

After the Choice: Abortion Sequelae in the Medical Literature

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Abortion Morbidity

- **Short term morbidity:** Retained products of conception, hemorrhage, infection, uterine perforation, cervical laceration, missed ectopic.
- **Long term morbidity:**
 - preterm birth (including placenta previa)
 - adverse psychological outcomes.
 - Increased risk of breast cancer.
 - Other morbidities under investigation.

Short term morbidity

- Hemorrhage
- Infection
- Incomplete abortion
- Reoperation
- The introduction of mifepristone (RU-486) has allowed for several studies comparing risks of mifepristone abortions vs surgical abortions. This has allowed for quantification of surgical abortion risks.

Niinimaki et Al. 2009

Immediate Complications After Medical Compared With Surgical Termination of Pregnancy

Maarit Niinimäki, MD, Anneli Pouta, MD, PhD, Aini Bloigu, Mika Gissler, BS, PhD, Elina Hemminki, MD, PhD, Satu Suhonen, MD, PhD, and Oskari Heikinheimo, MD, PhD

OBJECTIVE: To estimate the immediate adverse events and safety of medical compared with surgical abortion using high-quality registry data.

METHODS: All women in Finland undergoing induced abortion from 2000–2006 with a gestational duration of 63 days or less (n=42,619) were followed up until 42 days postabortion using national health registries. The incidence and risk factors of adverse events after medical (n=22,368) and surgical (n=20,251) abortion were compared. Univariable and multivariable association models were used to analyze the risk of the three main complications (hemorrhage, infection, and incomplete abortion) and surgical (re)evacuation.

RESULTS: The overall incidence of adverse events was fourfold higher in the medical compared with surgical abortion cohort (20.0% compared with 5.6%, $P<.001$). Hemorrhage (15.6% compared with 2.1%, $P<.001$) and incomplete abortion (6.7% compared with 1.6%, $P<.001$)

were more common after medical abortion. The rate of surgical (re)evacuation was 5.9% after medical abortion and 1.8% after surgical abortion ($P<.001$). Although rare, injuries requiring operative treatment or operative complications occurred more often with surgical termination of pregnancy (0.6% compared with 0.03%, $P<.001$). No differences were noted in the incidence of infections (1.7% compared with 1.7%, $P=.85$), thromboembolic disease, psychiatric morbidity, or death.

CONCLUSION: Both methods of abortion are generally safe, but medical termination is associated with a higher incidence of adverse events. These observations are relevant when counseling women seeking early abortion. (*Obstet Gynecol* 2009;114:795–804)

LEVEL OF EVIDENCE: II

Termination of pregnancy is one of the most common gynecologic procedures. For instance, in the United States, nearly half of pregnancies are unintended,¹ and 22% of all pregnancies (excluding miscarriages) end in termination.² Abortion practices have changed dramatically in recent years since the medical method with antiprogesterin mifepristone and prostaglandins was introduced. For example, in 2007 in Finland 64%,³ in Sweden 61%,⁴ and in the United Kingdom 35%⁵ of all abortions were performed using the medical method. Thus, the safety of induced abortion in general, especially that of the medical method, is of great public health interest.

Most previous studies focused on the short-term complications of induced abortion have been small or have not involved comparison of the two dominant methods of abortion (medical and surgical). In a large, register-based study, 5% of the patients had a complication (bleeding, infection, or (re)evacuation) after surgical abortion during a short-term follow-up period of 2 weeks.⁶ In a previous meta-analysis in which medical and surgical termination of pregnancy in the

- Methods: Registry
- All women in Finland 63 days gestation or less undergoing induced abortion from 2000-2006.
- (n= 42,619 women total)
- Medical ab n= 22,368
- Surgical ab n= 20,251
- Followed for 42 days post abortion.

From the Department of Obstetrics and Gynecology, Oulu University Hospital, the Graduate School of Circulatory Wellbeing, Health and Adaptation, and the National Institute for Health and Welfare, Oulu, Finland; and the National Institute for Health and Welfare and the Nordic School of Public Health, the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland.

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Financial Disclosure

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- Results:
- Overall medical abortion had four times higher total number of adverse events than surgical abortion.
- medical = 20% vs
- surgical = 5.6%
- $p < 0.001$

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● Results:

● HEMORRHAGE:

● medical = 15.6% vs

● surgical = 2.1%

● $p < 0.001$

● INCOMPLETE ABORTION:

● medical = 6.7%

● surgical = 1.6%

● $p < 0.001$

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● SURGICAL REEVACUATION:

- medical = 5.9% vs
- surgical = 1.8%
- $p < 0.001$

● OPERATIVE INJURIES:

- medical = 0,6%
- surgical = 0.03%
- $p < 0.001$

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in our data. Because medical abortion is being used increasingly in several countries, it is likely to result in an elevated incidence of overall morbidity related to termination of pregnancy.

Jensen et Al. 1999

- Prospective, non-concurrent
- 178 mifepristone Ab
- 199 suction curettage Ab
- 2 week follow up.

ORIGINAL RESEARCH ARTICLE



Outcomes of Suction Curettage and Mifepristone Abortion in the United States

A Prospective Comparison Study

Jeffrey T. Jensen,* Susan J. Astley,† Elizabeth Morgan,* and Mark D. Nichols*

A prospective, nonconcurrent cohort analysis of 178 mifepristone/misoprostol and 199 suction curettage abortion subjects, ages ≥ 18 years, with intrauterine pregnancies ≤ 63 days estimated gestational age, was conducted to compare the outcomes of suction curettage abortion to those of medical abortion. The medical abortion subjects received 600 mg of mifepristone orally, followed by 400 μ g of oral misoprostol 2 days later. Surgical abortion subjects underwent electronic vacuum aspiration. All subjects were followed for 2 weeks or until the absence of clinical bleeding. Outcome measures included a successful abortion (complete abortion without a surgical intervention), duration of bleeding, and morbidity. Overall, 18.3% medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (RR 3.93, 95% CI 1.87, 8.29). Four mifepristone subjects required curettage for acute bleeding, nine to manage ongoing pregnancy, and five for incomplete abortion. Fourteen mifepristone and eight surgical subjects required curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the medical abortion group (35 versus 8 days; Mann-Whitney $U = 17.0$, $p = 0.008$). Medical subjects experienced significantly longer bleeding (mean difference = 9.6 days, 95% CI 6.5, 12.4). No significant change in hemoglobin occurred in either group. Mifepristone patients reported significantly greater pain (77.1% vs 10.5%, RR 7.4, 95% CI 4.7, 11.5), and nausea or vomiting (68.6% vs 0.6%, RR 117.9, 95% CI 16.7, 834.7). Women receiving mifepristone/misoprostol are more likely to require an unplanned surgical intervention than women who undergo suction curettage. They experience more discomfort with their procedure and in the follow-up inter-

val, bleed for a longer period, and remain at risk for surgical completion curettage for several weeks. CONTRACEPTION 1999,59:153-159 © 1999 Elsevier Science Inc. All rights reserved.

KEY WORDS: abortion, suction curettage, mifepristone, misoprostol, comparison

Introduction

Despite extensive documentation of the safety and efficacy of medical abortion with mifepristone and misoprostol, few studies have directly compared the outcomes of this technique to suction curettage. Most of these studies have been small and have focused primarily on acceptability.¹⁻⁶ Winikoff et al.⁷ recently reported the experiences of 1373 women from China, India, and Cuba who self-selected either a medical abortion with mifepristone and misoprostol or surgical abortion. These workers concluded that the failure rates for medical abortion [5.2-16.0%] exceeded those of surgical abortion [0-4.0%]. Data from the Population Council's trial of 2121 women who received mifepristone/misoprostol abortion in the United States are now available.⁸ The present study reports on a comparison between a subset of these patients and a group of surgical abortion patients managed at the same clinical site. This enables a direct comparison of prospectively obtained outcome information for the two techniques.

Materials and Methods

A prospective, nonconcurrent, single center cohort comparison was performed. All medical and surgical subjects met the inclusion and exclusion criteria reported in the larger Population Council trial⁸ and provided informed consent. Subjects were recruited from among women ≥ 18 years of age who elected to undergo termination of an intrauterine pregnancy of ≤ 63 days of estimated gestational age (EGA), confirmed by transvaginal ultrasound. The protocol

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Jensen et Al. 1999

- Results:
- Overall failures requiring surgical (re)curettage:
- Mifepristone = 18.3%
- Surgical = 4.7%
- (RR 3.93;
95% CI 1.87, 8.29)

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- Of the Mifeprex patients who failed,
 - 12.5 % required emergency surgery for acute bleeding,
 - 43.8 percent for persistent bleeding,
 - 15.6 percent for incomplete abortion, and
 - 28.1 percent for ongoing pregnancy.
- By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.

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Accepted for publication February 11, 1999

Jensen et Al. 1999

- “If you looked at all the women who underwent Mifeprex abortions, 18.3 % failed and had to have a surgical abortion afterward.
- In addition, Mifepristone/misoprostol patients “... reported significantly longer bleeding ...” and “... significantly higher levels of pain ..., nausea ..., vomiting ..., and diarrhea ...” than their surgical counterparts”

ORIGINAL RESEARCH ARTICLE



Outcomes of Suction Curettage and Mifepristone Abortion in the United States

A Prospective Comparison Study

Jeffrey T. Jensen,* Susan J. Astley,† Elizabeth Morgan,* and Mark D. Nichols*

A prospective, nonconcurrent cohort analysis of 178 mifepristone/misoprostol and 199 suction curettage abortion subjects, ages ≥ 18 years, with intrauterine pregnancies ≤ 63 days estimated gestational age, was conducted to compare the outcomes of suction curettage abortion to those of medical abortion. The medical abortion subjects received 600 mg of mifepristone orally, followed by 400 μ g of oral misoprostol 2 days later. Surgical abortion subjects underwent electronic vacuum aspiration. All subjects were followed for 2 weeks or until the absence of clinical bleeding. Outcome measures included a successful abortion (complete abortion without a surgical intervention), duration of bleeding, and morbidity. Overall, 18.3% medical and 4.7% surgical patients failed their primary procedure and received an unanticipated suction curettage (RR 3.93, 95% CI 1.87, 8.29). Four mifepristone subjects required curettage for acute bleeding, nine to manage ongoing pregnancy, and five for incomplete abortion. Fourteen mifepristone and eight surgical subjects required curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the medical abortion group (35 versus 8 days; Mann-Whitney $U = 17.0$, $p = 0.008$). Medical subjects experienced significantly longer bleeding (mean difference = 9.6 days, 95% CI 6.5, 12.4). No significant change in hemoglobin occurred in either group. Mifepristone patients reported significantly greater pain (77.1% vs 10.5%, RR 7.4, 95% CI 4.7, 11.5), and nausea or vomiting (68.6% vs 0.6%, RR 117.9, 95% CI 16.7, 834.7). Women receiving mifepristone/misoprostol are more likely to require an unplanned surgical intervention than women who undergo suction curettage. They experience more discomfort with their procedure and in the follow-up inter-

val, bleed for a longer period, and remain at risk for surgical completion curettage for several weeks. CONTRACEPTION 1999,59:153-159 © 1999 Elsevier Science Inc. All rights reserved.

KEY WORDS: abortion, suction curettage, mifepristone, misoprostol, comparison

Introduction

Despite extensive documentation of the safety and efficacy of medical abortion with mifepristone and misoprostol, few studies have directly compared the outcomes of this technique to suction curettage. Most of these studies have been small and have focused primarily on acceptability.¹⁻⁶ Winikoff et al.⁷ recently reported the experiences of 1373 women from China, India, and Cuba who self-selected either a medical abortion with mifepristone and misoprostol or surgical abortion. These workers concluded that the failure rates for medical abortion [5.2-16.0%] exceeded those of surgical abortion [0-4.0%]. Data from the Population Council's trial of 2121 women who received mifepristone/misoprostol abortion in the United States are now available.⁸ The present study reports on a comparison between a subset of these patients and a group of surgical abortion patients managed at the same clinical site. This enables a direct comparison of prospectively obtained outcome information for the two techniques.

Materials and Methods

A prospective, nonconcurrent, single center cohort comparison was performed. All medical and surgical subjects met the inclusion and exclusion criteria reported in the larger Population Council trial⁸ and provided informed consent. Subjects were recruited from among women ≥ 18 years of age who elected to undergo termination of an intrauterine pregnancy of ≤ 63 days of estimated gestational age (EGA), confirmed by transvaginal ultrasound. The protocol

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Spitz et Al. 1998

- Mifepristone fails:
- 8% at 49 days or less (7 wks or less)
- 17% at 50-56 days (between 7-8 wks)
- 23% at 57-63 days (between 8-9 wks)
- 2% emergency hospitalization at 49 days or less
- 4% emergency hospitalization at greater than 49 days

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EARLY PREGNANCY TERMINATION WITH MIFEPRISTONE AND MISOPROSTOL IN THE UNITED STATES

IRVING M. SPITZ, M.D., D.Sc., C. WAYNE BARDIN, M.D., LAUR BENTON, M.D., AND ANN ROSSING, Ph.D.

ABSTRACT

Background: Mifepristone and a prostaglandin have been used successfully to terminate pregnancy in Europe and China. We report the results of a large U.S. study of mifepristone and misoprostol in women with pregnancies of up to nine weeks' duration.

Methods: We administered 600 mg of mifepristone and then 400 µg of misoprostol two days later to 2121 women seeking termination of their pregnancies at 17 centers. The women were observed for four hours after the administration of misoprostol and returned on day 16 for final assessment.

Results: Two thousand fifteen women completed the final assessment. Among them, pregnancy was terminated in 762 of the 827 women pregnant for <49 days (92 percent), 663 of the 678 women pregnant for 50 to 56 days (98 percent), and 396 of the 610 women pregnant for 57 to 63 days (65 percent) ($P < 0.001$). Termination occurred within 4 hours after the administration of misoprostol in 49 percent of the women and within 24 hours in 75 percent. Failures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of pregnancy. The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the <49-days group to 9 percent in the 57-to-63-days group ($P < 0.001$). Abdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age. Two percent of the women in the <49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids ($P = 0.008$).

Conclusions: This mifepristone-misoprostol regimen is effective in terminating pregnancies, especially in women with pregnancies of 49 days' duration or less. (N Engl J Med 1998;338:1241-7.)

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THE antiprogesterin mifepristone (RU 486) causes abortion by competitively blocking progesterone receptors.^{1,2} For maximal effectiveness, a prostaglandin should be given 48 hours after mifepristone.^{3,4} The rates of termination of pregnancies 49 days old or less are similar, ranging from 96 to 99 percent, whether mifepristone is used with gemeprost or misoprostol, both prostaglandin E₁ compounds.^{1,3,5,7} Gemeprost is expensive, requires refrigeration, and is not widely available, but misoprostol is inexpensive, stable at room temperature, and obtainable in many countries, including the United States.

