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Evidence for a 'healthy pregnant woman effect' in Niakhar, Senegal?

C Ronsmans,^a M Khlata,^b B Kodio,^c M Ba,^d L De Bernis^e and JF Etard^c

Background Although it is generally believed that pregnancy exposes women to a wide variety of excess health risks that go beyond the direct obstetric complications of pregnancy, the epidemiological evidence in support of such excess indirect risks is inconclusive. In this article we attempt to document the contribution of indirect causes of death to maternal mortality in rural Senegal by using an epidemiological approach whereby the time spent during pregnancy and postpartum is considered a transient period of exposure to the health hazards of childbearing.

Methods We use data from an ongoing demographic surveillance system in Niakhar, Senegal and calculate rate ratios comparing death rates in pregnant or recently pregnant women (exposed) with death rates in other women (unexposed), including and excluding direct obstetric deaths.

Results Between ages 20 and 44, pregnancy does not confer additional risks to women. After excluding direct obstetric deaths, exposed women aged 20-39 have surprisingly lower risks of death than unexposed women of the same age. For the very young (15-19) and the very old (45-49), on the other hand, the excess risks associated with pregnancy are considerable and, among women age 45 or older, persist even after excluding direct obstetric deaths.

Conclusion The apparent protective effect of pregnancy on women's health that is observed in this study illustrates the paradoxical nature of the concept of indirect causes of maternal mortality, and the difficulties in measuring the risks of death attributable to the pregnancy. Further studies aimed at separating risks attributable to the pregnancy from those that are incidental to the pregnancy are required.

Keywords Maternal mortality, cause of death, developing country, selection bias

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Over the last two decades, maternal mortality has gained increasing recognition as an important public health issue in developing countries, and is now considered as one of the most sensitive indicators of socioeconomic and health care inequalities. Despite increasing attention to the problem of maternal ill health, many uncertainties remain as to the nature and the magnitude of maternal mortality. In particular, a difficult and unresolved issue is the distinction between the risks attributable to childbearing and the risks of coincidental diseases.

Before the publication of the Ninth Revision of the International Classification of Diseases (ICD-9), deaths were classified as maternal only if they were a clear and direct consequence of complications arising during the pregnancy or puerperium (42 days after termination). ICD-9, however, expanded the concept of maternal mortality by introducing the notion of indirect maternal deaths, i.e. 'those resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy'.¹ The latest classification of disease, ICD-10, also embraced the notion of indirect deaths as an integral component of maternal mortality,² and introduced the concept of late maternal deaths (from 42 days to one year after termination) from direct or indirect obstetric causes.

There is no clear consensus as to what constitutes an indirect obstetric death. According to ICD-10, any cause that occurs during pregnancy or within 42 days, and even within one year, potentially qualifies as an indirect cause, except for accidents. In practice, those responsible for classifying maternal deaths often

^a Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, UK.

^b Institut National d'Études Démographiques, Paris, France.

^c Institut de Recherche pour le Développement (IRD), Dakar, Senegal.

^d Department of Obstetrics and Gynaecology, A.Le Dantec Hospital, Dakar, Senegal.

^e Department of Reproductive Health and Research (RHR), WHO, Geneva, Switzerland.

Reprint requests: Carine Ronsmans, Maternal and Child Epidemiology Unit, London School of Hygiene and Tropical Medicine, 49-51 Bedford Square, London WC1B 3DP, UK. E-mail: carine.ronsman@lshtm.ac.uk

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decide on a case-by-case basis whether or not they categorize certain causes as indirectly attributable to or incidental to the pregnancy. It is not surprising therefore that definitions vary. In a European study, for example, deaths from communicable diseases were classified as incidental to the pregnancy except for infections such as chickenpox, gonorrhoea, herpes and hepatitis C.³ In the system of confidential enquiries into maternal deaths in the UK, on the other hand, deaths from meningitis or pneumonia may qualify as being indirectly related to the pregnancy.⁴ Similarly, deaths from cancers of the colon or the brain were classified as indirect in the UK but as incidental in the European study. In developing country settings relying on verbal autopsy methods, the attribution of causes is even more complex. In such settings, all deaths in pregnant or recently delivered women are commonly included in the maternal mortality statistic (whether or not they are attributable to the pregnancy), except for deaths due to unintentional and intentional injuries.^{5,6}

