Heath Effects of Fertility Control

OUTLINE

1. Beneficial effects of oral contraceptives
2. Contraception and risks of STDs, PID, HIV, and infertility
3. Sterilization
4. Abortion
5. Maternal mortality and risks/benefits of contraception

Beneficial effects of contraception

Well-established major protective effects of oral contraceptives by problem or condition (UK or US)

Condition	Relative Risk		Influenced by Duration of Use	Influenced by OC Formulation
	Current Use	Past Use		
Menstrual problems	0.75	1.0	No	Yes - protection decreases with "low-dose" pills
Iron-deficiency anemia	0.75	1.0	No	Unknown
Benign breast cysts	0.5	1.0	Yes - protection increases as duration increases	Yes - protection increases as progestin increases
Pelvic inflammatory disease	0.5	1.0	Unknown	Unknown
Functional ovarian cysts	0.25	1.0	No	Probably not
Epithelial ovarian cancer	0.5	0.5	Yes - protection increases as duration increases	Probably not
Endometrial cancer	0.5	0.5	Yes - protection increases as duration increases	Probably not

Adapted from Vessey MP. The Jephcott Lecture, 1989: An Overview of the Benefits and Risks of Combined Oral Contraceptives." In: *Oral Contraceptives and Breast Cancer*. Mann RD, ed. Park Ridge, NJ: The Parthenon Publishing Group, 1990

Effects of Contraception on STDs

- **1. Barrier Methods**
  - Mechanical and chemical barriers protect against cervical and upper genital tract infections

2. **Oral and injectable contraceptives**
   - Protect against ascending infections due to ↑ cervical mucus viscosity (e.g., gonorrhea RR~0.5).
   - Oral contraceptives may increase the risk of chlamydia, due to increase in ectopy. (Possible detection bias)

Effects of Contraception on STDs, PID, and Tubal Infertility

3. IUD
   - Increased risk of PID within first 3 months after insertion. Due to introduction of infection at time of IUD insertion, increased menstrual bleeding, IUD tail and possible foreign body reaction.

4. Female Sterilization
   - Partially protective against PID in distal tube and peritoneal cavity.

Primary Tubal Infertility and Contraceptive Use

	Adj RR	95% CI
No History of PID		
IUD	1.7	1.2, 2.3
OC	1.1	0.8, 1.5
Barrier	0.7	0.5, 0.9
PID History		
IUD	3.9	2.0, 7.5
OC	1.8	0.7, 4.5
Barrier	0.5	0.2, 0.9

Contraception and HIV

1. **Barrier Methods**

- Male Condoms protect, dependent on consistency of use.

- Female condom, no data

- No clear evidence for effects of diaphragm or cervical cap (vaginal mucosa exposed).

- Microbicides:
  - Nonoxynol 9, no effect or increased risk. Increased ulceration
  - Cellulose sulphate, trial stopped for harm 2007

HIV Seroconversion and Condom Use in HIV Discordant Couples

Condom use	Number of Couples	Cumulative HIV Seroconversion over Two Years (95% CI)
Consistent	121	0
Inconsistent use	124	12.7 (5.9-19.5)
Inconsistent Users		
Use in <50% sex contacts	60	15.0 (9.7-20.3)
Use in ≥50% of contacts	60	10.3 (5.9-14.7)

Source: Vincenzi et al. NEJM 331: 341-6, 1984

Condom Use and Relative Risk of STD HIV, Rakai

	Inconsistent Use RR	**Consistent Use RR**
HIV	0.96 (0.5-1.7)	0.37 (0.2-0.9)
Syphilis	1.06 (0.9-1.2)	0.71 (0.5-0.9)
Gonorrhea/ Chlamydia	1.44 (1.1-2.0)	0.50 (0.3-1.0)
BV	1.11 (1.0-1.30	0.89 (0.7-1.1)
Ahmed et al *AIDS*	2001;15:2171	