Many American women do not have access to abortion,⁸ and in developing countries up to 200,000 women die annually of complications after illegal abortions.⁹ The availability of medical abortion in the United States and elsewhere could lead to greater access to safer abortion services. We conducted a multicenter trial of mifepristone and misoprostol to determine whether this combination could be used to terminate pregnancies of up to 63 days' duration.

METHODS

Participating Centers

From September 1994 to September 1995, we enrolled 2121 women, each with a documented pregnancy of 63 days' duration or less, requesting termination of pregnancy. Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feed-

From the Center for Biomedical Research, Population Council, 1230 York Ave., New York, NY 10021, where reprint requests should be addressed to Dr. Robbins.

The principal investigators and centers participating in the study are listed in the Appendix.

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Gary and Harrison 2006

- Analysis of the first 607 AERs: (approx 180/yr)
- 6 deaths
- 237 hemorrhages (42 life threatening) (68 transfusions)
- 7 cases of septic shock
- 235 emergent surgeries
- 17 unrecognized ectopics.

RESEARCH REPORTS

Women's Health

Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient

Margaret M Gary and Donna J Harrison

BACKGROUND: The systematic analysis of morbidity and mortality for the Food and Drug Administration (FDA)-approved medical abortion regimen using mifepristone is possible using data from the FDA's Adverse Event Reporting System.

OBJECTIVE: To assess mifepristone's mortality, morbidity, sentinel events, and quality of postmarketing surveillance using mifepristone adverse event reports (AERs).

METHODS: Six hundred seven unique mifepristone AERs submitted to the FDA over a 4 year span were coded using the National Cancer Institute's Common Terminology Criteria for Adverse Events. Coding was based only on data in AERs and may underestimate severity and treatment rendered. Two board-certified obstetrician/gynecologists, the authors, made individual evaluations, compared them, and agreed upon final coding.

RESULTS: The most frequent AERs were hemorrhage ($n = 237$) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious cases; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life threatening) and 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology; 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.

CONCLUSIONS: Hemorrhage and infection are the leading causes of mifepristone-related morbidity and mortality. AERs relied upon by the FDA to monitor mifepristone's postmarketing safety are grossly deficient due to extremely poor quality.

KEY WORDS: adverse event reporting system (AERS), medical abortion, Mifeprex, mifepristone, mifepristone adverse events, mifepristone-induced septic shock (MISS), RU486.

Ann Pharmacother 2006;40:1000.

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Fischer et Al. 2005

THE NEW ENGLAND JOURNAL OF MEDICINE

BRIEF REPORT

Fatal Toxic Shock Syndrome Associated with *Clostridium sordellii* after Medical Abortion

Marc Fischer, M.D., M.P.H., Julu Bhatnagar, Ph.D., Jeannette Guarnet, M.D., Sarah Reagan, M.P.H., Jill K. Hacker, Ph.D., Sharon H. Van Meter, M.D., Vadims Poukens, M.D., David B. Whiteman, M.D., Anthony Iton, M.D., J.D., M.P.H., Michele Cheung, M.D., M.P.H., David E. Dassey, M.D., M.P.H., Wun-Ju Shieh, M.D., Ph.D., and Sherif R. Zaki, M.D., Ph.D.

SUMMARY

Endometritis and toxic shock syndrome associated with *Clostridium sordellii* have previously been reported after childbirth and, in one case, after medical abortion. We describe four deaths due to endometritis and toxic shock syndrome associated with *C. sordellii* that occurred within one week after medically induced abortions. Clinical findings included tachycardia, hypotension, edema, hemoconcentration, profound leukocytosis, and absence of fever. These cases indicate the need for physician awareness of this syndrome and for further study of its association with medical abortion.

CLOSTRIDIUM SORDELLII IS A GRAM-POSITIVE ANAEROBIC BACILLUS THAT has been reported as a cause of infection in the female genital tract and fatal toxic shock syndrome. Of 10 cases identified in the literature, 8 occurred after delivery of live-born infants,¹⁻⁶ 1 occurred after a medical abortion,⁷ and 1 was not associated with pregnancy.⁸ We report four additional deaths due to *C. sordellii* toxic shock syndrome that occurred among previously healthy women after abortions that were medically induced with 200 mg of oral mifepristone and 800 µg of vaginal misoprostol.

From the Centers for Disease Control and Prevention, Atlanta (M.F., J.B., J.G., S.R., W.J.S., S.R.Z.); the California Emerging Infections Program, Richmond (J.K.H.); the Alameda County Coroners Office (S.H.V.M.) and Health Department (A.I.), Oakland, Calif.; the Department of the Coroner (M.P., D.B.W.) and the Department of Health Services (D.E.D.), Los Angeles; and the Orange County Health Care Agency, Santa Clara, Calif. (M.C.). Address reprint requests to Dr. Fischer at the Centers for Disease Control and Prevention, P.O. Box 2087, Mailstop P-02, Fort Collins, CO 80522, or at mfischer@cdc.gov.

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Fatal Infections Associated with Mifepristone-Induced Abortion

Michael F. Greene, M.D.

Related article, p. 2352

“These figures would suggest that the **risk of death from infection is less than 1 per 100,000.**”

The more appropriate comparison, however, is with the risk associated with other methods of inducing abortion. The overall maternal mortality rate associated with induced abortion in the United States is approximately 1 per 100,000.

That overall rate is a “blended” rate including all the procedures performed in the United States at all gestational ages.

The gestational-age–specific rate increases exponentially from 0.1 per 100,000 at 8 weeks’ gestation to 8.9 per 100,000 at 21 or more weeks’ gestation.

- Mifepristone is approved for the termination of pregnancies at less than seven weeks’ gestation. Therefore, **the appropriate comparison is with a risk of 0.1 per 100,000 for surgical abortions performed at less than eight weeks’ gestation.**”

Mifepristone (RU-486)

- DATA SYNTHESIS: Mifepristone
- * blocks both progesterone and glucocorticoid receptors
- *interferes with the controlled release and functioning of cortisol and cytokines.
- *Failure of physiologically controlled cortisol and cytokine responses results in an impaired innate immune system
- *that results in disintegration of the defense system necessary to prevent the endometrial spread of *C. sordellii* infection. The abnormal cortisol and cytokine responses due to mifepristone coupled to the release of potent exotoxins and an endotoxin from *C. sordellii* are the major contributors to the rapid development of lethal septic shock

ARTICLES

Women's Health

Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*

Ralph P Mlech

OBJECTIVE: To explain the role of mifepristone in medical abortions that results in fulminant and lethal septic shock due to *Clostridium sordellii*.

DATA SOURCES: MEDLINE, PubMed, and Google Scholar databases were searched (1984–March 2005). Key search terms were mifepristone, RU38486, RU486, Mifeprex, medical abortion, septic shock, innate immune system, cytokines, and *Clostridium sordellii*.

STUDY SELECTION AND DATA EXTRACTION: All articles identified from the data sources were evaluated and all information deemed relevant was included for the information related to the development of the understanding of the pathophysiology of mifepristone-induced septic shock due to *C. sordellii*.

DATA SYNTHESIS: The mechanisms of action of mifepristone were incorporated into the pathophysiology of septic shock due to *C. sordellii*. Mifepristone, by blocking both progesterone and glucocorticoid receptors, interferes with the controlled release and functioning of cortisol and cytokines. Failure of physiologically controlled cortisol and cytokine responses results in an impaired innate immune system that results in disintegration of the body's defense system necessary to prevent the endometrial spread of *C. sordellii* infection. The abnormal cortisol and cytokine responses due to mifepristone coupled to the release of potent exotoxins and an endotoxin from *C. sordellii* are the major contributors to the rapid development of lethal septic shock.

CONCLUSIONS: Theoretically, it appears that the mechanisms of mifepristone action favor the development of infection that leads to septic shock and intensifies the actions of multiple inflammatory cytokines, resulting in fulminant, lethal septic shock.

KEY WORDS: abortion, *Clostridium sordellii*, mifepristone, septic shock.

Ann Pharmacother 2005;39:xxxx.

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Miech, 2007

tem.^{1,2} The hemorrhages following mifepristone abortion appear to be more severe than those found in surgical or spontaneous abortions.^{3,4} This article proposes a pathopharmacologic mechanism that may account for excessive hemorrhage in mifepristone abortions.

Women's Health

ARTICLES

Pathopharmacology of Excessive Hemorrhage in Mifepristone Abortions

Ralph P Miech

Hemorrhage and infection are the leading causes of mifepristone-related morbidity and mortality in the Adverse Event Reports submitted to the Food and Drug Administration's MedWatch system.^{1,2} The hemorrhages following mifepristone abortion appear to be more severe than those found in surgical or spontaneous abortions.^{3,4} This article proposes a pathopharmacologic mechanism that may account for excessive hemorrhage in mifepristone abortions.

Antiseptic Protection of the Uterus in Abortions

In pregnancy, the decidual lining of the uterine cavity is protected from contamination by vaginal bacteria. Cervical glands, stimulated by rising progesterone levels, secrete a special type of mucus (Type G).⁵ Type G mucus blocks the cervical opening and functions as an essential biological valve that also possesses antimicrobial activity.^{6,7} Thus, the cervical canal is prevented from becoming a microbial portal of entry into the uterus. The blockade of the cervical canal by Type G mucus protects the embryo and the maternal decidua from bacterial ascending contamination. In abortions, the mucus plug is lost as the cervix dilates during the abortive process. It has been suggested that mifepristone may effect cervical ripening by modulating the influx of inflammatory cells into the cervix and inducing chemokine secretion by cervical tissue.⁸ In both medical and surgical abortions, vaginal bacteria enter the uterus via the open cervical canal but are removed by phagocytic cells of the innate immune sys-

OBJECTIVE: To explain a pathopharmacologic mechanism that initiates an increase in hemorrhage following medical abortions with mifepristone.

DATA SOURCES: MEDLINE, PubMed, and Google Scholar databases were searched (1990–July 2007). Key search terms were mifepristone, RU486, medical abortion hemorrhage, bleeding, inflammation, innate immune system, phagocytes, macrocytes, cytokines, interleukins, and nitric oxide.

STUDY SELECTION AND DATA EXTRACTION: All articles identified from the data sources were evaluated and all information deemed relevant was included for the information related to the development of the understanding of the pathopharmacology of mifepristone as the initiating cause of increased hemorrhage in medical abortions. Mifepristone's blockade of glucocorticoid receptors, prolonged generation of nitric oxide (NO), and postabortion vasodilatation of uterine vasculature by NO that favors excessive hemorrhage were the criteria used to determine whether information was relevant for inclusion.

DATA SYNTHESIS: Inescapable bacterial contamination of the decidua accompanies spontaneous, surgical, and mifepristone abortions and is routinely overcome by activation of the innate immune system. The combination of the induction of NO synthase (NOS) and local production of NO is one of the key features of the activation of the innate immune system's phagocytes. NO is a potent vasodilator and is associated with menstrual menorrhagia. Glucocorticoids prevent the overproduction of NOS and NO and thereby contribute to the control of hemorrhage in the postabortion phase.

CONCLUSIONS: Blockade of the glucocorticoid receptors by mifepristone can result in an excess of NO that is theorized to be the cause of excessive hemorrhage seen in mifepristone abortions.

KEY WORDS: abortion, glucocorticoids, hemorrhage, mifepristone, nitric oxide.

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Published Online, 23 Oct 2007, www.annals.com, DOI 10.1345/aph.1K351

tem so that myometritis usually does not occur. The cells of the innate immune system provide this protective mechanism during abortions by (1) chemokine recruitment of phagocytic cells, (2) synthesis and secretion of proinflammatory cytokines, and (3) the liberation of inflammatory mediators.

Postabortion Activation of the Innate Immune System

The maternal innate immune system generates a general, nonspecific, rapid, and highly orchestrated response to

Author information provided at the end of the text.

Miech, R “Pathophysiology of Excessive Hemorrhage in Mifepristone Abortions”

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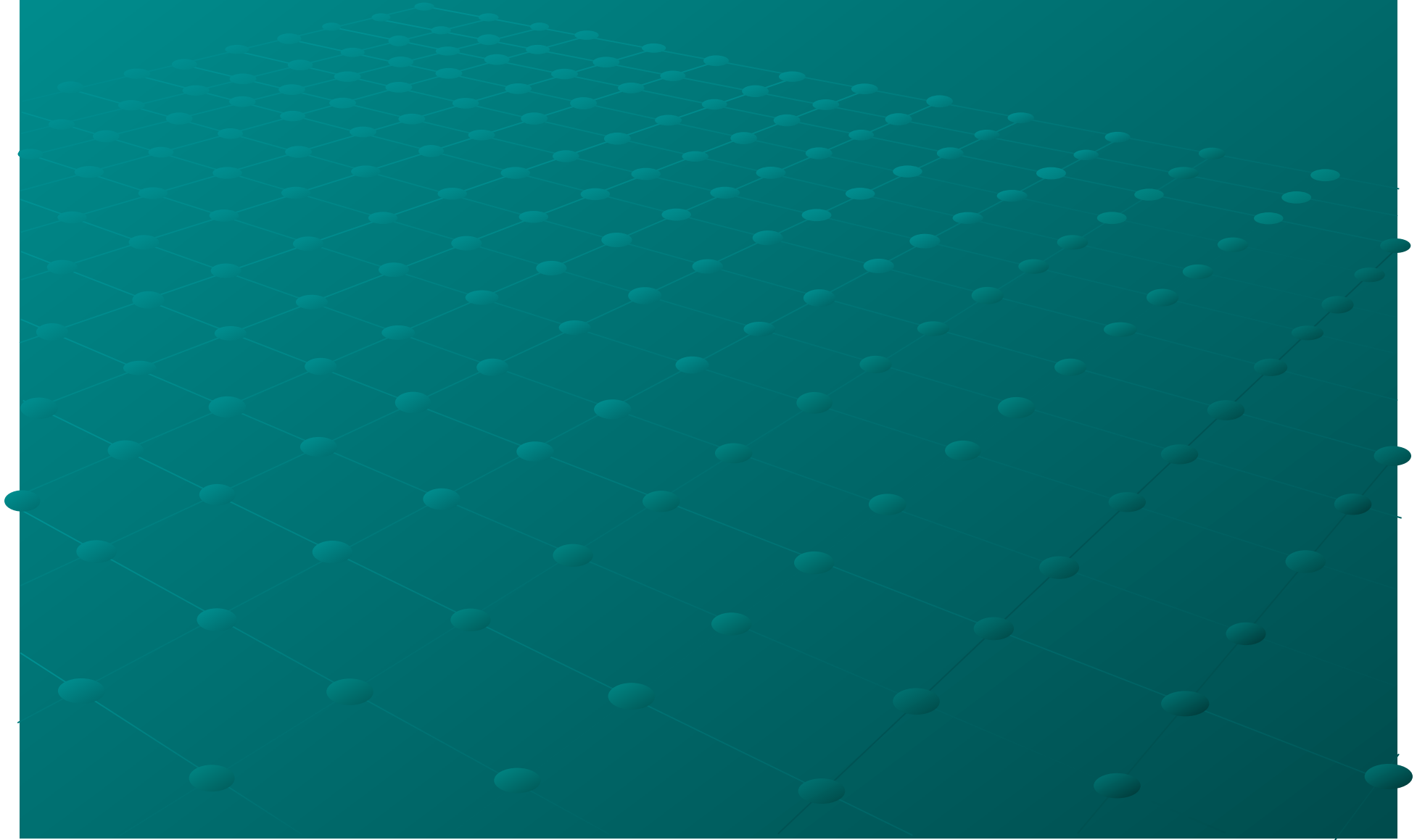
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Abortion: Long term morbidity



Bouyer, et. Al. 2002

- Case-Control study
- Regional register of ectopics between 1990 and 2000.
- 803 ectopics vs
- 1683 deliveries.