One way to gain a better understanding of causes indirectly attributable to pregnancy is to compare death rates from causes not directly related to the pregnancy in pregnant women to death rates in non-pregnant women. If certain diseases are aggravated by the pregnancy, then mortality from these diseases may be expected to be higher among pregnant than non-pregnant women. Although very few comparisons of this kind have been made to date, a recent study conducted in Bangladesh unexpectedly found that, once deaths from direct obstetric causes were excluded, the death rates among women during pregnancy or within 90 days after delivery were substantially lower than the death rates among women not exposed to childbearing.⁷ In certain age groups, death rates during pregnancy from causes other than direct obstetric causes were less than half the rate observed among non-pregnant women of the same age.

If similar findings are observed in other populations, we may have to rethink the concept of indirect causes of maternal mortality. The objective of this study is to compare death rates in pregnant or recently pregnant women with death rates in other women in a rural area in Senegal, including and excluding direct obstetric deaths.

Methods

Study population

The study was conducted in Niakhar (population approximately 29 000), a rural area about 150 km east of Dakar, the capital of Senegal. Three-quarters of the inhabitants in this area are Muslim and almost all belong to one ethnic group, the Sereer. The main source of income is subsistence farming. Three-quarters of the women have never been to school and fertility is very high with a total fertility rate of 7.21 in 1996.⁸

From 1983 onwards, yearly censuses were held to update demographic events.⁹ Information was collected per household, reconstituting its exact composition every year. From 1987 until 1997, data collection was done during weekly home visits, and events were updated during yearly censuses. From February 1997, quarterly home visits replaced the weekly visits. The demographic events recorded are live births, still births, deaths, marriages, divorces and in- and out-migration. Causes of deaths were routinely determined by interviewing family members

about the symptoms and signs occurring before the time of death, using a structured questionnaire.

Between 1996 and 1998, special efforts were made to identify all pregnancy-related deaths and their causes. The relatives of all the women aged 15–50 years who had died between 1984 and 1997 were visited by a physician (KB) who asked about the circumstances leading to the death and the signs and symptoms preceding death. The interview started with a free recording of the story as recalled by the relatives, followed by a structured questionnaire.

Two obstetricians (BM, DBL) independently allocated a probable cause of death using a structured summary of the interview. Deaths during pregnancy or within one year after delivery were divided into maternal and non-maternal causes based on the physicians' own judgement, guided by a list of causes for verbal autopsies suggested by the World Health Organization.¹⁰ When the two physicians disagreed on the maternal nature of the death, a third physician (RC) assigned a cause, and the death was considered maternal if two of the three physicians agreed on its nature. Maternal deaths were further divided into direct obstetric deaths (including deaths from abortion, hypertensive diseases of pregnancy, dystocia, haemorrhage and sepsis) and the so-called indirect obstetric deaths (e.g. tuberculosis, hepatitis, or cardiovascular diseases).

Analytical method

For this study we adopted an epidemiological approach whereby the time spent by women during pregnancy and postpartum was considered as a transient period of exposure to the health hazards of childbearing. Given that the postpartum period at risk is likely to be longer than 42 days, we have considered an exposure extending from pregnancy through 90 days postpartum.⁷

The total women-years of observation in women aged 15–49 years were obtained from the demographic surveillance data. Women-years of exposure were derived from the number of live births, assuming that each live birth contributes to an exposure period of one year including a period of gestation of 9 months followed by a puerperal period of 90 days. The number of live births was inflated by 15% to account for miscarriages and stillbirths.¹¹ Since pregnancies that end up in fetal losses may have a shorter period of exposure we repeated the analysis assuming a period of exposure of 6 months for miscarriages and stillbirths.

