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Pregnancy loss: A 40-year nationwide assessment

Øjvind Lidegaard[1,2] | Anders P. Mikkelsen[1,2] | Pia Egerup[3,4] | Astrid M. Kolte[2,3] | Steen Christian Rasmussen[1] | Henriette S. Nielsen[2,3,4]

[1]Department of Gynecology 4232, Rigshospitalet University Hospital, University of Copenhagen, Copenhagen, Denmark

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]The Fertility Clinic and the Danish Recurrent Pregnancy Loss Unit, Rigshospitalet University Hospital, University of Copenhagen, Copenhagen, Denmark

[4]Department of Obstetrics and Gynecology, Hvidovre Hospital, Hvidovre, Denmark

Correspondence
Øjvind Lidegaard, Department of Gynecology, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen Ø, Denmark.
Email: oejvind.lidegaard@regionh.dk

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Abstract

Introduction: Pregnancy loss is frequent. We aimed to assess the frequency and trends in pregnancy losses according to female age and mode of conception over a 40-year follow-up period.

Material and methods: In a national historical prospective cohort study, we followed all Danish women 10-49 years over the 40-year study period 1978-2017. Data on pregnancies and their outcomes were obtained from the National Health Registry, the Medical Birth Registry and the National Fertility Registry. Incidence rates per 100 pregnancies and per 1,000 women-years as well as lifetime risks per 100 women were calculated. Women included in the lifetime analysis were followed from age 12 to age 49. Pregnancy loss included spontaneous abortion, missed abortion and anembryonic pregnancy.

Results: In 3 519 455 recorded pregnancies, 337 008, or 9.6%, were diagnosed with a pregnancy loss. The proportion increased from 7.5% in 1978-1979, peaked at 10.7% in 2000 and thereafter decreased to 9.1% in 2015-2017. Pregnancy loss rate in women 10-14 years was 3.9%, increasing gradually with age to 26.9% in pregnant women 45-49 years, a 6.9-fold increase. Loss rates were slightly lower in naturally conceived pregnancies than in assisted pregnancies except for women above 45 years, where the risk of loss was higher in the spontaneously conceived group. Lifetime risk of specific numbers of losses were: 0: 76.9%, 1: 17.9%, 2: 3.9%, 3: 0.87%, and 4+: 0.35%.

Conclusions: The proportion of women experiencing pregnancy loss has changed little throughout four decades and is still primarily influenced by female age. More than 75% of pregnant women are never recorded with a pregnancy loss, and <1.5% will experience three or more losses.

KEYWORDS
anembryonic pregnancy, miscarriage, missed abortion, pregnancy loss, spontaneous abortion

1 | INTRODUCTION

Human reproduction still faces important challenges. An increasing proportion of couples struggle to conceive. However, the biggest challenge is still the high frequency of pregnancy losses after successful conception. Previous studies have documented in the order of 10% recorded pregnancy losses,[1–3] hiding however, a further 10%-15% early losses never being seen in the hospital or clinic[4,5] and therefore not recorded in the discharge diagnosis registries. Some of these losses occur so early in pregnancy that women do not recognize them as a loss.

Figures on pregnancy loss are also substantially influenced by inclusion or exclusion of induced abortions in the denominators when

frequencies are calculated, exclusion generally providing 20%-25% higher loss rates than if these induced abortions are included.

The traditional understanding is that pregnancy losses are due to a desirable selection discarding fetuses with genetic or structural malformations and ensuring a high proportion of healthy babies being born at term.

This consideration has been challenged, as some pregnancy losses seem to be due to maternal or perhaps paternal factors.[6,7] Previous pregnancies[8] and environmental factors may also play a role,[9] especially in recurrent pregnancy losses.[10] On the other hand, whereas aneuploidy has been found to account for more than half of all pregnancy losses, microdeletions and point mutations have recently been found to add further to losses caused by fetal genetic abnormalities.[11–13]

A first step in increasing understanding of the etiology of pregnancy loss is to construct long-term assessments of these events, stratified according to calendar time, maternal age, mode of conception and life-time statistics. The aim of this study was to establish such data.

Key message

Despite being the most frequent complication in pregnancy, <25% of all women in reproductive ages have ever been referred with a pregnancy loss; <1.5% of pregnant women will be referred with three or more pregnancy losses.

2 | MATERIAL AND METHODS

2.1 | Study design

A historical prospective national cohort study over the 40-year period 1978-2017.

2.2 | Study population

We included all women in Denmark 10-49 years of age during the study period.