Studies of Condom Breakage

Study	Year	Population	Location	Recall Period	Breakage Rage (%)
Cross-sectional					
vanGriensven et al	1988	Gay men	Amsterdam	6 mos	2 to 4
Tindall et al.	1989	Gay and bisexual men	Sydney	6 mos	5 to 7 (anal)
Golombok et al	1989	Gay men	England	12 mos	3 to 5 (anal)
Consumers Union	1989	Men and women	US	12 mos	1 (anal), 0.6 (vaginal)
Albert et al	1991	Women	US	Lifetime	1
		Family planning clients	US	12 mos	0.8
Cohort					
Richters et al	1988	Male prostitutes	Sydney	4 mos	0.5 (anal), 0.8 (vaginal)
Trussell et al	1992	Family planning clients	US	16 days	1.5 to 2.0
Trussell et al	1992	Family planning clients	US	21 days	1.2 to 1.3

Microbicides and HIV Acquisition

b. ***Spermicides/Microbicides*****:**

Nonoxynol-9 (N-9) viricidal in vitro and protective in monkey experiments.

- No evidence of protective effects in humans. One trial showed increased HIV risk
- All trials in CSWs with high frequency of intercourse
- N-9 may increase transmission due to micro-ulceration of cervical and vaginal epithelium.
- Clinical trials confounded by concurrent condom use.

Summary of randomized trials of N-9 versus placebo

Outcome	RR	95% CI
HIV	1.12	0.88-1.42
Gonorrhea	.91	0.67-1.24
Chlamydia	.88	0.77-1.01
Cervical infection	1.01	0.84-1.22
Trichomoniasis	.84	0.69-1.02
Bacterial vaginosos	.88	0.74-1.04
Candidiasis	.97	0.84-1.12
Genital ulcer	**1.18**	**1.02-1.36**

Source: Wilkinson D. et al. *Lancet Infectious Diseases,* 2002; 2:613-7.

Oral and Injectable Contraceptives

- Monkey studies of vaginal inoculation with simian immunodeficiency virus (SIV) show higher rates of infection with progesterone (thinning of mucosa and endometrium).

- Human studies suggest higher viral shedding in genital tract secretions of women taking oral contraceptives

- Cross-sectional and prospective observational studies provide inconsistent evidence (problem of behavioral confounding due to increased sexual activity of OC and DMPA users?).