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Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-based Study in France

Jean Bouyer¹, Joël Coste¹, Taraneh Shojaei¹, Jean-Luc Pouly², Hervé Fernandez^{1,3}, Laurent Gerbaud⁴, and Nadine Job-Spira¹

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This case-control study was associated with a regional register of ectopic pregnancy between 1993 and 2000 in France. It included 803 cases of ectopic pregnancy and 1,683 deliveries and was powerful enough to investigate all ectopic pregnancy risk factors. The main risk factors were infectious history (adjusted attributable risk = 0.33; adjusted odds ratio for previous pelvic infectious disease = 3.4, 95% percent confidence interval (CI): 2.4, 5.0) and smoking (adjusted attributable risk = 0.35; adjusted odds ratio = 3.0, 95% CI: 2.6, 5.0 for >20 cigarettes/day vs. women who had never smoked). The other risk factors were age (associated parous with a risk of ectopic pregnancy), prior spontaneous abortions, history of infertility, and previous use of an intrauterine device. Prior medical induced abortion was associated with a risk of ectopic pregnancy (adjusted odds ratio = 2.8, 95% CI: 1.1, 7.2); no such association was observed for surgical abortion (adjusted odds ratio = 1.1, 95% CI: 0.8, 1.6). The total attributable risk of all the factors investigated was 0.76. As close associations were found between ectopic pregnancy and infertility and between ectopic pregnancy and spontaneous abortion, further research into ectopic pregnancy should focus on risk factors common to these conditions. In terms of public health, increasing awareness of the effects of smoking may be useful for ectopic pregnancy prevention.

abortion, induced; case-control studies; infertility, female; pregnancy, ectopic; registries; risk factors; sexually transmitted diseases; tobacco

Abbreviation: CI, confidence interval

During the 1980s and 1990s, the incidence of ectopic pregnancy in developed countries increased by a factor of 3–4 (1–5), reaching 100–175 per 1,000,000 women aged 15–44 years.

Several risk factors for ectopic pregnancy have been identified (3, 6–8) including pelvic inflammatory disease, smoking, and previous ectopic pregnancy. Other factors, such as age, surgical history, and obstetric history, are also thought to be involved. However, the role played by these factors remains unclear because of problems with the sample size or the design of previous studies. Published meta-analyses of ectopic pregnancy risk factors (9–11) only partly answered the questions addressed, mainly because their ability to adjust for confounders was limited (12, 13). This

problem is particularly severe in analyses of ectopic pregnancy, which has a large number of highly correlated risk factors. The selection of studies to be included in the meta-analysis and assessment of their quality may also cause difficulties. Strikingly, in the two most recent meta-analyses on this subject, two different sets of studies were selected (9, 10).

The ectopic pregnancy register of Auvergne (France) (14) and associated case-control studies provide an opportunity to analyze the risk factors for ectopic pregnancy in a large sample, representative of a geographically defined population. Results concerning women using contraception at the time of conception have already been published (15). This study focuses on women not using contraception at the time

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Bouyer, et. Al. 2002

- Main Risk Factors:
- Infectious hx - “adjusted odds ratio for previous pelvic infectious disease = 3.4, 95% percent confidence interval (CI): 2.4, 5.0”
- Smoking- “smoking (adjusted odds ratio = 3.9, 95% CI: 2.6, 5.9 for >20 cigarettes/day vs. women who had never smoked)”



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Jean Bouyer¹, Joël Coste¹, Taraneh Shojaei¹, Jean-Luc Pouly², Hervé Fernandez^{1,3}, Laurent Gerbaud⁴, and Nadine Job-Spira¹

¹ INSERM U569, IFR69 (The French Institute of Health and Medical Research), Le Kremlin-Bicêtre, France.

² Centre Hospitalier Hôtel-Dieu, Service de Gynécologie-Obstétrique, Clermont-Ferrand, France.

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Bouyer, et. Al. 2002

- Main Risk Factors:
- “Prior medical induced abortion was associated with a risk of ectopic pregnancy (adjusted odds ratio = 2.8, 95% CI: 1.1, 7.2); no such association was observed for surgical abortion (adjusted odds ratio = 1.1, 95% CI: 0.8, 1.6).”
- “age (associated per se with a risk of ectopic pregnancy), prior spontaneous abortions, history of infertility, and previous use of an intrauterine device.”



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Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-based Study in France

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This case-control study was associated with a regional register of ectopic pregnancy between 1993 and 2000 in France. It included 903 cases of ectopic pregnancy and 1,683 deliveries and was powerful enough to investigate all ectopic pregnancy risk factors. The main risk factors were infectious history (adjusted attributable risk = 0.33; adjusted odds ratio for previous pelvic infectious disease = 3.4, 95% percent confidence interval (CI): 2.4, 5.0) and smoking (adjusted attributable risk = 0.35; adjusted odds ratio = 3.0, 95% CI: 2.6, 5.0 for >20 cigarettes/day vs. women who had never smoked). The other risk factors were age (associated *per se* with a risk of ectopic pregnancy), prior spontaneous abortions, history of infertility, and previous use of an intrauterine device. Prior medical induced abortion was associated with a risk of ectopic pregnancy (adjusted odds ratio = 2.8, 95% CI: 1.1, 7.2); no such association was observed for surgical abortion (adjusted odds ratio = 1.1, 95% CI: 0.8, 1.6). The total attributable risk of all the factors investigated was 0.76. As close associations were found between ectopic pregnancy and infertility and between ectopic pregnancy and spontaneous abortion, further research into ectopic pregnancy should focus on risk factors common to these conditions. In terms of public health, increasing awareness of the effects of smoking may be useful for ectopic pregnancy prevention.

abortion, induced; case-control studies; infertility, female; pregnancy, ectopic; registries; risk factors; sexually transmitted diseases; tobacco

Abbreviation: CI, confidence interval.

During the 1980s and 1990s, the incidence of ectopic pregnancy in developed countries increased by a factor of 3–4 (1–5), reaching 100–175 per 1,000,000 women aged 15–44 years.

Several risk factors for ectopic pregnancy have been identified (3, 6–8) including pelvic inflammatory disease, smoking, and previous ectopic pregnancy. Other factors, such as age, surgical history, and obstetric history, are also thought to be involved. However, the role played by these factors remains unclear because of problems with the sample size or the design of previous studies. Published meta-analyses of ectopic pregnancy risk factors (9–11) only partly answered the questions addressed, mainly because their ability to adjust for confounders was limited (12, 13). This

problem is particularly severe in analyses of ectopic pregnancy, which has a large number of highly correlated risk factors. The selection of studies to be included in the meta-analysis and assessment of their quality may also cause difficulties. Strikingly, in the two most recent meta-analyses on this subject, two different sets of studies were selected (9, 10).

The ectopic pregnancy register of Auvergne (France) (14) and associated case-control studies provide an opportunity to analyze the risk factors for ectopic pregnancy in a large sample, representative of a geographically defined population. Results concerning women using contraception at the time of conception have already been published (15). This study focuses on women not using contraception at the time

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Virk et Al. 2007

We chose not to compare women who had medical abortions directly with women who had no prior abortions, since these groups differ with respect to factors that affect pregnancy outcomes, such as socioeconomic status, smoking status, and other health-related conditions and behaviors.¹⁷

The implications of our data for the long-term safety of medical abortion therefore rely on the premise that surgical abortion in the first trimester is safe, which is supported by the majority of studies in the literature. A review of available data

CONCLUSIONS

We found no evidence that a previous medical abortion, as compared with a previous surgical abortion, increases the risk of spontaneous abortion, ectopic pregnancy, preterm birth, or low birth weight.

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Medical Abortion and the Risk of Subsequent Adverse Pregnancy Outcomes

Jasveer Virk, M.S., M.P.H., Jun Zhang, Ph.D., M.D., and Jørn Olsen, M.D., Ph.D.

ABSTRACT

BACKGROUND

The long-term safety of surgical abortion in the first trimester is well established. Despite the increasing use of medical abortion (abortion by means of medication), limited information is available regarding the effects of this procedure on subsequent pregnancies.

METHODS

We identified all women living in Denmark who had undergone an abortion for non-medical reasons between 1999 and 2004 and obtained information regarding subsequent pregnancies from national registries. Risks of ectopic pregnancy, spontaneous abortion, preterm birth (at <37 weeks of gestation), and low birth weight (<2500 g) in the first subsequent pregnancy in women who had had a first-trimester medical abortion were compared with risks in women who had had a first-trimester surgical abortion.

RESULTS

Among 11,814 pregnancies in women who had had a previous first-trimester medical abortion (2710 women) or surgical abortion (9104 women), there were 274 ectopic pregnancies (respective incidence rates, 2.4% and 2.3%), 1426 spontaneous abortions (12.2% and 12.7%), 552 preterm births (5.4% and 6.7%), and 478 births with low birth weight (4.0% and 5.8%). After adjustment for maternal age, interval between pregnancies, gestational age at abortion, parity, cohabitation status, and urban or non-urban residence, medical abortion was not associated with a significantly increased risk of ectopic pregnancy (relative risk, 1.04; 95% confidence interval [CI], 0.76 to 1.41), spontaneous abortion (relative risk, 0.87; 95% CI, 0.72 to 1.05), preterm birth (relative risk, 0.88; 95% CI, 0.66 to 1.18), or low birth weight (relative risk, 0.82; 95% CI, 0.61 to 1.11). Gestational age at medical abortion was not significantly associated with any of these adverse outcomes.

CONCLUSIONS

We found no evidence that a previous medical abortion, as compared with a previous surgical abortion, increases the risk of spontaneous abortion, ectopic pregnancy, preterm birth, or low birth weight.

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Surgical Abortion: Long term morbidity

Physical morbidity:

Preterm Birth

Placenta Previa

Breast Cancer



Surgical Abortion: Long term morbidity

- Adverse Mental Health Outcomes:
- Depression
- Suicide
- Substance abuse
- Intimate bonding dysfunction



Thorpe 2003

- inclusion criteria:
- study population >100 subjects,
- follow up >60 days.

CHIEF EDITOR'S NOTE: This article is part of a series of continuing education activities in this Journal through which a total of 36 AMA/PRA category 1 credit hours can be earned in 2003. Instructions for how CME credits can be earned appear on the last page of the Table of Contents.

Long-Term Physical and Psychological Health Consequences of Induced Abortion: Review of the Evidence

John M. Thorp, Jr., MD,* Katherine E. Hartmann, MD, PhD†
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Induced abortion is a prevalent response to an unintended pregnancy. The long-term health consequences are poorly investigated and conclusions must be drawn from observational studies. Using strict inclusion criteria (study population >100 subjects, follow up >60 days) we reviewed an array of conditions in women's health. Induced abortion was not associated with changes in the prevalence of subsequent subfertility, spontaneous abortion, or ectopic pregnancy. Previous abortion was a risk factor for placenta previa. Moreover, induced abortion increased the risks for both a subsequent preterm delivery and mood disorders substantial enough to provoke attempts of self-harm. Preterm delivery and depression are important conditions in women's health and avoidance of induced abortion has potential as a strategy to reduce their prevalence. Only review articles including the single published meta-analysis exploring linkages between abortion and breast cancer were relied upon to draw conclusions. Reviewers were mixed on whether subsequent breast neoplasia can be linked to induced abortion, although the sole meta-analysis found a summary odds ratio of 1.2. Whatever the effect of induced abortion on breast cancer risk, a young woman with an unintended pregnancy clearly sacrifices the protective effect of a term delivery should she decide to abort and delay childbearing. That increase in risk can be quantified using the Gail Model. Thus, we conclude that informed consent before induced abortion should include information about the subsequent risk of preterm delivery and depression. Although it remains uncertain whether elective abortion increases subsequent breast cancer, it is clear that a decision to abort and delay pregnancy culminates in a loss of protection with the net effect being an increased risk.

Target Audience: Obstetricians & Gynecologists, Family Physicians

Learning Objectives: After completion of this article, the reader will be able to define the terms abortion rate and abortion ratio, to outline the epidemiologic problems in studying the long-term consequences of abortion, and to list the associated long-term consequences of abortion.

In the late 1960s and early 1970s, abortion was legalized in most of the western world. Legalization culminated in more women choosing termination

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The authors have disclosed no significant financial or other relationship with any commercial entity.

than had been expected (1, 2), with young, socially deprived, and childless women making up the largest proportion (3). Initially, research focused on early complications, immediate maternal mortality, and optimization of abortion technique (4). Subsequent interest in the potential long-term health consequences entered scientific discussion later, not primarily driven by specific hypotheses, but rather by

Thorpe et Al. 2003

“Preterm birth is a common problem affecting around 10% of deliveries in the Western World and is the leading cause of infant morbidity and mortality.

Despite substantial investigative effort, primary preventive measures to lower the rate of preterm births have proven futile and rates have been steady or increased over the past two decades.

The population-based studies contained in our table suggest that *induced abortion increases the risk of preterm birth in subsequent pregnancies.*”



Abortion and Preterm Birth

Thorpe, et.al. ObGyn Survey 58 (1) 67-79.

“In light of these data, we believe that women considering abortion should be informed that the procedure may increase the likelihood of subsequent preterm births.”



Rooney et Al. 2003

- 49 studies
- Stratified risk by gestational age:
 - Early premature <32 weeks gestation
 - Extremely Early premature <28 weeks gestation

Induced Abortion and Risk of Later Premature Births

Brent Rooney
Byron C. Calhoun, M.D.

ABSTRACT

At least 49 studies have demonstrated a statistically significant increase in premature births (PB) or low birth weight (LBW) risk in women with prior induced abortions (IAs). This paper will focus on the risk of early premature births (EPBs) (< 32 weeks gestation) and extremely early premature births (XPBs) (< 28 weeks gestation). Large studies have reported a doubling of EPB risk from two prior IAs. Women who had four or more IAs experienced, on average, nine times the risk of XPB, an increase of 800 percent.