2.3 | Data sources

The Danish National Health Registry was established in 1976, collecting discharge diagnoses and surgical codes from all public and private hospitals.[14,15] Abortion statistics, both spontaneous and induced, have been recorded since. The Danish Fertility Registry, established in 1994, provided information about pregnancies achieved by assisted reproductive technology, including in vitro fertilization, intracytoplasmic sperm injection, oocyte donation and frozen embryo transfer. A personal identification code assigned to all Danish citizens at birth or immigration, allows merge of data from several registries, and enables long-term follow up of all Danish woman during the 40-year study period. The specific information provided from each Registry is given in Table S1. Some women receiving treatment abroad may be coded with "assisted pregnancy" in the Danish National Health Registry. Those not appearing in the Fertility Registry but who have been recorded with an "assisted pregnancy" code in the Health Registry, were considered "foreign fertility treatments", a substantial part of which, in older women, are anticipated to be oocyte or embryo donation.

2.4 | Statistical analyses

Pregnancy losses were defined as either a spontaneous abortion, a missed abortion or an anembryonic pregnancy (blighted ovum). The specific diagnosis codes for these events are given in Table S2.

Statistics were elaborated assessing pregnancy losses according to periods, different age groups, time in pregnancy and different mode of conceptions—natural or assisted, defined as methods implying culture in vitro. Statistics on the influence of mode of conception were restricted to the period from 1994, where information about fertility treatments was available. We applied a restriction period after each loss diagnosis of 8 weeks, during which a woman could not be counted with a new pregnancy loss, despite having further discharge diagnoses in the Registry, because women with early pregnancy complications are often seen several times during the course of a pregnancy loss.

Incidence rates of losses per 100 pregnancies and per 100 exposure years in the general population according to specific age groups were established, as were cumulative frequencies according to age. We calculated lifetime statistics of 0, 1, 2, 3 and 4+ pregnancy losses, respectively.

The specific study population for each sub-analysis is outlined in Figure S1.

The denominator for all main calculations made on pregnant women included induced abortions, as most pregnancy losses occur during early pregnancy, most often before any termination of pregnancy is effectuated. For some statistics, sensitivity analyses were also conducted with exclusion of induced abortions.

Rate ratios were calculated with 95% confidence intervals. SAS Version 9.4 (SAS Institute, Charlotte, NC, USA) was used for data management and statistical calculations.

2.5 | Ethical approval

Permission to conduct the study was given by the Danish Data Protection Agency (J-no 0-201-03-8/1/KIKR).

3 | RESULTS

Through the study period of 43.5 million observation years, 3 519 455 pregnancies were recorded in our national registries, and 337 008, or 9.58%, of these were recorded as pregnancy losses.

The incidence rate of pregnancy loss per 100 registered pregnancies in women 15-44 years old increased from 7.5% in 1978-79 to 10.9% around 2000, and thereafter declined to 9.1% in 2015-2017 (Figure S2, Table S3). The corresponding rates per 100 person-years in the general population also including nonpregnant women were 0.6%, 1.0% and 0.7%, respectively.

Among pregnant women, pregnancy loss rates increased with age from 3.9% in the 10- to 14-year age group to 26.9% in women aged 45-49 years, or by 6.9-fold (Figure 1, Table S4). The consequence of excluding induced abortion from the denominator, is illustrated in Figure S3A,B.

The corresponding trend for pregnancy losses by increasing age in the general population demonstrated incidence rates rising and falling almost symmetrically around the peaking age of 25-29 years, with 1.4% pregnancy losses per 100 women-years.

The cumulated average risk of a pregnancy loss among all ever-pregnant women was 30.1%. This estimate, however, does not discriminate between several events in one woman and one event in others. In Figure 2 (and Table S5), we assess the cumulative proportion of women experiencing a specific number of pregnancy losses during their lifetime by increasing age. In this stacked figure, 76.9% never experienced a diagnosed pregnancy loss and 23.1% experienced at least one pregnancy loss—17.9% had one pregnancy loss in a lifetime, 3.9% had two, 0.87% had three, and 0.35% had four or more pregnancy losses.

The incidence rates of pregnancy losses among all women, also including those never pregnant, are illustrated in Figures S4 and S5. The incidence rates for all pregnancy losses peaked around 30 years of age. The cumulated curves peaked at 35 years for one pregnancy loss and at 40 years for two or more losses.

Pregnancy loss was diagnosed earlier in pregnancy by time (Figure 3). In 1995-1999, 11.1% of pregnancy losses were diagnosed before seven completed weeks. This proportion had increased to 23.6% in 2015-2017.

The pregnancy losses among women who had conceived after assisted reproductive techniques were compared with losses in pregnancies naturally conceived or established by insemination. To make the curves comparable, women recorded with oocyte donation or treated in foreign countries were first excluded (Figure 4, Table S6). There were slightly more losses in pregnancies achieved by assisted reproductive techniques in the age groups up to 40 years. In women above 40 years, however, the rate of pregnancy losses was significantly lower in assisted pregnancies than in spontaneous pregnancies, despite exclusion of recorded oocyte donations and exclusion of treatments outside Denmark.