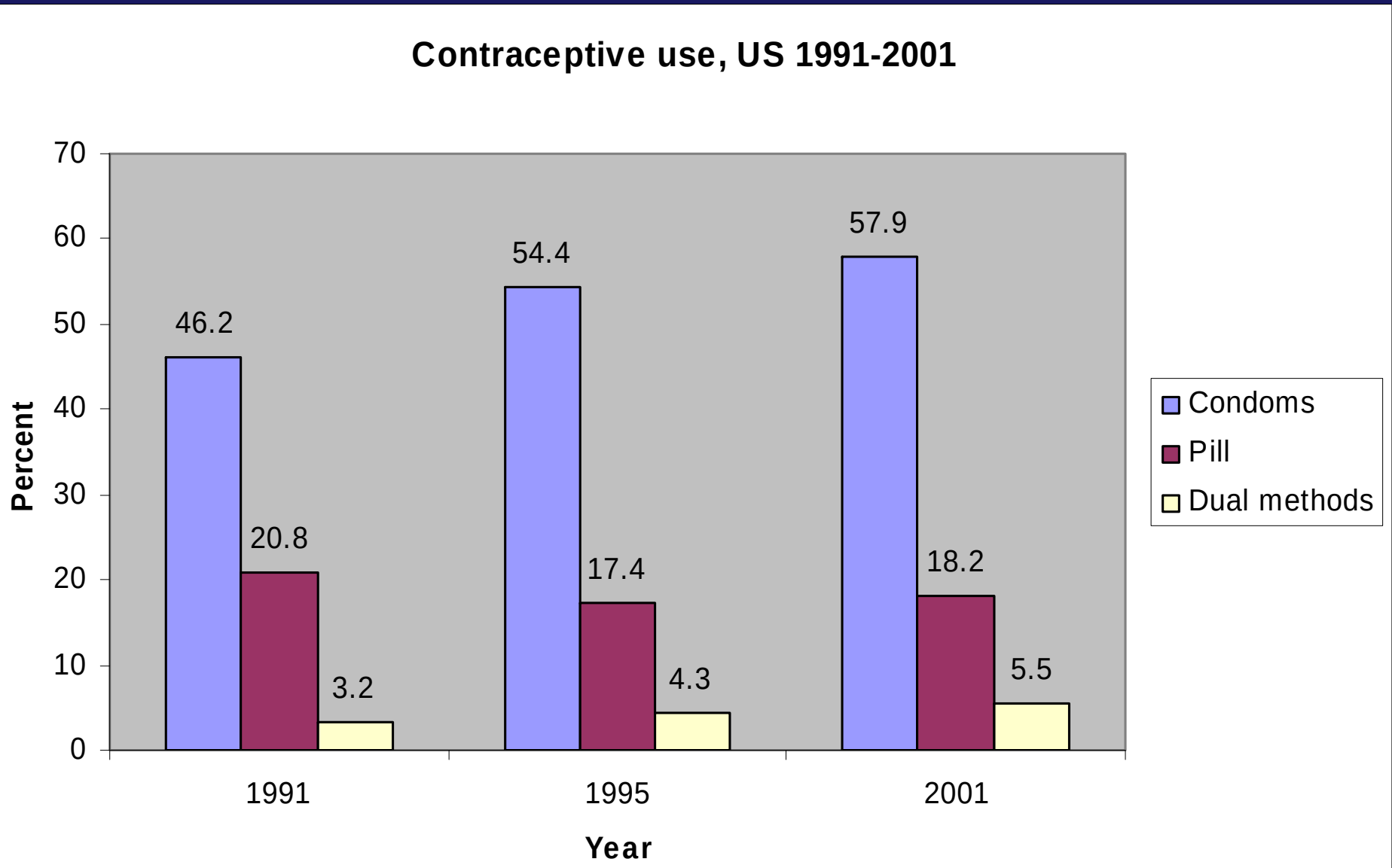
Hormonal Contraception and HIV Acquisition, Rakai, Uganda

	Horm. Users HIV Incid per100 py	Non-Users HIV Incid Per 100 py	Adjusted RR (95% CI)
All	2.3	1.5	0.94 (0.5-1.6)
Pills	2.5	1.5	1.12 (0.5-2.6)
Injection	2.3	1.5	0.84 (0.4-1.7)

Kiddugavu et al *AIDS* 2003;17:233

Contraception and HIV/STD Prevention

- Condoms prevent HIV/STDs, but are not very effective for pregnancy prevention
- Hormonal methods do not protect against HIV/STDs, but are effective for prevention of unwanted pregnancy
- Women at high risk, ideally should use dual methods


Contraceptive use, US 1991-2001
Percent
70
60
50
40
30
20
10
0
46.2
20.8
3.2
54.4
17.4
4.3
57.9
18.2
5.5
1991
1995
2001
Year
Condoms
Pill
Dual methods

Hormonal Contraception and HIV Shedding in HIV+ women

- 101 HIV+ Kenyan women observed before and after start of oral contraception (OC) or depot Provera
- Measured cervical HIV shedding
- All hormonal contraception, shedding increased from 42% to 52%
- No change in genital tract viral load (i.e., intensity of shedding)
  - Wang et al AIDS 2004;18:205

IUDs and HIV

- Theoretical risk with increased menstrual blood loss, foreign body inflammatory reaction, endometrial disruption.

- Cross-sectional studies suggest increased risk of prevalent HIV infection. (Behavioral confounding?)