These results suggest that women contemplating IA should be informed of this potential risk to subsequent pregnancies, and that physicians should be aware of the potential liability and possible need for intensified prenatal care.

Informed consent for an elective surgical procedure must generally cover long-term consequences and not just immediate risk. A woman considering an induced abortion (IA) should thus expect to be informed of potential effects on her fertility and the health of future infants, as well as her own future health. An elevated risk of bearing a child afflicted with a serious disability such as cerebral palsy might influence her decision, as well as future liability determinations by courts.

Low birth weight (LBW) and premature birth (PB) are the most important risk factors for infant mortality or later disabilities¹ as well as for lower cognitive abilities and greater behavioral problems² and thus contribute importantly to the liability exposure of obstetricians.

A literature review retrieved 49 studies that demonstrated at least 95 percent confidence in an increased risk of preterm birth (PB), or surrogates such as low birth weight or second-trimester spontaneous abortion, in association with previous induced abortions. A list of these studies, which probably does not comprise all such studies, is appended to this article. If these 49 statistically significant associations were the result of chance alone, as may happen in 5 of 100 tests, IA should be associated with a reduction in PBs, with $P < .05$, in an equivalent number of tests. Not one such instance has been found in the literature.

A MedLine search from 1966 to March, 2003, retrieved 8 studies that purportedly failed to show a significant increase in premature births after IA.³⁻¹⁰ Most showed an increase that did not reach statistical significance because of the small sample size: fewer than 1,000 pregnancies following an IA. In one, an increased risk of PB in women who had had an IA was nonsignificant when controlled for parity.³ These studies did not consider separately the risk of EPBs or XPBs, or the effect of multiple IAs, except one that showed a statistically significant increase of EPB, despite the statement in the abstract that "in the Netherlands there are no significant indications that spontaneous midtrimester abortions or premature deliveries are caused by a previous induced abortion."⁶

A 1986 review concluded that "more research is needed before it is clear whether multiple induced abortions carry an increased risk of adverse pregnancy outcomes."¹¹ The more recent, large studies discussed here help supply this lack.

Australian Study

A 1993 study in Victoria, Australia,¹² involved 121,305 total births and compared the risk of PB and XPB in women with various numbers of IAs, compared with a control group of women who had no prior pregnancies (see Table 1, derived from data in this report).

Gestational age	Number of prior IAs		
	1	2	3 or more
20-27 weeks (XPBs)	1.6	2.5	5.6
28-31 weeks	1.6	1.1	2.6
32-36 weeks	1.1	1.6	2.4

[RR = relative risk]

Table 1: Premature birth risk by number of prior induced abortions (IAs) compared with outcome of first pregnancies, Victoria, 1986-1990¹²

As Lumley explains:

The associations are different in the three gestation categories (20-27, 28-31, and 32-36 weeks), being particularly striking for births before 28 weeks. In this category, there is also evidence for a dose-response relationship between number of prior lost pregnancies and the prevalence of preterm birth: relative risks of 1.66 and 1.55 for one spontaneous or induced abortion, of 2.94 and 2.46 for two, and of 5.89 and 5.58 for three or more. These last four relative risks are substantially greater than any of those associated with maternal age, marital status, parity or socioeconomic status: that is, the association is most unlikely to be explained by confounding factors of a sociodemographic kind.¹²

Lumley's argument that "small single possible confounders cannot explain big risk factors such as 2.46 and 5.58" would also apply to any attempt to pose smoking or drug abuse as an explanation for the entire abortion-premature birth association.

The great majority of the Australian IAs were via vacuum aspiration; thus the PB risk cannot be attributed to dilation & curettage IAs.

The author noted that cross-sectional studies show that the relative risk of preterm delivery increases with the number of the previous preterm births, but that the risk of subsequent preterm births diminishes with each full-term delivery.¹² Thus, IA removes the protective potential of a full-term delivery, as others have also observed.¹³

Induced Abortion and Risk of Later Premature Births

	Number of prior IAs		
	1	2	3 or more
Gestational age	RR	RR	RR
20-27 weeks (XPBs)	1.6	2.5	5.6
28-31 weeks	1.6	1.1	2.6
32-36 weeks	1.1	1.6	2.4

[RR = relative risk]

Table 1: Premature birth risk by number of prior induced abortions (IAs) compared with outcome of first pregnancies, Victoria, 1986-1990¹²



Induced Abortion and Risk of Later Premature Births

Gestational age	Number of prior IAs		
	1	2	3 or more
	OR (95% CI)	OR (95% CI)	OR (95% CI)
<32 weeks	2.5 (1.96-3.27)	5.2 (3.28-8.34)	8.0 (3.89-16.6)
<37 weeks	1.5 (1.35-1.76)	2.1 (1.54-2.81)	3.6 (2.25-5.62)

Table 2: Odds ratio (OR) for premature births by number of prior induced abortions (IAs)¹⁵

Induced Abortion and Risk of Later Premature Births

It has been claimed that “induced abortion...is directly responsible for many thousands of cases of cerebral palsy—in North America alone—that otherwise would not have occurred.”²³ Supporting this assertion is the fact that the cerebral palsy risk in XPB is about 38 times higher than in the overall population of newborns,¹ in which the risk of cerebral palsy is approximately 2-3 per 1,000 births.²⁴ As the liability costs for cerebral palsy are exceptionally high, induced abortion, particularly without very detailed informed consent, may carry an unsupportable legal liability. Courts may not require defin-



Calhoun et Al. 2007

“ Cost consequences of induced abortion as an attributable risk for preterm birth and impact on informed consent.” J Reprod Med. 2007 Oct;52(10):929-37

OBJECTIVE: To investigate the human and monetary cost consequences of preterm delivery as related to induced abortion (IA), with its impact on informed consent and medical malpractice.



Calhoun et Al. 2007

RESULTS: IA increased the early preterm delivery rate by 31.5%, with a yearly increase in initial neonatal hospital costs related to IA of > \$1.2 billion.

The yearly human cost includes 22,917 excess early preterm births (EPB) (< 32 weeks) and 1096 excess CP cases in very-low-birth-weight newborns, <1500 g.

.



Calhoun 2007

- **“CONCLUSION: IA contributes to significantly increased neonatal health costs by causing 31.5% of EPB.**
- Providers of obstetric care and abortion should be aware of the risk of preterm birth attributable to induced abortion, with its significant increase in initial neonatal hospital costs and CP cases.”



THE EUROPOP STUDY

■ Human Reproduction, Vol 19, No. 3, 29 Jan 2004, pp. 734-740

■ 17 countries

■ concluded that the risk of **very preterm birth** (22 to 32 weeks) **increased by 50% after one abortion,**

■ **and increased by 80% after 2 abortions**



The EPIPAGE study

- Moreau C. et al. “*Previous induced abortions and the risk of very preterm delivery*”. Br J OBGyn,2005;112:430-437
- Among women who had **one abortion** there was a **50% (1.5 times higher)** increase in very preterm births,(**22-32 wks**);
- **Two or more** abortions resulted in a **160% increase (2.6 times higher rate)**.
- There was a **70% (1.7 times higher)** increase in **extremely preterm** deliveries (**22-27 weeks**) for those who had at least one prior abortion.



REPORT BRIEF • JULY 2006

PRETERM BIRTH: CAUSES, CONSEQUENCES, AND PREVENTION

The rate of preterm births in the United States is a growing public health problem that has significant consequences for families, and costs society at least \$26 billion a year. Preterm births, defined as occurring before 37 weeks of gestation, now account for the troubling figure of 12.5 percent of all births in the United States (see Figure 1)—an increase of 30 percent since 1981. Full term infants are born between 38 and 42 weeks.

There are very troubling and persistent disparities in preterm birth rates among different racial and ethnic groups (see Figure 2). The highest rates are for African American women, and the lowest are for Asian or Pacific Islander women. In 2003, the rate for African-American women was 17.8 percent, while the rates were 10.5 percent for Asian and Pacific Islander women and 11.5 percent for white women. The most notable increases from 2001 to 2003 were for white, American Indian, and Hispanic groups. These disparities can not be fully explained by differences in socioeconomic conditions or maternal behaviors, such as smoking or drug use.

The growing problem of preterm births is not receiving the attention and funding necessary to fully understand its causes and identify ways to reduce the number of preterm deliveries. A report by the Institute of Medicine, *Preterm Birth: Causes, Consequences, and Prevention*, examines what is currently known about the causes of preterm birth; addresses the health, social-emotional, and economic consequences of preterm birth; and establishes a framework for action in addressing a range of priority issues, including a research and policy agenda for the future.



Preterm births, defined as occurring before 37 weeks of gestation, now account for the troubling figure of 12.5 percent of all births in the United States...

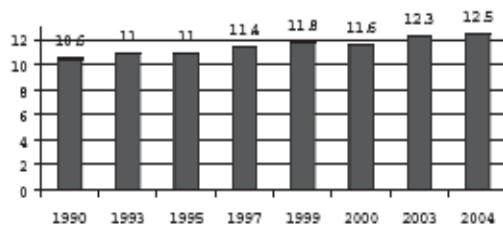


FIGURE 1. Preterm births as a percentage of live births in the United States, 1990 to 2004. SOURCES: CDC (2001, 2002, 2004a, 2005a).



IOM Report 2006

- **“Preterm births, defined as occurring before 37 weeks of gestation, now account for the troubling figure of 12.5 percent of all births in the United States...**
- **Babies born before 32 weeks have the greatest risk for death and poor health outcomes, however infants born between 32 and 36 weeks...are still at higher risk for health and developmental problems compared to those infants born full term.”**



IOM Report 2006

Appendix, on page 519, abortion is noted as an “immutable” risk factor

TABLE 5 Immutable Medical Risk Factors Associated with Preterm Birth

Previous low birth weight or preterm delivery*
Multiple 2nd trimester spontaneous abortion
Prior first trimester induced abortion
Familial and intergenerational factors
History of infertility
Nulliparity
Placental abnormalities
Cervical and uterine anomalies
Gestational bleeding
Intrauterine growth restriction
In utero diethylstilbestrol exposure
Multiple gestations*
Infant sex
Short stature
Low prepregnancy weight/low body mass index
Urogenital infections
Pre-eclampsia

IOM report: African American women and Preterm Birth

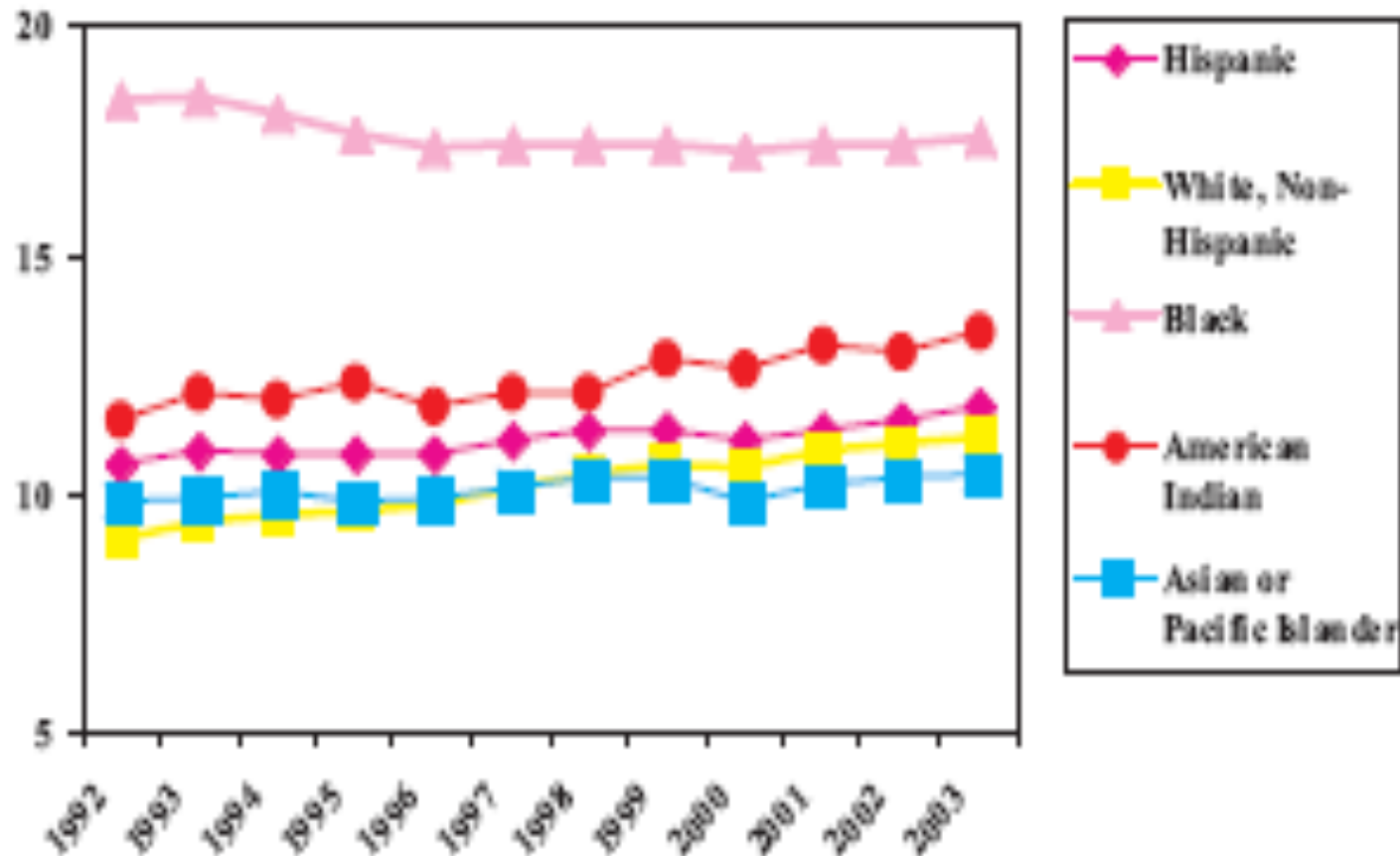


FIGURE 2. Preterm Births as a Percent of Live Births, by race and ethnicity, 1992 to 2003.
SOURCE: CDC (2004a).

IOM report: African American women and Preterm Birth

“African-American women deliver their infants before 37 weeks of gestation twice as often as women of other races, and deliver their infants before 32 weeks of gestation **three** times as often as white women...”



African American women and Preterm Birth

- **The IOM report establishes the fact that African American women have triple the rate of “very” preterm birth (<32 Wk) compared to Caucasian women.**
- **SES and behavioral factors do not account for the difference.**
- **According to CDC statistics, African American women, per capita, have about triple the rate of induced abortion as compared with Caucasian women.**



Induced termination of pregnancy and low birthweight and preterm birth: a systematic review and meta-analyses

PS Shah,^{a,b} J Zao^a on behalf of Knowledge Synthesis Group of Determinants of preterm/LBW births*

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Accepted 19 May 2009.