Deaths occurring during pregnancy or within 90 days postpartum were subdivided into direct obstetric deaths and deaths from other causes. As the assignment of the causes of death slightly differed between the two obstetricians, we used two separate estimates of the numbers of direct obstetric deaths (referred to as A and B, respectively, in the Tables). Death rates from all causes, and from those other than direct obstetric causes were calculated in women while exposed, and while unexposed. The latter included deaths from intentional and unintentional injuries. Rates were compared using rate ratios (RR) with confidence intervals (CI) based on the assumption of a Poisson distribution.

Results

Descriptive data: women-years of observation, live births and deaths

Among women aged 15–49 in Niakhar between 1984 and 1997 there were 73 000 women-years of observation, 16 812 live

Table 1 Deaths by cause, live births and woman-years of observation in women aged 15–49 years, Niakhar 1984–1997

	Age group							
	15–19	20–24	25–29	30–34	35–39	40–44	45–49	15–49
No. of deaths								
Regardless of exposure	42	50	45	46	35	51	48	317
While exposed ^a	17	19	15	15	9	11	14	100
Observer A								
Direct obstetric causes	13	11	10	10	7	6	9	66
Other causes ^b	4	8	5	5	2	5	5	35
Observer B								
Direct obstetric causes	9	12	8	8	6	5	8	56
Other causes ^b	8	7	7	7	3	6	6	44
While not exposed ^c	25	31	30	31	26	40	34	217
Total no. of live births	2108	4102	3913	3303	2232	958	196	16 812
No. of women-years of observation								
Regardless of exposure	14 556	12 938	11 951	10 567	8966	7245	6777	73 000
By exposure, assuming fetal losses contribute one year to exposure								
While exposed	2424	4717	4500	3798	2567	1102	225	19 334
While not exposed	12 131	8221	7451	6769	6399	6143	6552	53 666
By exposure, assuming fetal losses contribute 6 months to exposure								
While exposed	2266	4410	4206	3551	2399	1030	211	18 073
While not exposed	12 290	8528	7745	7016	6567	6215	6566	54 927

^a During pregnancy or within 3 months after pregnancy termination.

^b Deaths from other causes include 10 deaths from intentional and unintentional injuries. There was one death from injuries among exposed women, and nine deaths among unexposed women (two aged 15–19, one aged 20–24, three aged 30–34 and three aged 35–39).

^c Neither pregnant nor within 3 months after pregnancy termination.

births and 317 deaths (Table 1). Deaths during pregnancy and 90 days postpartum represented 31.5% of all deaths in women age 15–49 years, and most of those deaths (66% and 56% according to observers A and B, respectively) have been attributed to direct obstetric causes. Deaths from intentional or unintentional injuries accounted for a very small proportion (3%) of deaths from other causes (one and nine deaths among exposed and unexposed women aged 15–49, respectively). The distribution of live births and women-years of exposure reflect the typical bell-shape of age-specific fertility rates with a low below age 20, a maximum between ages 20 and 34 and a decline thereafter.

Death rates according to age

As expected, the death rate from all causes among all women increases with age (Table 2). The pattern among exposed women, on the other hand, follows a U-shape with high rates among the very young and the very old. Pregnant or recently delivered women aged 45–49, for example, have a death rate which is 18 times higher than that of women aged 35–39 (RR = 17.7, 95% CI: 7.2–46.5), and those aged 15–19 years have twice the death rate of the 20–24 age group (RR = 1.7, 95% CI: 0.9–3.5). Death rates from direct obstetric causes follow a similar U-shape, regardless of the choice of observer.