Reproduction, hormones and Cardiovascular Disease (CVD)

- Hormones and CVD
- Effects of Hormonal Contraceptives
- Postmenopausal Hormone Supplementation
- Mechanisms
- Observational studies
- Randomized trials

Cardiovascular Disease (CVD) and Gender

- Male CVD mortality exceeds female mortality during the reproductive ages.
- The sex differential in CVD diminishes after menopause.
- Therefore, female hormones may be protective against CVD?

Effects of Estrogen on the Vascular System

(Epstein FH *NEJM* 1999;340:1801)

- Local Acute Effects:
  - **Estrogen causes vasodilatation and inhibit endothelial injury**
  - mediated by estrogen receptors on endothelium
  - ↑ Nitric oxide (NO)
- Systemic Effects:
  - ↓ low density lipoprotein cholesterol (LDL)
  - ↑ high density lipoprotein cholesterol (HDL)
  - ↓ fibrinogen and ↓ anticoagulant proteins (increased clotting propensity)

Progestins Lipid Changes

- Progestins, particularly androgenic progestins such as norethisterone,
  - ↓ HDL and ↑ LDL.

- Second generation progestins may affect clotting mechanisms

Evidence of CVD and Oral Contraception
1960-1980

- Risk of CVD deaths in OC users. Cohort study (RCGP *Lancet* 1981;1:541)
- Relative Risks of CVD by age and smoking

	Smokers	Non-Smokers
– 25-34	3.4	1.6
– 35-44	4.2	3.3
– 45+	7.4	4.6

- Prescribing practice changed to exclude use by women >35 and discourage use by smokers or persons with CVD risk factors

Cardiovascular Complications

- Venous Thromboembolism (VTE)
  - Deep vein thrombosis of the legs
  - Pulmonary embolism
  - Due to disturbance of clotting mechanisms associated with estrogen dose and new generation of progestins.

Venous Thromoboembolism. Case-control study WHO *Lancet* 1995;346:1575-82

Venous Thrombosis Embolism (VTE) Diagnosis	Europe OR (CI)	Developing Countries OR (CI)
Definite	3.9 (2.7, 5.6)	4.8 (3.1, 7.3)
Probable	4.9 (2.8, 8.6)	3.1 (2.3, 4.3)

VTE and Type of Progestin in OCs

Jick Lancet 1995

Progestin	VTE Incidence/1000 py	RR (CI)
Levonorgestrel	16.3	1.0
Desogestrel 2nd generation	29.3	2.2 (1.1-4.4)
Gestodene 2nd generation	28.1	2.1 (1.0-4.4)

Blood Pressure

- Increased Blood Pressure
  - Increase in mean diastolic and systolic blood pressure
  - Increased incidence of hypertension
  - Associated with progestin dose

Arterial Thrombosis

- Myocardial infarction (MI) and ischemic heart disease (IHD)
- Other arterial thromboses
- Increased risk of thrombotic, embolic, and hemorrhagic stroke
- Due to changes in lipid metabolism, clotting mechanisms and blood pressure, associated with estrogen and progestin dose

Coronary Heart Disease (CHD) / Myocardial Infarction (MI)

- Oral contraceptives increase the risk of MI and of fatal MI

- Risk increased with age, smoking and other CVD risk factors.

- Risk associated with current use and not related to duration of use.

- No residual risk with past use. (i.e., no “carry-over” effect)

Net CVD Effects of Combined Oral Contraceptives

- The effects of oral contraceptives depend on the ratio of estrogen to progestin dose, and the type of progestin.