Background History of induced termination of pregnancy (I-TOP) is suggested as a precursor for infant being born low birthweight (LBW), preterm (PT) or small for gestational age (SGA). Infection, mechanical trauma to the cervix leading to cervical incompetence and scarred tissue following curettage are suspected mechanisms.

Objective To systematically review the risk of an infant being born LBW/PT/SGA among women with history of I-TOP.

Search strategy Medline, Embase, CINAHL and bibliographies of identified articles were searched for English language studies.

Selection criteria Studies reporting birth outcomes to mothers with or without history of induced abortion were included.

Data collection and analyses Two reviewers independently collected data and assessed the quality of the studies for biases in sample selection, exposure assessment, confounder adjustment, analytical, outcome assessments and attrition. Meta-analyses were

performed using random effect model and odds ratio (OR), weighted mean difference and 95% confidence interval (CI) were calculated.

Main results Thirty-seven studies of low-moderate risk of bias were included. A history of one I-TOP was associated with increased unadjusted odds of LBW (OR 1.35, 95% CI 1.20–1.52) and PT (OR 1.36, 95% CI 1.24–1.50), but not SGA (OR 0.87, 95% CI 0.69–1.09). A history of more than one I-TOP was associated with LBW (OR 1.72, 95% CI 1.45–2.04) and PT (OR 1.93, 95% CI 1.28–2.71). Meta-analyses of adjusted risk estimates confirmed these findings.

Conclusions A previous I-TOP is associated with a significantly increased risk of LBW and PT but not SGA. The risk increased as the number of I-TOP increased.

Keywords Birth outcomes, infant-low birthweight, infant-premature, therapeutic termination of pregnancy.

Please cite this paper as: Shah P, Zao J on behalf of Knowledge Synthesis Group of Determinants of preterm/LBW births. Induced termination of pregnancy and low birthweight and preterm birth: a systematic review and meta-analyses. BJOG 2009;116:1425–1442.

Background

Low birthweight (LBW) and preterm (PT) births are public health issues with physical, emotional, psychological and financial impact.¹ The research to identify relative contribution of various factors leading to preterm births spans several decades. First or even second-trimester-induced termination of pregnancy (I-TOP) are often considered minor and benign procedures; however, some studies report significant consequences to childbearing

potentials and possibilities of LBW and PT births. Current theories linking previous I-TOP to PT/LBW births include (a) overt or covert infection following I-TOP,² (b) mechanical trauma to the cervix leading to increased risk of cervical insufficiency³ and (c) surgical procedures including curettage resulting in scarred tissue that may increase the probability of faulty placental implantation and subsequent placenta previa.⁴ It is also likely that circumstances that made women to choose I-TOP such as socio-economic status may lead to LBW. Women who chose I-TOP may be inherently different from women who continue pregnancy and may be a risk factor for adverse pregnancy outcomes.

* Members of Knowledge Synthesis Group of Determinants of LBW/preterm births are listed in the Appendix.

Shaw and Zao

BJOG 2009;116:1425–1442.

 37 studies

Shaw and Zao 2009

- “Results:
- A history of **one I-TOP increased** unadjusted odds of:
- **LBW (OR 1.35, 95% CI 1.20–1.52)**
and
- **PT (OR 1.36, 95% CI 1.24–1.50),**
- **but not SGA (OR 0.87, 95% CI 0.69–1.09).”**



Shaw and Zao 2009

- “A history of **more than one I-TOP** was associated with
- **LBW (OR 1.72, 95% CI 1.45–2.04)** and
- **PT (OR 1.93, 95% CI 1.28–2.71).**
- Meta-analyses of adjusted risk estimates confirmed these findings.”



Abortion and Preterm Birth

- Between 1989 and 1993, Poland's induced abortion rate decreased 98% due to a new restrictive abortion law.
- The Demographic Yearbook of Poland reports that, between 1995 and 1997 the rate of extremely preterm births (<28 weeks gestation) dropped by 21%.



Abortion and Placenta Previa



Abortion and Placenta Previa

- Thorpe, et.al. “Long term physical and psychological health consequences of induced abortion:a review of the evidence” ObGyn Survey 58 (1) 67-79.
- “Placenta previa affects 0.3-0.8% of pregnancies and is the leading cause of uterine bleeding in the third trimester and medically indicated preterm birth.
- Pregnancies complicated by placenta previa result in high rates of preterm birth, low birth weight, and perinatal death



Abortion and Placenta Previa

- Thorpe, et.al. “Long term physical and psychological health consequences of induced abortion:a review of the evidence” ObGyn Survey 58 (1) 67-79.
- Both the observational studies included in our review and Ananth et al's meta-analysis showed a linkage between placenta previa and previous induced abortion”
- Two series: one 30% increase, second 70% increase.



Abortion and Placenta Previa

Seven-fold increase in risk of placenta previa with induced abortion, Barrett, et al. American Journal of Obstetrics and Gynecology, 1981.

Risk of placenta previa in subsequent pregnancy after induced abortion OR = 1.28 (95% CI = 1.00-1.63)

Taylor et.al. Obstetrics and Gynecology, 1993

Two or more induced abortions OR = 2.1 (95% CI = 1.2, 3.5)

Hendricks, et.al. Journal of OB&GYN Research, 1999



Abortion and Breast Cancer



Dolle et Al. 2010

Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years

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Divisions of ¹Public Health Sciences and ²Human Biology, Fred Hutchinson Cancer Research Center; ³Department of Epidemiology, University of Washington, Seattle, Washington; and ⁴Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland

Abstract

Little is known about the etiologic profile of triple-negative breast cancer (negative for estrogen receptor/progesterone receptor/human epidermal growth factor), a breast cancer subtype associated with high mortality and inadequate therapeutic options. We undertook this study to assess the risk for triple-negative breast cancer among women 45 years of age and younger in relation to demographic/lifestyle factors, reproductive history, and oral contraceptive use. Study participants were ascertained in two previous population-based, case-control studies. Eligible cases included all primary invasive breast cancers among women ages 20 to 45 years in the Seattle-Puget Sound area, diagnosed between January 1983 and December 1992, for whom complete data was obtained for estrogen receptor, progesterone receptor, and human epidermal growth factor status ($n = 897$; including $n = 187$ triple-negative breast cancer cases). Controls were age matched and ascertained via random digit dialing. Oral contraceptive use ≥ 1 year was associated with a 2.5-fold increased risk for triple-negative breast cancer (95% confidence

interval, 1.4-4.3) and no significantly increased risk for non-triple-negative breast cancer ($P_{\text{heterogeneity}} = 0.008$). Furthermore, the risk among oral contraceptive users conferred by longer oral contraceptive duration and by more recent use was significantly greater for triple-negative breast cancer than non-triple-negative breast cancer ($P_{\text{heterogeneity}} = 0.02$ and 0.01 , respectively). Among women ≤ 40 years, the relative risk for triple-negative breast cancer associated with oral contraceptive use ≥ 1 year was 4.2 (95% confidence interval, 1.9-9.3), whereas there was no significantly increased risk with oral contraceptive use for non-triple-negative breast cancer among women ≤ 40 years, nor for triple-negative breast cancer or non-triple-negative breast cancer among women 41 to 45 years of age. In conclusion, significant heterogeneity exists for the association of oral contraceptive use and breast cancer risk between triple-negative breast cancer and non-triple-negative breast cancer among young women, lending support to a distinct etiology. (Cancer Epidemiol Biomarkers Prev 2009;18(4):1157-66)



Dolle et Al. 2010

- Primary invasive breast cancer in
- women age 20-45
- January 1983-Dec 1992, Seattle, WA
- (n = 897; including n = 187 triple-negative breast cancer cases).



Dolle et Al. 2010

■ “Specifically, older age, family history of breast cancer, earlier menarche age, **induced abortion**, and oral contraceptive use were associated with an increased risk for breast cancer”.



Dolle et Al. 2010

- Induced abortion increases the risk of breast cancer by 40%: (Table 1.)
- triple negative=OR 1.4 (CI 0.9-2.2)
- non triple negative = OR 1.4 (CI 1.1 – 1.8)



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Prolonged breastfeeding reduces risk of breast cancer in Sri Lankan women: A case–control study

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ABSTRACT

Goal: To assess the association between duration of breastfeeding and the risk of breast cancer in Sri Lankan women. **Methods:** We conducted a case–control study in women aged 30–64 years in selected health care facilities in the Western province. A total of 100 recent cases of breast cancer (histologically confirmed) and 203 controls (age and parity matched) were included. Detailed information regarding breastfeeding, menstruation, reproductive factors, passive smoking and other confounders was collected using a structured questionnaire. Adjusted odds ratios and 95% confidence intervals were calculated using multiple logistic regressions. **Principle results:** Multivariate analysis found that those women who breastfed for ≥ 24 months during lifetime had significantly lower risk of breast cancer than those who breastfed for less than 24 months (OR = 0.40; 95%CI = 0.22, 0.73). Compared to 0–11 months of lifetime breastfeeding, there was a 66.3% reduction in breast cancer risk in women who breastfed for 12–23 months, 87.4% reduction in 24–35 months and 94% reduction in 36–47 months categories. The mean duration of breastfeeding per child for ≥ 12 months was also associated with reduced risk of breast cancer (OR = 0.52; 95%CI = 0.28, 0.94). The significant factors associated with increased risk of breast cancer were: post-menopausal women (OR = 1.74; 95%CI = 1.01, 3.01); having an abortion in the past (OR = 3.42; 95%CI = 1.75, 6.66) and exposure to passive smoking (OR = 2.96, 95%CI = 1.53, 5.75). **Major conclusions:** Prolonged breastfeeding significantly reduces the risk of breast cancer and this protective effect was supported by a dose–response relationship. Risk due to passive smoking should be emphasized in anti-smoking programmes.

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DeSilva et Al. 2010

- The significant factors associated with increased risk of breast cancer were:
- post-menopausal women (OR = 1.74; 95%CI = 1.01, 3.01);
- **having an abortion in the past (OR = 3.42; 95%CI = 1.75, 6.66) and**
- exposure to passive smoking (OR = 2.96, 95%CI = 1.53, 5.75).

Daling et Al. 1994

- “Risk of Breast Cancer Among Young Women: Relationship to Induced Abortion,” 86 Journal of the National Cancer Institute; (1994);1584]
- Teenagers under age 18 and women over 29 years of age who procure an abortion increase their breast cancer risk by more than 100% by age 45.
- **Daling’s most alarming finding was that teenagers with a family history of breast cancer who procure an abortion face a risk of breast cancer that is incalculably high.** All 12 women in her study with this history were diagnosed with breast cancer by the age of 45.



Innes and Byers 2004

Cases=2,522

Controls=10,052

Int. J. Cancer: 112, 306–311 (2004)
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FIRST PREGNANCY CHARACTERISTICS AND SUBSEQUENT BREAST CANCER RISK AMONG YOUNG WOMEN

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There is growing evidence that perinatal factors associated with altered gestational hormones may influence subsequent breast cancer risk in the mother. Events occurring during the first pregnancy may be particularly important. In this matched case-control study, we investigated the relation between characteristics of a woman's first pregnancy and her later breast cancer risk using linked records from the New York State birth and tumor registries. Cases were 2,522 women aged 22 to 55 diagnosed with breast cancer between 1978 and 1995 and who had also completed a first pregnancy in New York State (NY) at least 1 year prior to diagnosis. Controls were 10,052 primiparous women not diagnosed with breast or endometrial cancer in NY and matched to cases on county of residence and date of delivery. Information on factors characterizing the woman's first pregnancy was obtained from the pregnancy record of each subject. The association of these factors to breast cancer risk was assessed using conditional logistic regression. Extreme prematurity (< 32 weeks gestational age) was associated with elevated maternal breast cancer risk [adjusted odds ratio (OR)=2.1, 95% confidence interval (CI) 1.2,3.9], as were abruptio placentae (OR = 1.8, CI 1.1,3.0) and multifetal gestation (OR=1.8, CI 1.1,3.0). Preeclampsia was associated with a marked reduction in breast cancer risk among women who bore their first child after age 30 (OR=0.3, CI 0.2,0.7) and in the first 3 years after delivery (OR=0.2 (0.1–0.9)). These findings suggest that certain perinatal factors influence maternal breast cancer risk and offer indirect support for a role of gestational hormones, and particularly gestational estrogens, in the etiology of breast cancer.

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Key words: pregnancy; breast cancer; hormones; estrogens; prematurity; multiple birth; birth weight; preeclampsia; abruptio placentae

Pregnancy, and especially first pregnancy, clearly has an important influence on subsequent breast cancer risk. A first pregnancy completed prior to age 30 has a dual effect, conferring both a transient elevation and a later long-term reduction in breast cancer risk.^{1–3} In contrast, late first pregnancy increases both short- and long-term risk for breast cancer.^{2,3} The exact mechanisms underlying the influence of pregnancy on breast cancer risk remain unclear, but hormonal factors affecting the growth and differentiation of mammary cells are likely involved.⁴ Pregnancy is accompanied by dramatic elevations of estrogens and other steroids, as well as altered levels of other hormonal factors which have been linked to both mammary gland development and breast cancer risk.⁵

To explore the role of pregnancy hormones in the development of breast cancer, several studies have examined the associations between conditions associated with altered gestational hormones and breast cancer risk. Such conditions have included high birth weight,⁶ multiple birth,^{7–14} preterm birth^{15,16} and pregnancy-related hypertension.^{11,17–21} Findings concerning the relation between multiple birth and breast cancer have been conflicting, and studies regarding the influence of perinatal factors other than multiple birth remain few. In particular, there has been little attention to the relation between breast cancer risk and events occurring during the first pregnancy^{9,11,18} when breast tissue is less differentiated^{3,4} and thus potentially more susceptible to mutagenesis than in subsequent pregnancies.^{3,22} In this population-based

study, we examine the relation of factors characterizing a woman's first pregnancy to subsequent risk for early-onset breast cancer.

METHODS

We investigated the relationship of factors characterizing a woman's first pregnancy to her subsequent risk for breast cancer using a case-control design and linked, computerized vital record and cancer registry data from New York State. The anonymous, linked data set was supplied by the Bureau of Biometrics, New York State Department of Health (NYSDOH), in collaboration with the New York State Cancer Registry (NYSDOH) and the New York City Health Department.

Cases were defined as all women diagnosed with breast cancer in New York State between 1979 and 1995 and who also completed a first pregnancy in New York State after 1977 and at least 1 year prior to the diagnosis of cancer. Tumor record information for each case was linked to the birth records of her first born infant(s). A total of 2,522 cases were matched to their first pregnancy records. Among matched cases, age at diagnosis ranged from 22 to 55 years and averaged 37.6 ± 5.5 years. Table I shows the distribution of matched cases with respect to age at diagnosis, interval between completion of pregnancy and cancer diagnosis, and year and tumor stage at breast cancer diagnosis.