Death rates according to exposure

The all-cause mortality RR (Table 3, Figure 1) are markedly different across age categories with a distinct pattern emerging at both ends of the age distribution (χ^2 test for heterogeneity (6) = 61.0, $P < 0.0001$). Between ages 20 and 44, pregnancy does not appear to confer additional risks to women as none

of the RR are significantly different from one. After excluding direct obstetric deaths, exposed women aged 20–39 have a lower risk of death than unexposed women of the same age. Using the data from observer A, for example, the RR comparing exposed and unexposed women range between 0.45 in women aged 20–24 to 0.19 in women aged 35–39.

For the very young and the very old, on the other hand, the excess risks associated with pregnancy are considerable (RR = 3.4, 95% CI: 1.7–6.6 in women aged 15–19 and RR 12.0, 95% CI: 5.9–22.9 in women aged 45–49). In women age 45 or older, these excess risks persist even after excluding direct obstetric deaths (for example, using observer A's data the RR is 4.3 (95% CI: 1.3–11.0)).

Robustness of the findings

Although the estimates based on the two obstetricians' coding schemes or on the models with differing assumptions for the duration of exposure to miscarriages and stillbirths do differ, their pattern of variations are consistent with the above observations. Excluding deaths from injuries from these estimates did not alter the findings (data not shown).

Discussion

Pregnancy is traditionally considered as a particularly vulnerable period in the life of women and it is generally accepted that pregnancy exposes women to a wide variety of excess health risks that go beyond the direct obstetric complications of pregnancy. Given the occurrence of direct obstetric deaths, it would be logical to expect higher death rates from all causes in pregnant or

Table 2 Death rates (per 1000 women-years) according to exposure status in women aged 15-49 years, Niakhar 1984-1997

	Age group						
	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Regardless of exposure (all causes)	2.9	3.9	3.8	4.3	3.9	7.0	7.1
By exposure, assuming fetal losses contribute one year to exposure							
While exposed^a							
All causes	7.0	4.0	3.3	3.9	3.5	10.0	62.2
Observer A							
Direct obstetric causes	5.4	2.3	2.2	2.6	2.7	5.4	40.0
Other causes	1.6	1.7	1.1	1.3	0.8	4.5	22.2
Observer B							
Direct obstetric causes	3.7	2.5	1.8	2.1	2.3	4.5	35.6
Other causes	3.3	1.5	1.6	1.8	1.2	5.4	26.7
While not exposed^b	2.1	3.8	4.0	4.6	4.1	6.5	5.2
By exposure, assuming fetal losses contribute 6 months to exposure							
While exposed^a							
All causes	7.5	4.3	3.6	4.2	3.7	10.7	66.4
Observer A							
Direct obstetric causes (A)	5.7	2.5	2.4	2.8	2.9	5.8	42.6
Other causes (A)	1.8	1.8	1.2	1.4	0.8	4.9	23.7
Observer B							
Direct obstetric causes (B)	4.0	2.7	1.9	2.2	2.5	4.8	37.9
Other causes (B)	3.5	1.6	1.7	2.0	1.2	5.8	28.4
While not exposed^b	2.0	3.6	3.9	4.4	4.0	6.4	5.2

^a During pregnancy or within 3 months after pregnancy termination.

^b Neither pregnant nor within 3 months after pregnancy termination.

Table 3 Rate ratios (RR) comparing death rates while exposed to death rates while not exposed in women aged 15-49 years, Niakhar 1984-1997