- Estrogen dose decreased relative to progestins since 1980s

Case control study of Cardiovascular Disease and OCs

WHO *Lancet* 1997;349:1202-09

Region & Type of Use	OR (CI) with OCs
Europe	
Users	5.01 (2.5, 9.9)
Past Users	1.2 (0.7, 2.3)
Developing Countries	
Users	4.78 (2.5, 9.1)
Past Users	1.48 (0.9, 2.5)

Case-Control Study Cardiovascular Disease

Lancet 1997;349:1202-09

Risk Factors	Europe OR (CI) with OCs	Developing Countries OR (CI) with OCs
< 35 yrs	7.3 (2.2, 24.0)	4.1 (1.3, 13.2)
35+	3.5 (1.5, 8.2)	5.2 (2.5, 11.0)
CVD risk factors	37.3 (15.2, 91.7)	20.8 (9.1, 47.2)
Smokers	41.3 (12.5, 136)	21.0 (4.9, 89)

Stroke

- Types of stroke:
  - Ischemic due to occlusion of arterial flow
  - Venous due to thrombosis of veins
  - Hemorrhagic
- Stroke 11 per 100,000 in women of reproductive age, 15-44 years).

Summary of OC and Stroke

- WHO studies suggest increased risks of ischemic and hemorrhagic stroke (WHO, *Lancet* 1996;348:498)

- US data suggest no significant increased risk (Pettiti, *NEJM* 1996;335:8-15)

- UK data suggest increased risk of fatal stroke.

- Risk of stroke with OC use higher with age, smoking, hypertension and in some studies, estrogen dose.

WHO Case-Control Study Stroke

Lancet 1996;348:505-10

	Europe OR (CI)	Developing Countries OR (CI)
Ischaemic	2.7 (1.3, 5.5)	2.9 (2.1, 4.0)
Hemorrhagic	1.4 (0.8, 2.3)	1.8 (1.3, 2.3)

Summary Oral Contraceptive and CVD

- Consistent evidence of increased risks of CVD with oral contraceptives
- Stroke effects variable
- No randomized trials

Postmenopausal Hormone Supplements and Cardiovascular Disease (CVD)

Trials trump observational studies

Postmenopausal Estrogen and Cardiovascular Disease (CVD)

- CVD is the major cause of death among postmenopausal women (aged 50-75)
- incidence of CVD is 700/100,000; case-fatality ratio of 0.60)

Hormonal Supplements and CVD

- **Observational studies** (case-control and cohort) suggest that use of postmenopausal estrogens reduce the risk of CVD and of death from CVD (RR ~ 0.5).
  - Risks lower with higher dose estrogens.
  - Risks reduced with current and recent estrogen use (< 3 years since last use), but not longer-term (no “carry-over” effect).
  - Addition of progestin does not appear to attenuate the estrogen effects.

- Stroke and deep vein thrombosis risks may be increased.

Problems of Interpretation in Observational Studies

- **Self-selection** (i.e. healthier women, higher SES or educational status adopt supplements).

- **Physician prescribing habits** (avoid high risk patients).

- **Duration** of observation and duration of estrogen use is often limited

- **Age:** Women often relatively young (<60 years).