For each case matched to her first pregnancy record, we selected as controls the next 6 women, as identified on their infants' birth records, who resided and delivered in the same county and who were not subsequently diagnosed with breast or endometrial cancer in New York State. Those controls who were not primiparous at the time of the index pregnancy were excluded (N=5,080), yielding a total of 10,052 eligible matched controls. Attained age for each control was scored as age in years at the index pregnancy plus the interval between that pregnancy and the diagnosis of the corresponding matched case. Although it is possible that some controls died following delivery and prior to the age of 56, such deaths are likely to be few. Some controls may also have been diagnosed with breast cancer outside New York State. However, only 0.3% of women with an age distribution comparable to that of the controls would be expected to develop breast cancer (estimates based on SEER cancer statistics²³).

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Innes and Byers 2004

women, Melbye *et al.*¹⁵ found an increase in breast cancer risk among women who had delivered before 32 weeks gestation, similar in magnitude to that observed in our study. Mammary cells are thought to proliferate during the first and second trimester of pregnancy, and to differentiate in the third trimester.³⁵ Extreme prematurity has been characterized by high maternal estrogen levels,^{36,37} which could increase breast cell proliferation. Increased breast hyperplasia, followed by termination of pregnancy, prior to full differentiation of mammary stem cells, may increase the breast's susceptibility to neoplasia.



Abortion and Adverse Mental Health Outcomes



Fergusson DM. *“Abortion and mental health”*.
Psychiatr Bull R Coll Psychiatr 2008; 32: 321-324

- *“Although decisions on whether to proceed with induced abortion are made on the basis of clinical assessments of the extent to which abortion poses a risk to maternal mental health, these clinical assessments are not currently supported by population-level evidence showing the provision of abortion reduces mental health risks for women having unwanted pregnancy.”*

Abortion-Adverse Mental Health

- There are over 100 studies in the mental health literature supporting an association between abortion and subsequent adverse mental health outcomes.
- The most rigorous 41 studies demonstrate an association between induced abortion and suicide, substance abuse, depression, and intimate bonding dysfunction.

Abortion-Adverse Mental Health

- There are ZERO studies in the medical literature showing an improvement in mental health outcomes* for women who abort vs. women who give birth.
- *Suicide rate, depression, substance abuse, intimate partner bonding, maternal child bonding.

Abortion-Suicide

- Gissler (STAKES)
- Reardon (California MediCal records)

Gissler 1997

Gissler, M., et.al., "***Pregnancy-Associated Deaths in Finland 1987-1994 – Definition Problems and Benefits of Record Linkage***", Acta Obstetrica et Gynecologica Scandinavica, 76:651-657, 1997

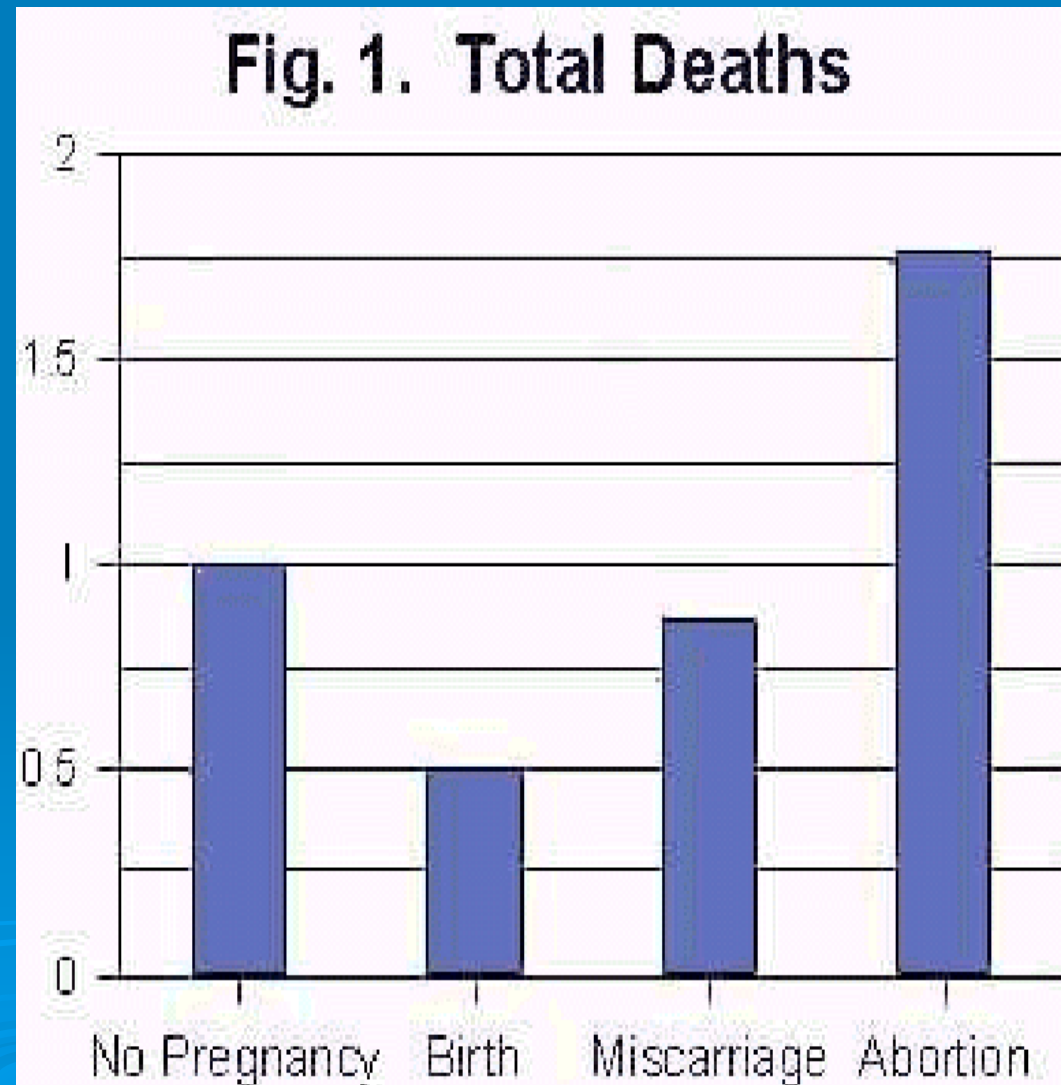
In 1997, Mika Gissler, et. al. of STAKES, the statistical analysis unit of Finland's National Research and Development Center for Welfare and Health published their landmark study.

- Retrospective record review of all death certificates for women of reproductive age (15-49) that died between 1987-1994 (n=9,192)

Gissler 1997

Compared with women who carried to term, those who aborted were 3.5 times more likely to die of all causes within a year.

(All cause includes suicide, accidents, (55) homicide and “unknown causes”(26 [10 violent, 16 nonviolent]) and “natural causes”)

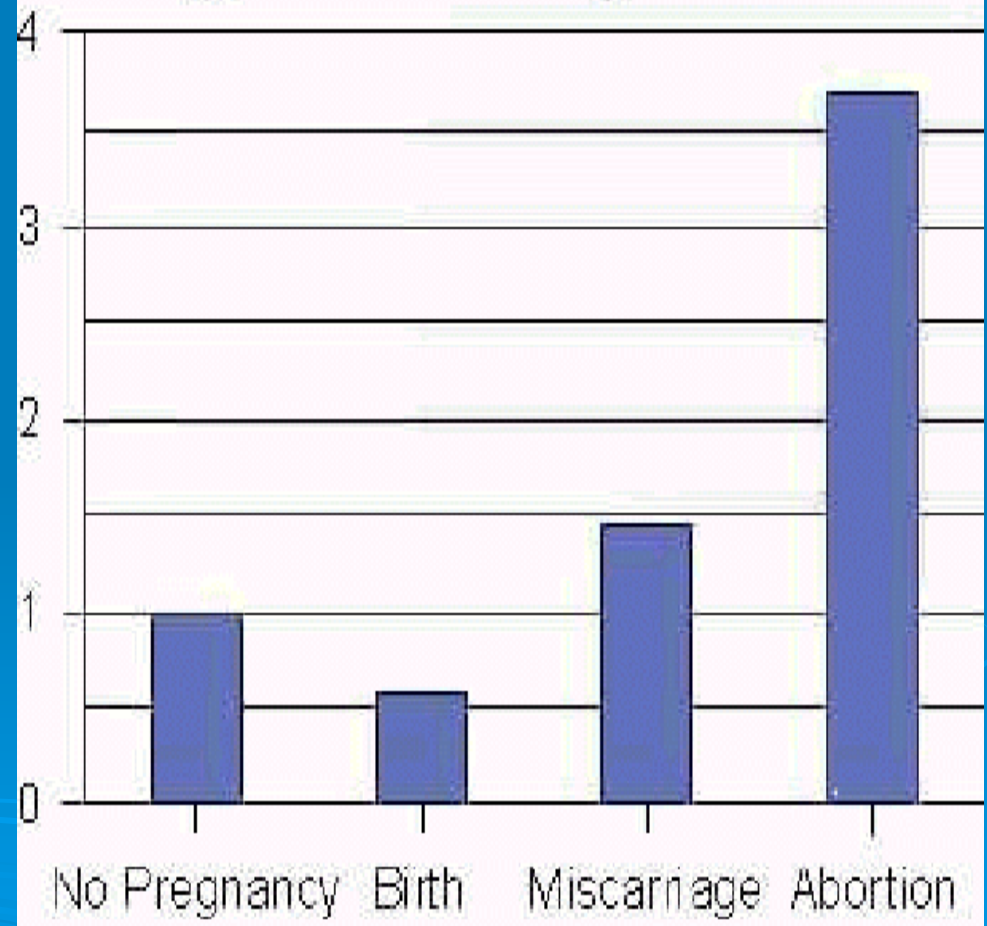


Gissler 1997

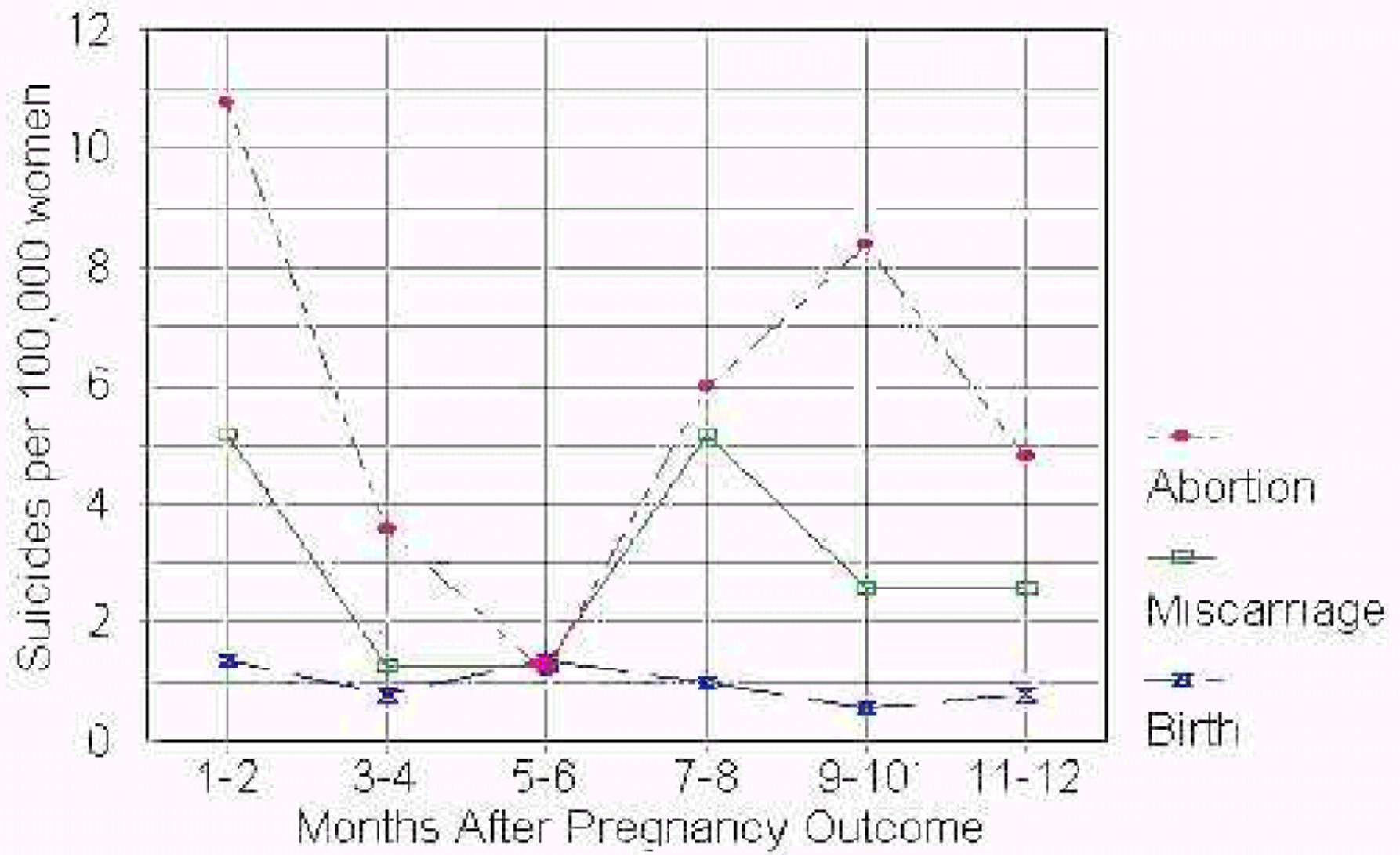
The risk of suicide following a birth was about half that of the general population of women. This finding is consistent with previous studies that have shown that an undisturbed pregnancy actually reduces the risk of suicide.