	Age group						
	15-19	20-24	25-29	30-34	35-39	40-44	45-49
Assuming fetal losses contribute one year to exposure							
All causes							
RR (95% CI)	3.40 (1.72-6.56)	1.07 (0.57-1.95)	0.83 (0.41-1.59)	0.86 (0.43-1.65)	0.86 (0.36-1.90)	1.53 (0.71-3.04)	11.97 (5.94-22.94)
Causes other than direct obstetric							
RR (95% CI) (A)	0.80 (0.20-2.32)	0.45 (0.18-1.00)	0.28 (0.08-0.72)	0.29 (0.09-0.75)	0.19 (0.02-0.77)	0.70 (0.21-1.77)	4.27 (1.31-11.01)
RR (95% CI) (B)	1.60 (0.62-3.66)	0.39 (0.15-0.91)	0.39 (0.14-0.90)	0.40 (0.15-0.93)	0.29 (0.06-0.94)	0.84 (0.29-1.98)	5.13 (1.76-12.38)
Assuming fetal losses contribute 6 months to exposure							
All causes							
RR (95% CI)	3.68 (1.87-7.11)	1.18 (0.63-2.16)	0.92 (0.46-1.77)	0.96 (0.48-1.82)	0.95 (0.39-2.09)	1.66 (0.77-3.30)	12.81 (6.35-24.51)
Causes other than direct obstetric							
RR (95% CI) (A)	0.87 (0.22-2.51)	0.50 (0.20-1.11)	0.31 (0.09-0.80)	0.32 (0.10-0.83)	0.21 (0.02-0.84)	0.75 (0.23-1.91)	4.58 (1.40-11.76)
RR (95% CI) (B)	1.73 (0.68-3.97)	0.44 (0.16-1.01)	0.43 (0.16-0.99)	0.45 (0.17-1.03)	0.32 (0.06-1.03)	0.91 (0.31-2.15)	5.49 (1.88-13.23)

recently pregnant women than in other women. Also, if certain diseases are aggravated by the pregnancy, it can be predicted that death rates from causes other than direct obstetric causes will be higher during pregnancy and postpartum than outside this period.

The findings of this study provide a somewhat different picture. In this rural Senegalese population death rates from all causes are no higher in pregnant or recently delivered women than in women who have not had a recent birth, except for the very young (15-19 years) and old (45-49 years) maternal