Clinical Trials of HRT

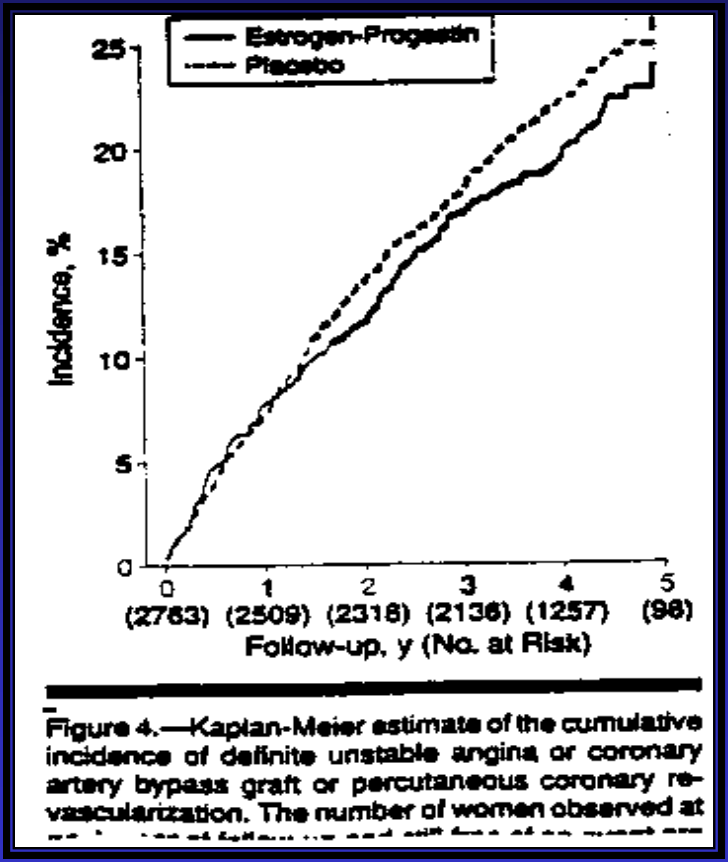


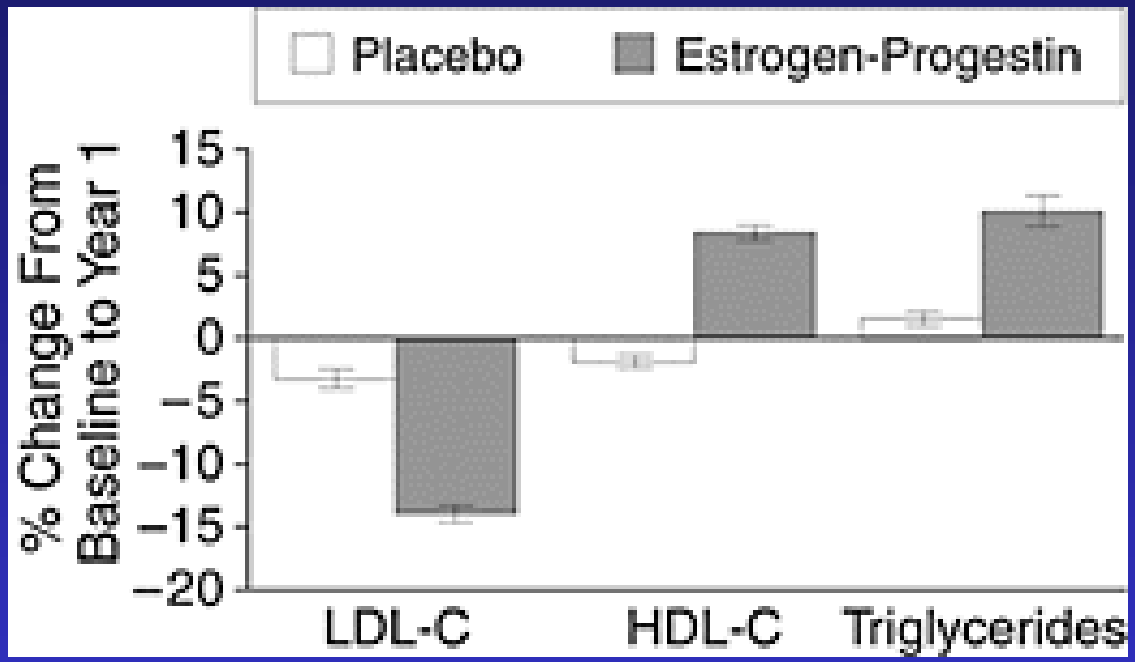
Figure 4.—Kaplan-Meier estimate of the cumulative incidence of definite unstable angina or coronary artery bypass graft or percutaneous coronary revascularization. The number of women observed at

Clinical trial of women with established CVD

- Estrogen/medroxyprogesterone N=1380 vs Placebo N=1383
- Follow up 4.1 years
- No benefit observed

Hulley S. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-613.

Effects on Lipids



Mean change in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels during the first year of the study, expressed as percent change ± SEM.

Hulley S. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605-613.