- Abortion carried a six fold higher risk of suicide compared with birth
- This statistical finding is corroborated by **interview-based studies** which have consistently shown extraordinarily high levels of **suicidal ideation (30-55 percent)** and reports of **suicide attempts (7-30 percent)** among women who have had an abortion. In many of these studies, the women interviewed have explicitly described the abortion as the cause of their suicidal impulses

Fig. 2. Deaths by Suicide

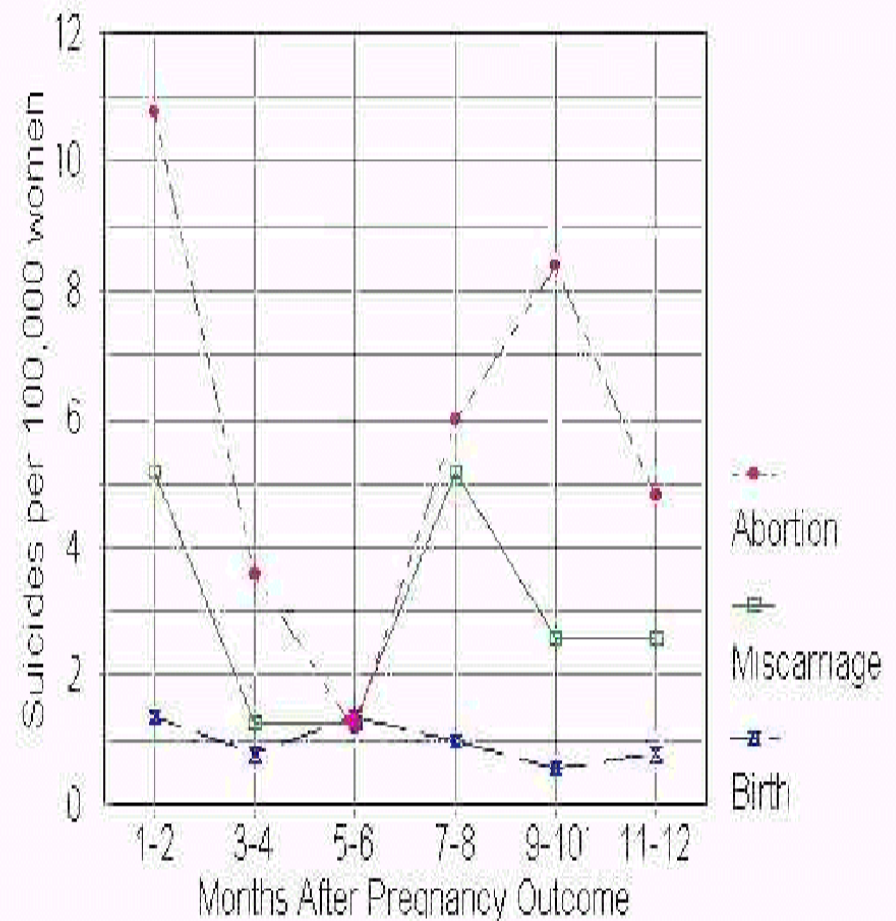


Gissler 1997



Gissler 1997

- The peak is near the expected due date of the aborted or miscarried pregnancy.
- “Our data may **underestimate the number of suicides** associated with pregnancy. We used the official cause of death to define suicide. Apart from the 73 pregnancy associated suicides, there were also **26 pregnancy associated deaths with an unclear cause** (10 violent and 16 non-violent), and 55 accidents (accidental deaths). **Some of these 81 cases might have been suicides.**”



Reardon 2002

- “Deaths Associated with Pregnancy Outcome: A Record Linkage Study of Low Income Women”,

Reardon, D. et.al., *So. Med. J.*, 95:8, 834-841, 2002

- Examined California Medicaid Records of women who had an abortion or delivery in 1989 (n=173,279) and these were linked to death certificates for 1989 to 1997. (reported as death rate/100,000)

	Delivery	eAb only
➤ All deaths	549	854
➤ Violent death	232	414
➤ Suicides	25	63
➤ Accidents	129	204
➤ Homocides	78	148

Shadigian et Al. 2005

- Shadigian E, Bauer S; Pregnancy- Associated Death: A Qualitative Systematic Review of Homicide and Suicide; OB GYN Survey, Vol 60, No 3 (2005).
- “both case-control studies show that suicide is 3 to 6 times greater in women obtaining an induced abortion than in women who deliver at term.”
- “There is no standardized method used to identify pregnancy at the time of death or close to the time of a woman’s death. ...The U.S. FBI (and other similar national and international agencies) does not report statistics on whether or not women are pregnant at the time of homicide or suicide... Many studies rely totally on death certificates, which have very strict guidelines for reporting a maternal death, but do not report pregnancy as a category, or if a woman has been pregnant in the last year.... Thus, underreporting of pregnancy-associated mortality is inevitable.”

Abortion and Suicide

- Garfinkle, B., et. al., “Stress, Depression, and Suicide: A study of Adolescents in Minnesota” (Minneapolis: Univ Minnesota Extension Service, 1986):
 - **rate of attempted suicide in the six months prior to the study increased 10 fold—from 0.4% for girls who had not aborted to 4% for teens who had aborted in the previous six months.**
- Morgan, C., et. al., “Mental health may deteriorate as a direct effect of induced abortion,” letter section, Brit. Med. Journal 314:902, 22 Mar 97:
 - after abortions, there were 8.9 suicide attempts per 1000, compared to 1.9 suicide attempts per 1000 among those who gave birth (more than 4X).

Abortion and Depression



Psychiatric admissions of low-income women following abortion and childbirth

David C. Reardon, Jesse R. Cogle, Vincent M. Rue, Martha W. Shuping, Priscilla K. Coleman, Philip G. Ney

See related article page 1257

Abstract

Background: Controversy exists about whether abortion or childbirth is associated with greater psychological risks. We compared psychiatric admission rates of women in time periods from 90 days to 4 years after either abortion or childbirth.

Methods: We used California Medicaid (Medi-Cal) records of women aged 13–49 years at the time of either abortion or childbirth during 1989. Only women who had no psychiatric admissions or pregnancy events during the year before the target pregnancy event were included ($n = 56\,741$). Psychiatric admissions were examined using logistic regression analyses, controlling for age and months of eligibility for Medi-Cal services.

Results: Overall, women who had had an abortion had a significantly higher relative risk of psychiatric admission compared with women who had delivered for every time period examined. Significant differences by major diagnostic categories were found for adjustment reactions (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.1–4.1), single-episode (OR 1.9, 95% CI 1.3–2.9) and recurrent depressive psychosis (OR 2.1, 95% CI 1.3–3.5), and bipolar disorder (OR 3.0, 95% CI 1.5–6.0). Significant differences were also observed when the results were stratified by age.

Interpretation: Subsequent psychiatric admissions are more common among low-income women who have an induced abortion than among those who carry a pregnancy to term, both in the short and longer term.

CMAJ 2003;168(10):1253–6

Researchers who study women's psychological adjustment to abortion have faced a number of major methodological problems. Most published studies contain little or no objective information about women's psychological state before conception and are also limited in their follow-up to an evaluation a few months, weeks or even hours after an abortion.^{1,2}

The importance of longer-term evaluation has been underscored by several recent studies showing delayed reactions to abortion among a minority of women.^{3,4} Major and colleagues,³ for example, carried out an investigation analyzing the psychological state of women 1 hour before abortion and 1 hour, 1 month and 2 years post abortion. In the post-abortion interviews, they found that depression, negative emotions and dissatisfaction with the abortion decision increased with time.

Other problems faced by researchers in this field are high attrition rates among women between the time of their abortion and subsequent interviews and concealment of past abortions. Fifty percent to 60% attrition or concealment rates are common.^{5,6,7}

The problems of concealment, nonparticipation, insufficient time for follow-up and lack of information about previous psychological condition can be circumvented by means of record-based investigations. Unfortunately, very little research of this type has been conducted. The one important and widely cited exception is a record-based study by David and colleagues.⁸ They used a Danish registry system to examine psychiatric admissions for 3 months post partum and post abortion for all residents under the age of 50 years and found that the overall rate of psychiatric admission was 18.4 per 10 000 population for women who had had an abortion and 12.0 per 10 000 population for women who had given birth.

The goal of the present investigation was to further previous record-based research by examining psychiatric admissions relative to previous pregnancy outcome over a longer period of time, while controlling for previous psychiatric history, socioeconomic status, age and months of eligibility for state-funded medical care. In addition, the present study examined specific diagnoses among women admitted for psychiatric treatment, because the literature shows that the psychiatric illnesses most likely to be associated with previous abortion are psychotic, neurotic and affective in type.^{9–11} Women who have had an abortion also have significantly higher depression scores compared with women who carry unintended pregnancies to term.¹² Additional research has shown that a small percentage of women (from 1.4%³ to 18.8%¹³) experience abortion as a traumatic event resulting in the symptoms of post-traumatic stress disorder.¹⁴

Methods

The California Department of Health Services (DHS) identified 249 625 women who had received funding for either an abortion or delivery in calendar year 1989 under the government-funded medical insurance program for low-income individuals known as Medi-Cal. In that year, pregnant women were eligible if

Reardon 2003

- California Medical Records
- Women age 13-49
- No prior psychiatric admissions for 1 year before pregnancy.
- N=56,741
- Endpoint: subsequent psychiatric admissions

Psychiatric admissions of low-income women following abortion and childbirth

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Methods

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Reardon 2003

- Women who aborted had higher risk of:
- Single episode depressive psychosis- OR 2.1 (1.3-3.5)
- Recurrent depressive psychosis- OR 2.1 (1.3-3.5)
- Bipolar disorder- OR 3.0 (1.5-6.0)

Fergusson 2006

Journal of Child Psychology and Psychiatry 47:1 (2006), pp 16–24

doi:10.1111/j.1469-7610.2005.01538.x

Abortion in young women and subsequent mental health

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Background: The extent to which abortion has harmful consequences for mental health remains controversial. We aimed to examine the linkages between having an abortion and mental health outcomes over the interval from age 15–25 years. **Methods:** Data were gathered as part of the Christchurch Health and Development Study, a 25-year longitudinal study of a birth cohort of New Zealand children. Information was obtained on: a) the history of pregnancy/abortion for female participants over the interval from 15–25 years; b) measures of DSM-IV mental disorders and suicidal behaviour over the intervals 15–18, 18–21 and 21–25 years; and c) childhood, family and related confounding factors. **Results:** Forty-one percent of women had become pregnant on at least one occasion prior to age 25, with 14.6% having an abortion. Those having an abortion had elevated rates of subsequent mental health problems including depression, anxiety, suicidal behaviours and substance use disorders. This association persisted after adjustment for confounding factors. **Conclusions:** The findings suggest that abortion in young women may be associated with increased risks of mental health problems. **Keywords:** Abortion, pregnancy, mental disorder, depression, anxiety, suicidal behaviour, substance dependence.

Fergusson 2006

Table 1 Rates of disorder (15–18, 18–21, 21–25 years) by cumulative history of pregnancy/abortion to age 18, 21, 25 years respectively

Measure	Not Pregnant	Pregnant No Abortion	Pregnant Abortion	<i>p</i>
Mean (SD) number of mental health problems				
15–18 years	1.01 (1.13)	1.07 (1.39)	1.93 (.73)	
18–21 years	.61 (.96)	.90 (1.14)	1.20 (1.20)	
21–25 years	.50 (.85)	.81 (1.05)	1.27 (1.30)	
Pooled risk ratio (95% CI) ¹	.57 ^a (.45–.72)	.66 ^a (.50–.87)	1 ^b	<.001
Sample sizes				
15–18 years	478	28	14	
18–21 years	375	84	51	
21–25 years	301	131	74	

¹The results of planned comparisons of the rate of each outcome across the three groups are indicated by the superscripts (^a, ^b). Different superscripts indicate that the groups were significantly ($p < .05$) different on their rates of disorder. Similar superscripts indicate that groups were not significantly different in their rates of disorder.

Fergusson 2006

Table 1 Rates of disorder (15-18, 18-21, 21-25 years) by cumulative history of pregnancy/abortion to age 18, 21, 25 years respectively

Measure	Not Pregnant	Pregnant No Abortion	Pregnant Abortion	<i>p</i>
Major depression (%)				
15-18 years	31.2	35.7	78.6	
18-21 years	27.5	34.5	45.1	
21-25 years	21.3	30.5	41.9	
Pooled risk ratio (95% CI) ¹	.35 ^a (.20-.59)	.49 ^a (.27-.91)	1 ^b	<.001

Fergusson 2006

Table 1 Rates of disorder (15-18, 18-21, 21-25 years) by cumulative history of pregnancy/abortion to age 18, 21, 25 years respectively

Measure	Not Pregnant	Pregnant No Abortion	Pregnant Abortion	<i>p</i>
Anxiety disorder (%)				
15-18 years	37.9	35.7	64.3	
18-21 years	15.2	25.0	25.5	
21-25 years	16.9	29.8	39.2	
Pooled risk ratio (95% CI) ¹	.35 ^a (.19-.63)	.54 ^{a, b} (.27-1.07)	1 ^b	.001

Fergusson 2006

Table 1 Rates of disorder (15-18, 18-21, 21-25 years) by cumulative history of pregnancy/abortion to age 18, 21, 25 years respectively

Measure	Not Pregnant	Pregnant No Abortion	Pregnant Abortion	<i>p</i>
Suicidal ideation (%)				
15-18 years	23.0	25.0	50.0	
18-21 years	12.5	17.9	25.5	
21-25 years	8.0	13.0	27.0	
Pooled risk ratio (95% CI) ¹	.25 ^a (.13-.50)	.31 ^a (.14-.69)	1 ^b	<.001

Fergusson 2006

1. For all outcomes, except alcohol dependence, there were significant ($p < .001$) associations between pregnancy history and rates of disorder. These associations reflected a tendency for rates of mental health problems to be highest amongst those having abortions and lowest amongst those who had not become pregnant, with those who became pregnant but did not have an abortion having rates that were intermediate between these extremes.

Rees and Sabia 2007

- *“The relationship between abortion and depression: New evidence from the fragile families and child wellbeing study.”*
- Daniel I. Rees and Joseph Sabia; Medical Science Monitor 2007; 13 (10) CR 430-436 PMID 17901849
- Data from Fragile Families Database
- 2844 mothers who participated in three interviews
- Baseline interview at birth of a child.
- Interviews at 1 and 3 years after baseline.

Rees and Sabia 2007

- **Category 1** = Women who had an **abortion** between interviews, with no other pregnancies.
- **Category 2** = Women who had a **miscarriage or stillbirth** between interviews with no other pregnancies.
- **Category 3** = Women who had a **live birth** between interviews, with no other pregnancies
- **Category 4** = Women who had **no pregnancies** between interviews

Rees and Sabia 2007

Percentage of women with symptoms of MD
at 1 year follow-up interview:

Category 1 (abortion) = **20.3%**

Category 2 (miscarriage/stillbirth) = 20.1%

Category 3 (live birth) = **14.0%**

Category 4 (no pregnancies) = 13.0%

(data from Table 1)

Rees and Sabia 2007

Percentage of women with symptoms of MD at 3 year follow-up interview:

Category 1 (abortion) = 31.6% (11% increase)

Category 2 (miscarriage or stillbirth) = 20.2% (0.1% increase)

Category 3 (live birth) = 21% (7% increase)

Category 4 (no pregnancies) = 15.5% (2.5% increase)

Rees and Sabia 2007

- “Abortion was associated with depressive symptomatology even after adjusting for factors such as race, ethnicity, age, household income, education, marital status and number of children. In fact, adjusting for these factors, abortion was associated with a more than two-fold increase in the risk of symptoms of MD as compared to not becoming pregnant.”