During the period with Fertility Registry (from 1995), 12.2% of women with losses after 40 years were recorded with oocyte donation in the Fertility Registry or with a "foreign treatment" code in the National Health Registry. In women over 45 years, the corresponding figure was 58.0%. When these pregnancies were added

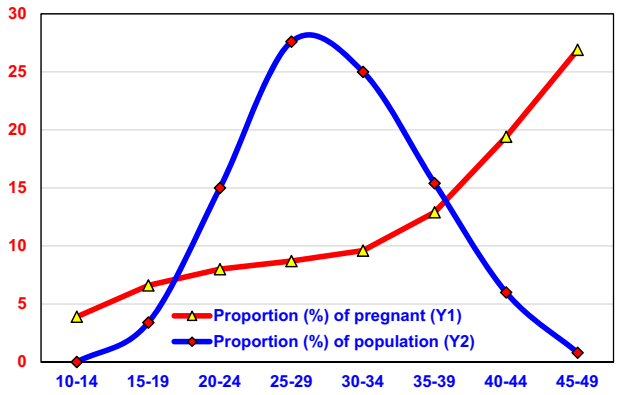

FIGURE 1 Pregnancy loss (%) by age in pregnant women (Y1) and per year in the general population of women (Y2). See Table S4 for exact data [Color figure can be viewed at wileyonlinelibrary.com]

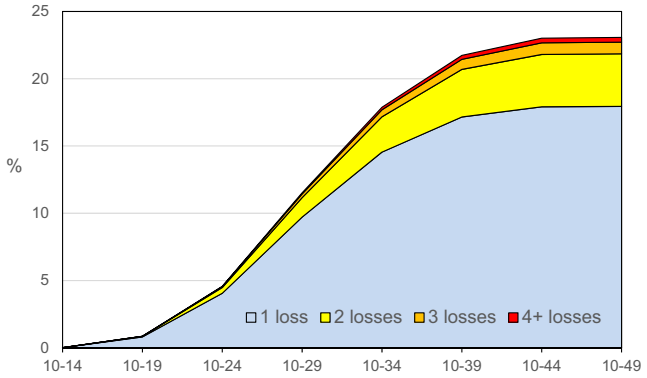

FIGURE 2 Lifetime risk of 1, 2, 3 and 4 + pregnancy losses per 100 women followed from 12 to 49 years during 1978-2017. The areas are stacked. See Table S5 for exact data [Color figure can be viewed at wileyonlinelibrary.com]

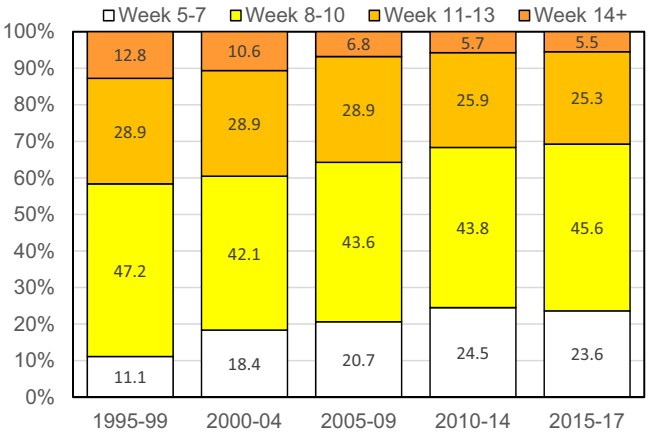

FIGURE 3 Gestational ages when pregnancy losses were diagnosed in 1995-2017. Age group 15-44 years. Week 5-7 goes from 4^{+0} through 6^{+6} weeks [Color figure can be viewed at wileyonlinelibrary.com]

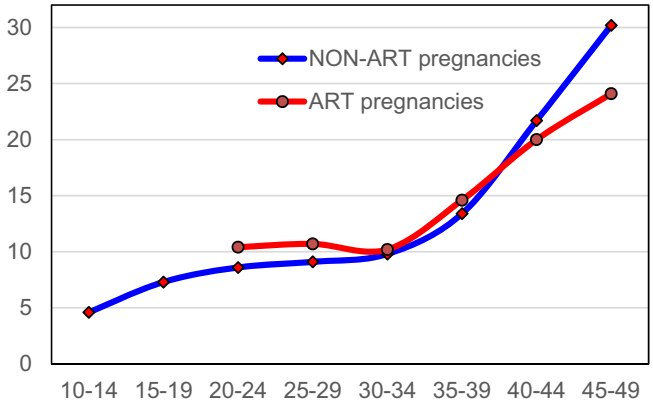

FIGURE 4 Risk of pregnancy loss (%) according to mode of conception. Assisted reproductive techniques (ART) include in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) and frozen embryo transfer (FET). Women pregnant after oocyte donation are excluded. See also Table S6 and Figure S5 [Color figure can be viewed at wileyonlinelibrary.com]

to the data in Figure 4, the loss frequency in assisted pregnancies decreased after 40 years, explained by the low loss rates seen in women after oocyte donation (Figure S6, Table S6).