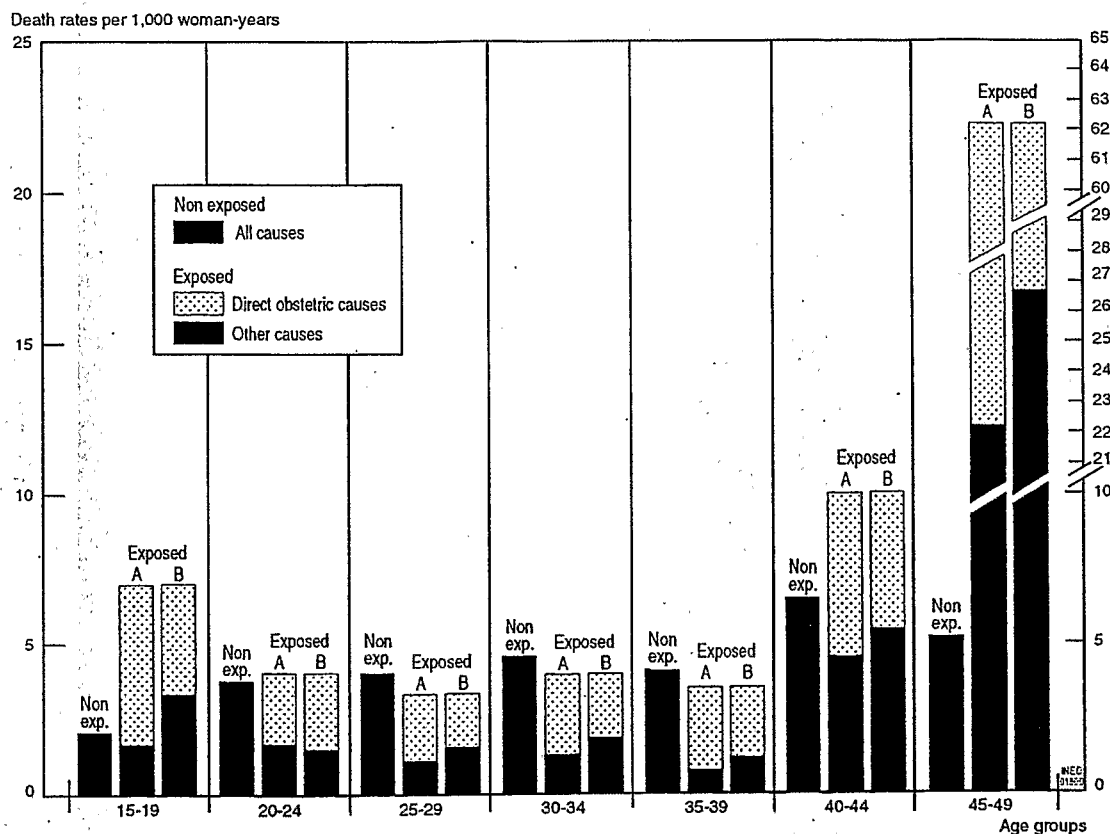


Figure 1 Death rates among exposed and non-exposed women by age group, assuming fetal losses contribute one year to exposure, Niakhar, 1984-1997

ages where pregnancy carries an added risk. When deaths directly related to pregnancy are excluded, currently or recently pregnant women aged 20-39 are between two and five times less likely to die than women not recently pregnant, suggesting that pregnancy may have a protective effect on women's health.

Data quality may be a concern in this study, although it is unlikely to explain the observed findings. Death reporting is likely to be complete given the comprehensive nature of the demographic surveillance system. Because of the efforts made to identify pregnancy-related deaths, we might have inflated the death rates among pregnant women. However, had we been able to correct for a differential ascertainment of this type, we would have found an even stronger 'healthy pregnant woman effect'.

The cause of death ascertainment based on verbal autopsies may have been unreliable.⁶ Early pregnancy deaths may have been misclassified as deaths not related to pregnancy and obstetricians may have over-emphasized the role of direct obstetric causes among pregnant women. For example, a death from haemorrhage with an underlying anaemia would have been classified as a direct rather than an indirect obstetric death. The resulting underestimation of death rates from indirect causes among the exposed cannot, however, explain the large differences observed. Although the consistency of the effects across the different cause attributions by two independent obstetricians gives some confidence in the data quality, these results fundamentally depend on the initial verbal autopsy. While we

were not able to validate our findings, a recent study found that direct causes of maternal mortality can be determined by verbal autopsy with a reasonable level of confidence.¹² Moreover, the persistence of the patterns regardless of the assumptions made for the length of exposure to miscarriages and stillbirths also suggests that errors in these assumptions are unlikely to explain the findings.

To date, there have been very few studies comparing the mortality of pregnant or recently delivered women to that of other women but the available evidence supports our findings. In Bangladesh, pregnant or recently delivered women aged 20-44 were half as likely to die from causes not directly related to the pregnancy than women who had not given birth recently.⁷ In Finland, the age-adjusted risk of a natural death within a year after a birth or a miscarriage was half that of women without a recent pregnancy.¹³ Similarly, in the US, women who had delivered a live or stillborn infant in the previous year were less likely to die than women who had not recently delivered.¹⁴

There are two possible explanations for the lower death rates from causes not directly related to the pregnancy comparing pregnant and non-pregnant women. The first one is that pregnancy confers benefits to women either because pregnant women are more concerned with their health and get better care, or because the physiological changes during pregnancy directly protect women from severe disease and death. The second one is a selection bias whereby the health status of women influences their likelihood of becoming pregnant.