Psychological impact on women after second and third trimester termination of pregnancy due to fetal anomalies versus women after preterm birth—a 14-month follow up study

Anette Kersting · Kristin Kroker · Johannes Steinhard · Isabell Hoernig-Franz · Ute Wesselmann · Katharina Luedorff · Patricia Ohrmann · Volker Arolt · Thomas Suslow

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Abstract The objective of this study was to compare psychiatric morbidity and the course of posttraumatic stress, depression, and anxiety in two groups with severe complications during pregnancy, women after termination of late pregnancy (TOP) due to fetal anomalies and women after preterm birth (PRE). As control group women after the delivery of a healthy child were assessed. A consecutive sample of women who experienced a) termination of late pregnancy in the 2nd or 3rd-trimester ($N=62$), or b) preterm birth ($N=43$), or c) birth of a healthy child ($N=65$) was investigated 14 days (T1), 6 months (T2), and 14 months (T3) after the event. At T1, 22.4% of the women after TOP were diagnosed with a psychiatric disorder compared to 18.5% women after PRE, and 6.2% in the control group. The corresponding values at T3 were 16.7%, 7.1%, and 0%. Shortly after the event, a broad spectrum of diagnoses was found; however, 14 months later only affective and anxiety disorders were diagnosed. Posttraumatic stress and clinician-rated depressive symptoms were highest in women after TOP. The short-term emotional reactions to TOP in late

pregnancy due to fetal anomaly appear to be more intense than those to preterm birth. Both events can lead to severe psychiatric morbidity with a lasting psychological impact.

Keywords Termination of pregnancy · Fetal anomaly · Preterm birth · Psychiatric morbidity · Posttraumatic stress

Introduction

Pregnancy and giving birth are major life events, sometimes with unexpected severe complications for the child, like severe fetal anomalies or very low birth weight, and in turn with traumatic impact on the parents. Developments in prenatal diagnostics have increasingly allowed fetal abnormalities to be diagnosed and prognostically assessed in the first and second trimester of pregnancy, yet the opportunities of prenatal therapy remain limited. Once the diagnoses have been made, parents are confronted with a traumatic reality and a difficult emotional choice: to continue or to end the pregnancy. While the diagnosis alone imposes a severe strain on any woman, the question of whether or not to terminate the pregnancy is a crucial decision to be made. To continue the pregnancy has far-reaching effects, but to terminate the pregnancy implies opting for the death of her own fetus, followed by an agonizing waiting for labour pains to set in and the delivery of a stillborn fetus. However, most pregnancies are terminated when prenatal severe fetal anomalies are diagnosed (Kramer et al. 1998, Mansfield et al. 1999).

Several studies have reported negative reactions of women after the traumatic experience of a termination of pregnancy due to fetal anomaly (TOP) (Iles and Gath 1993,

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Kersting 2008

- Women with fetal anomalies who terminated (n=62) or gave birth (n=43) compared with women who birthed a normal child (n=65).

Psychological impact on women after second and third trimester termination of pregnancy due to fetal anomalies versus women after preterm birth—a 14-month follow up study

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Kersting 2008

- 22.4% of abortion group had psychiatric diagnosis vs
- 18.5% of birth group
- 6.2% of control group

Abortion and mental health disorders: evidence from a 30-year longitudinal study[†]

David M. Fergusson, L. John Horwood and Joseph M. Boden

Background

Research on the links between abortion and mental health has been limited by design problems and relatively weak evidence.

Aims

To examine the links between pregnancy outcomes and mental health outcomes.

Method

Data were gathered on the pregnancy and mental health history of a birth cohort of over 500 women studied to the age of 30.

Results

After adjustment for confounding, abortion was associated with a small increase in the risk of mental disorders; women

who had had abortions had rates of mental disorder that were about 30% higher. There were no consistent associations between other pregnancy outcomes and mental health. Estimates of attributable risk indicated that exposure to abortion accounted for 1.5% to 5.5% of the overall rate of mental disorders.

Conclusions

The evidence is consistent with the view that abortion may be associated with a small increase in risk of mental disorders. Other pregnancy outcomes were not related to increased risk of mental health problems.

Declaration of interest

None. Funding detailed in Acknowledgements.

Fergusson 2008

- **Results:** “After adjustment for confounding , abortion was associated with a small increase in the risk of mental disorders; **women who had had abortions had rates of mental disorders that were about 30% higher.** There were no consistent associations between other pregnancy outcomes and mental health. Estimates of attributable risk indicated that exposure to abortion accounted for 1.5% to 5.5% of overall rate of mental disorders.

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conclusions.

- (a) Exposure to induced abortion was consistently associated with increased rates of mental disorders, with ORs for individual disorders ranging from 1.86 to 7.08. These trends are reflected in the fact that those exposed to abortion between ages 15–30 had overall rates of mental health problems that were 1.54 (95% CI 1.28–1.85) times higher than those not exposed to abortion ($P < 0.001$).

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(b) Exposure to pregnancy loss was also associated with modest but consistent increases in risks of mental health problems, with ORs for individual disorders ranging from 1.76 to 3.30. These trends are reflected in the fact that, overall, those who had experienced pregnancy loss had rates of mental disorder that were 1.49 (95% CI 1.21–1.84) times higher than those who had not ($P < 0.001$).

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Finally, the findings of this study have some important implications for the legal status of abortion in societies such as New Zealand and the UK, where over 90% of abortions are authorised on the grounds that proceeding with the pregnancy would pose a serious threat to the woman's mental health.^{48,49}

In general, there is no evidence in the literature on abortion and mental health that suggests that abortion reduces the mental health risks of unwanted or mistimed pregnancy. Although some studies have concluded that abortion has neutral effects on mental health,^{4,5,12,14} no study has reported that exposure to abortion reduces mental health risks. These trends are evident in the present study, which shows that although abortion was associated with increased risks of mental health problems, no increase was evident for those having unwanted pregnancies that came to term.

Abortion-Substance Abuse

- Coleman 2002
- Pederson 2007
- Dingle 2008
- Coleman 2008

Coleman 2002

A history of induced abortion in relation to substance use during subsequent pregnancies carried to term

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and Jesse Cougle, MSc^d

Sewanee, Tenn, Springfield, Ill; Stratham, NH, and Austin, Tex

OBJECTIVE: Previous research has revealed a general association between induced abortion and substance use. The purpose of this study was to examine the correlation when substance use is measured specifically during a subsequent pregnancy.

STUDY DESIGN: A nationally representative sample of women was surveyed about substance use during pregnancy shortly after giving birth. Women with a previous induced abortion, whose second pregnancy was delivered, were compared separately with women with one previous birth and with women with no previous births.

RESULTS: Compared with women who gave birth, women who had had an induced abortion were significantly more likely to use marijuana (odds ratio, 10.29; 95% CI, 3.47-30.56), various illicit drugs (odds ratio, 5.60; 95% CI, 2.39-13.10), and alcohol (odds ratio, 2.22; 95% CI, 1.31-3.76) during their next pregnancy. The results with only first-time mothers were very similar.

CONCLUSION: Psychosocial mechanisms that may explain the findings are discussed. Screening for abortion history may help to identify pregnant women who are at risk for substance use more effectively. (*Am J Obstet Gynecol* 2002;187:1673-8.)

Key words: Induced abortion, substance use, pregnancy

Coleman 2002

- “ Results: Compared with women who gave birth, women who had had an induced abortion were significantly more likely to
- use marijuana (OR 10.29, 95% CI 3.47-30.56)
- Use various illicit drugs (OR 5.60, 95% CI 2.39-13.10)
- And use alcohol (OR 2.22, 95% CI 1.31-3.76) during their first pregnancy

Pederson 2007

RESEARCH REPORT

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Childbirth, abortion and subsequent substance use in young women: a population-based longitudinal study

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ABSTRACT

Aims To investigate the possible linkages between deliveries, abortions and subsequent nicotine dependence, alcohol problems and use of cannabis and other illegal drugs from the ages of 15–27 years. **Methods** Data were gathered as part of the Young in Norway Longitudinal Study, an 11-year follow-up of a representative sample of Norwegian adolescents and young adults. **Design, setting and participants** Information was obtained on (i) the history of child-births and induced abortions for the participants between the ages of 15–27 years; (ii) measures of nicotine dependence, alcohol problems and use of cannabis and other illegal drugs; and (iii) socio-demographic, family and individual confounding factors. **Results** Those who had had an abortion had elevated rates of substance use and problems. Those who gave birth to a child had reduced rates of alcohol problems and cannabis use. These associations persisted after control for confounders. However, those women who still lived with the father of the aborted fetus were not at increased risk. **Conclusions** Abortion in women may, under some circumstances, be associated with increased risk of nicotine dependence, alcohol problems and use of cannabis and other illegal drugs. The birth of a child may reduce the use of some substances.

Keywords Abortion, alcohol problems, cannabis, childbirth, longitudinal, nicotine dependence.

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- Young in Norway Longitudinal study
- 11 year follow-up
- Hx of childbirth and abortions for women 15-27 years
- Measures of nicotine, alcohol, cannabis and other illegal drug use.
- Controlled for confounding factors.

Table 1 Rates of substance use and problems at age 27, by history of delivery/abortion.

	Not pregnant (n = 461)	Delivery (n = 183)	Abortion (n = 76)	Delivery and abortion (n = 49)	P*
Nicotine dependence					
(%)	6.7	9.8	26.3	12.2	0.0001
OR (95 CI)†	1.0	1.5 (0.8–2.8)	5.0 (2.6–9.3)	1.9 (0.8–4.9)	
Alcohol problems					
(%)	13.2	2.7	30.3	14.3	0.0001
OR (95 CI)	1.0	0.2 (0.1–0.5)	2.8 (1.6–5.0)	1.1 (0.5–2.5)	
Cannabis use last 12 months					
(%)	9.1	3.8	31.6	8.2	0.0001
OR (95 CI)	1.0	0.4 (0.2–0.9)	4.6 (2.6–8.2)	0.9 (0.3–2.6)	
Other illegal drug use last 12 months					
(%)	2.6	2.7	17.1	4.1	0.0001
OR (95 CI)	1.0	1.1 (0.4–3.0)	7.7 (3.4–17.7)	1.6 (0.3–7.3)	

* χ^2 test of independence. †Non-adjusted odds ratios (OR) with 95% confidence intervals (CI).

Pederson 2007

1. The women who reported a history of abortions had elevated rates of substance use and problems when compared to those who did not become pregnant during the follow-up period. Those who delivered a child reported lower rates of alcohol problems and cannabis use.
2. These associations persisted after control for a range of confounding factors, suggesting a link between history of childbirths and abortions and subsequent substance use.
3. A more detailed study of the abortion group revealed that only the women who did not have a present partner relationship with the father of the aborted fetus had elevated risk rates.

Dingle 2008

BJPsych

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Pregnancy loss and psychiatric disorders in young women: an Australian birth cohort study

Kaeleen Dingle, Rosa Alati, Alexandra Clavarino, Jake M. Najman and Gail M. Williams

Background

Recent evidence has linked induced abortion with later adverse psychiatric outcomes in young women.

Aims

To examine whether abortion or miscarriage are associated with subsequent psychiatric and substance use disorders.

Method

A sample ($n=1223$) of women from a cohort born between 1981 and 1984 in Australia were assessed at 21 years for psychiatric and substance use disorders and lifetime pregnancy histories.

Results

Young women reporting a pregnancy loss had nearly three

times the odds of experiencing a lifetime illicit drug disorder (excluding cannabis): abortion odds ratio (OR)=3.6 (95% CI 2.0–6.7) and miscarriage OR=2.6 (95% CI 1.2–5.4). Abortion was associated with alcohol use disorder (OR=2.1, 95% CI 1.3–3.5) and 12-month depression (OR=1.9, 95% CI 1.1–3.1).

Conclusions

These findings add to the growing body of evidence suggesting that pregnancy loss *per se*, whether abortion or miscarriage, increases the risk of a range of substance use disorders and affective disorders in young women.

Declaration of interest

None. Funding detailed in Acknowledgements.

Dingle 2008

- “Method: A sample (n=1223) of women from a cohort born between 1981 and 1984 in Australia were assessed at 21 years for psychiatric and substance abuse disorders and lifetime pregnancy history.”

Dingle 2008

- Results: Young women reporting a pregnancy loss had nearly **three times the odds of experiencing a lifetime illicit drug disorder** (excluding cannabis):
- abortion odds ratio (OR)=3.6 (95% CI 2.0–6.7) and miscarriage OR=2.6 (95% CI 1.2–5.4).
- Abortion was associated with alcohol use disorder (OR=2.1, 95% CI 1.3–3.5) and 12-month depression (OR=1.9, 95% CI 1.1–3.1).

Coleman 2008

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Induced abortion and anxiety, mood, and substance abuse disorders: Isolating the effects of abortion in the national comorbidity survey

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ABSTRACT

The purpose of this study was to examine associations between a abortion history and a wide range of anxiety (panic disorder, panic attacks, PTSD, Agoraphobia), mood (bipolar disorder, mania, major depression), and substance abuse disorders (alcohol and drug abuse and dependence) using a nationally representative US sample, the national comorbidity survey. Abortion was found to be related to an increased risk for a variety of mental health problems (panic attacks, panic disorder, agoraphobia, PTSD, bipolar disorder, major depression with and without hierarchy), and substance abuse disorders after statistical controls were instituted for a wide range of personal, situational, and demographic variables. Calculation of population attributable risks indicated that abortion was implicated in between 4.3% and 16.6% of the incidence of these disorders. Future research is needed to identify mediating mechanisms linking abortion to various disorders and to understand individual difference factors associated with vulnerability to developing a particular mental health problem after abortion.

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Coleman et. Al. 2008

4. Discussion

The results of this study revealed that women who have aborted are at a higher risk for a variety of mental health problems including anxiety (panic attacks, panic disorder, agoraphobia, PTSD), mood (bipolar disorder, major depression with and without hierarchy), and substance abuse disorders when compared to women without a history of abortion after controls were instituted for a wide range of personal, situational, and demographic factors. As

Conclusions

- Elective induced abortion can result in significant reproductive, psychological and physical harm to women.
- Adverse consequences of elective induced abortion are being increasingly documented in the medical literature.
- Knowledge of these risks is an important part of truly informed choice.

Recommendations

- Informed consent prior to abortion needs to include information about the increased risks of extremely early preterm birth in subsequent pregnancies, and
- The increased risks of major depression, suicide, substance abuse and affective disorders.
- Screening for risk factors for affective disorders should be done prior to abortion.

Recommendations

- In light of increased depression in women with termination of pregnancy for fetal anomalies, the option of perinatal hospice should be available and offered to patients who screen positive for fetal anomalies.

- American Association of Pro-Life Obstetricians and Gynecologists
 - www.aaplog.org
 - Life. It's Why We Are Here.