4 | DISCUSSION

This long-term reproductive follow-up study of more than 3.5 million pregnancies demonstrated overall incidence rates of pregnancy losses among pregnant women of between 7.5% and 10.9%, and an almost 7-fold increase in risk with increasing age, consistent with previous findings.[16] The possibility of prospectively following a whole population over four decades made it possible to assess the lifetime risk of specific numbers of diagnosed pregnancy losses, showing that 76.9% women never experience such events, 17.9 one such event, 3.9% two events, and 1.25% three or more pregnancy losses; thus 23.1% experienced at least one pregnancy loss. The losses were detected still earlier in pregnancy through the study period, and risks seen among spontaneously conceived pregnancies did not differ much from pregnancies with assisted conception, except for pregnancies after oocyte donation, which had lower rates of losses.

In this study, pregnancy loss was defined as the sum of spontaneous abortion, missed abortion and anembryonic pregnancies. Not included were ectopic pregnancies, mole and pregnancies with unknown localization, as the majority of these are expected to be ectopic. This should be kept in mind, as other studies may define pregnancy losses differently.

The steady rise in the rate of pregnancy losses from 1978 until year 2000 could reflect both the increasing age at first birth from 24 years in 1978 to 29 years in year 2000, the widespread introduction of ultrasound throughout the study period, and more sensitive pregnancy tests, revealing pregnancy losses which previously were not recognized as such. Such a rise has been described also in the US data, although at a 4% higher level, reflecting the latter being statistics based on a self-reported pregnancy losses.[17]

A critical circumstance, which did not change throughout the study period, was the free and unlimited access to public healthcare hospitals and clinics, which could imply a barrier for being diagnosed in other countries.

The fall in rate of pregnancy loss since 2000, on the other hand, could be due to the new practice from about that time of not surgically evacuating miscarriages routinely.[18] Thereby, some women with early recognized losses would not necessarily be referred to a hospital but rather be seen by a private gynecologist or sustain the pregnancy loss without medical aid, therefore not being recorded in the diagnosis registries.

In our lifetime statistics, we were able to calculate cumulative counts of pregnancy losses for each woman, whereas previous studies have counted each event independently of previous experiences. If we assume that women in the category "four or more losses" had on average five pregnancy losses, the total percentage of pregnancy losses in all pregnancies was 30.1%, closer to previously reported figures[19] than the 23.1% affected women according to the long-term follow-up figures in this study. As we do not have data on pregnancy losses outside hospital or clinics, our 23.1% lifetime risk of one or more pregnancy losses is conservative.

That oocyte age is the primary cause of the more frequent pregnancy losses by increasing age is supported by the fall in losses among pregnant women past 40 and particularly after 45 years, when oocyte donations and treatment outside Denmark are included in the statistics. These oocytes are typically donated from younger women, and thus explain this fall. Fertility treatment in Denmark is not allowed after a woman turns 40 years at public clinics and after 45 years at private clinics.

The strengths of this study were the full coverage of an entire national female population, the compulsive registration of pregnancies referred to hospital, the complete follow up, and the long follow-up period, making lifetime reproductive histories feasible. For epidemiological purposes, the generally good validity of the discharge diagnoses and treatment codes in our health registries were also strengths.[20]

The most important limitation is the aforementioned lack of routine registration of pregnancies not referred to hospital or clinics, which are assumed to account for as many losses as those included in our national registries.

5 | CONCLUSION

In conclusion, 77% of women never experienced a diagnosed pregnancy loss, 23% of women experienced at least one pregnancy loss throughout their reproductive life, and the risk of pregnancy loss increased almost 7-fold by age. Around 1% of women experienced three or more losses in a lifetime. Finally, pregnancy losses were detected still earlier in pregnancy by time.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

ORCID

Øjvind Lidegaard https://orcid.org/0000-0002-7071-5496
Anders P. Mikkelsen https://orcid.org/0000-0002-7583-9826
Pia Egerup https://orcid.org/0000-0002-8047-2459
Astrid M. Kolte https://orcid.org/0000-0002-8250-6798
Steen Christian Rasmussen https://orcid.org/0000-0003-1809-0449
Henriette S. Nielsen https://orcid.org/0000-0003-2106-8103

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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