With regard to the protective effects of pregnancy on health, differential care-seeking is unlikely to explain the findings as the coverage of antenatal care is low and access to modern health care services for adults is poor.¹⁵ In addition, very poor nutrition and hard physical work during pregnancy lead to significant energy deficiency¹⁶ and there is little support for the hypothesis that pregnant women are protected from severe illness because of better nutrition or other healthy behaviour. Similarly, there is as yet no evidence of any direct protective effect against certain diseases during pregnancy or immediately after childbirth, and, if any, most of the evidence points to a harmful effect. Clearly, the association between diseases and pregnancy is complex: for breast cancer for example, there appears to be an adverse effect in the short term, as opposed to a beneficial effect in the long term.¹⁷

Selection bias is an alternative explanation for the findings. If women suffering from ill health are less likely to become pregnant than their healthier peers, unhealthy women may be over-represented and inflate the death rates among the non-exposed. The group of non-exposed women, as we have defined it here, is heterogeneous, and two types of selection processes may have operated.

First, the non-exposed women include a group of women for whom pregnancy is not possible, either because they are infertile, or because they have no partner, and the biological or behavioural causes of the childlessness, or the childlessness itself may have induced higher mortality among these women. The prevalence of infertility is not known in this population, but very few women remain childless at the end of their reproductive life.¹⁸ Sexually transmitted infections potentially causing infertility, including HIV, are relatively uncommon.¹⁹ Even if mortality were higher in this sub-group, its contribution to the non-exposed group is likely to be so small that the ensuing bias would be minimal.

Second, a more important selection bias may be operating among fertile women. The non-exposed fertile women are those who have not yet started childbearing, who are between two pregnancies or who have completed their families. Severely ill women or women suffering from chronic diseases may be less likely to become pregnant, as has been shown for tuberculosis and HIV.^{20,21} The selection of healthier women among the pregnant population may lower death rates from communicable or non-communicable diseases in pregnant women. If this bias is important, it may even annihilate the excess mortality from causes that are more lethal among pregnant women.

Older women appear to behave differently in that pregnancy confers an added risk, even after excluding direct obstetric causes. The increased risk associated with pregnancy in older women is

well known, but the magnitude of the excess risk is unusually large.^{22,23} In this population, pregnant or recently delivered women age 45–49 experienced mortality rates that were 18 times higher than death rates in younger pregnant women, and 12 times higher than in non-pregnant women of the same age. Direct and indirect obstetric causes appeared to be equally important in explaining the high death rates. Although women may have misreported their ages at the time of the first census in 1983, it is unlikely that this bias operated differentially in pregnant and non-pregnant women. Older women are likely to be of high parity, and grand multiparae are known to be at higher risk of postpartum haemorrhage, an important cause of maternal death.^{24,25} Why mortality remains higher in older women after excluding direct obstetric causes is puzzling however, as we would have expected the same selection bias to operate among older and younger women.

The low death rate from intentional and unintentional injuries among pregnant women contrasts with findings from other studies.²⁶ In some populations, violence during pregnancy has been associated with illegitimate pregnancy.²⁷ In this rural Senegalese population, premarital pregnancy is common, and prenuptial conceptions tend to be legitimized by a marriage during pregnancy or on the day of the child's baptism.⁸ Deaths from induced abortion are also very rare in this population.²⁸ Although there appears to be a trend towards lowering fertility, fertility is still extremely high, and motherhood remains highly valued.⁸

Conclusion

This study illustrates the paradoxical nature of the concept of indirect causes of maternal mortality, and the difficulties in measuring the risks of death attributable to the pregnancy. Further studies aimed at separating risks attributable to the pregnancy from those that are incidental to the pregnancy are required, as the inclusion of incidental causes could falsely inflate maternal mortality statistics. This may be particularly important in settings with a high prevalence of HIV, where non-obstetric causes are emerging as major causes of death during pregnancy.²⁹

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KEY MESSAGES

- pregnancy is traditionally considered as a particularly vulnerable period in women's lives
- in rural Senegal, pregnant women aged 20–44 years do not experience higher mortality risks than non-pregnant women
- when excluding direct obstetric deaths, women aged 20–39 years have lower mortality than non-pregnant women
- the most likely explanation is the selection of the healthiest women into pregnancy, although alternative factors are discussed

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