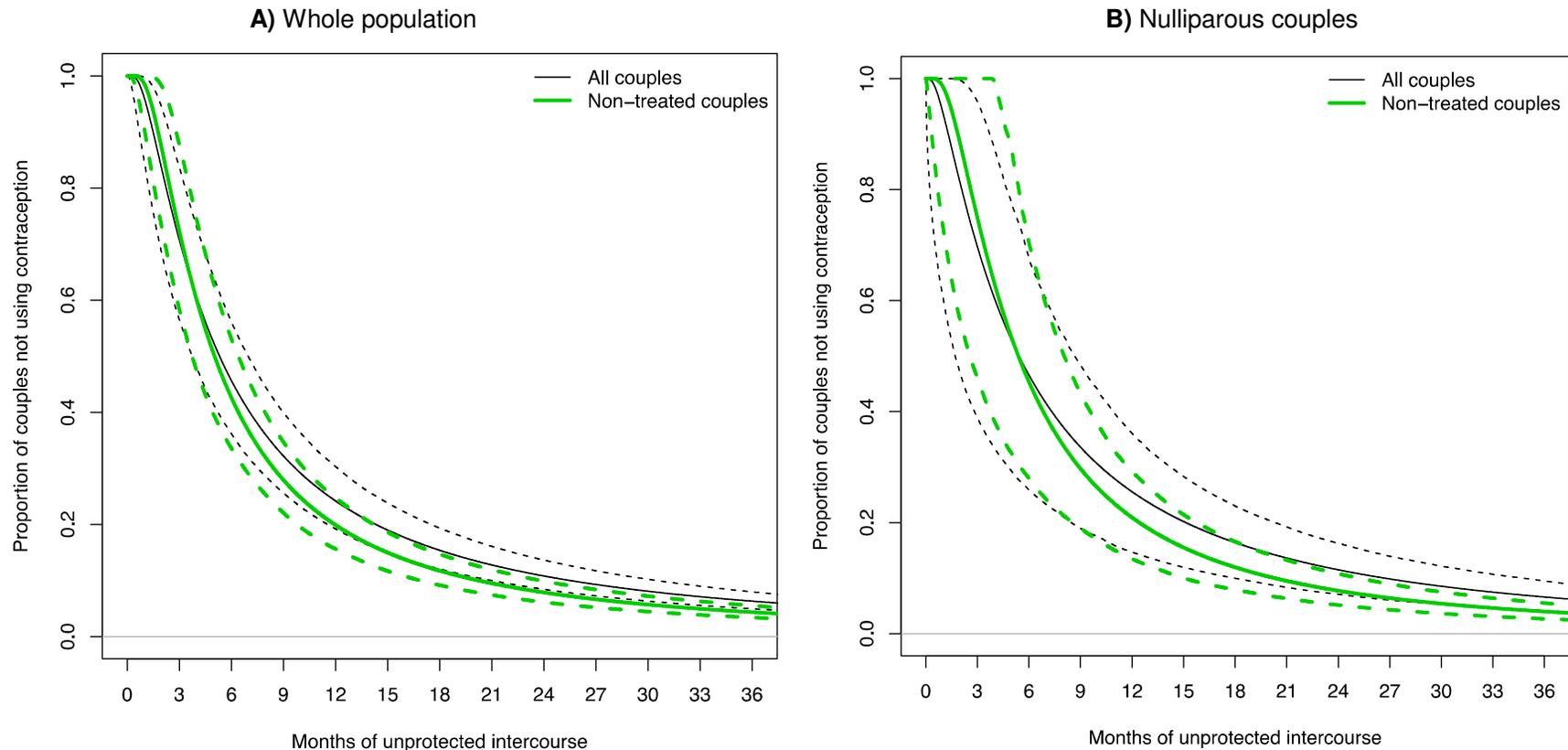
The survival function corresponding to time until pregnancy or end of the period of unprotected intercourse without pregnancy is indicated by the black solid line (estimated from the whole population at risk of pregnancy at inclusion). The green curve is the same estimate, but recomputed after exclusion of couples who had begun treatment for infertility. Dotted curves indicate 95% confidence intervals.

30