Randomized trial (HERS Study)

Hulley *JAMA* 1998;280:605

- **Venous Thromoboembolism**
  - Deep vein thrombosis: RR = 3.2 (1.4-7.0)
  - Pulmonary Embolism: RR = 2.8 (0.9-8.8)
  - Any thromboembolism: RR = 2.9 (1.5-5.6)
- **Stroke/Transient Ischemia**
  - RR = 1.13 (0.85-1.48)

Estrogen replacement and progression of coronary atherosclerosis

- RCT in women with established CVD
- Neither estrogen with or without progestin affected progression atherosclerosis
  - Herrington NEJM 2000;343:522-9.

Estrogen replacement after ischaemic stroke

- RCT in women with ischaemic stroke estradiol vs placebo

- Recurrent stroke RR = 1.1 (0.8-1.4)
- Fatal recurrent stroke RR = 2.9 (0.9-9.0)

  – Viscoli *NEJM* 2001;345:1243.

Women's Health Initiative (WHIS) Study (*JAMA* 2002;288:321)

- 16,608 **healthy women** **50-75**
- Randomized to conjugated estrogens + medroxyprogesterone acetate and placebo
- Follow up 5.2 years
- Trial stopped due to increased risk of breast cancer and lack of net benefit

WHIS Study CVD Results

Outcome	RR (95%CI)
CHD	1.29 (1.02-1.63)
Stroke	1.41 (1.07-1.85)
Pulmonary embolism	2.13 (1.39-3.25)
All CVD	1.22 (1.09-1.36)

Excess events per 10000py: CHD = 7, strokes = 8, PE= 8

Summary of HRT and CVD

- Observational Studies of women with long-term follow-up; suggest reduced risk, but inadequate control for confounding

- Metabolic studies, including randomized trials show estrogen reduced LDL (due to liver catabolism) and increased HDL.

- All clinical trials of supplementation in women shows no benefits and some show increased risk

When (if ever) should HRT be used?

- Short-term relief of menopausal syndrome (good efficacy)

- Prevention of osteoporosis

No need to use HRT other effective treatments:

  - Raloxifene (estrogen antagonist in breast) but agonist in bones. Vertebral fracture RR = 0.70,
  - Alendronate (biposphonate) vertebral fracture RR = 0.53,
    - Delmas *Lancet* 2002;359:2018

Tubal Ligation

Tubal ligation is the most common method of family planning in U.S. (> 10 million) and worldwide (> 100 million)

- Mortality 1.5/100,000 procedures (U.S., and U.K.), 12-21/100,000 in less developed countries

- Reversal of sterilization requested by 1-3%. Successful reversal varies with method of occlusion (approximately 25 - 70%).

Tubal Ligation and pregnancy.

Cumulative ten year pregnancy rates 1.9/100 women years.

Pregnancy increased in younger women

Method of occlusion. Lowest with unipolar or postpartum salpingectomy (~ 0.8/100 wy), highest with bipolar or clip (~ 2.5-3.7/100 wy).

- 33% of failures ectopic. Rates of ectopic pregnancy are 0.73/100 women over 10 years

Induced Abortion

- Measuring Rates of Abortion
  - Abortion rate per 1,000 women
  - Abortion ratio per 1,000 births
  - Total abortion rate: Average number of abortions per women during the childbearing years
- Measurement difficult due to underreporting, particularly of illegal procedures
- 26-31 million legal and 10-22 million illegal abortions (e.g. 36-53 million total)

Induced Abortion, cont.

- Rates vary by country.
  - Historic reasons (e.g., lack of contraception in ex-Communist block)
  - Cultural acceptance (religion?)
  - Contraception

- Legal status
- (% of women living in different countries):
  - 40% abortion on demand,
  - 23% social grounds,
  - 12% broad medical grounds,
  - 25% life-endangerment.

Abortion Rates/1000 women 15-49 in Developed Countries

Former USSR	110/1000
Hungary	40/1000
USA	23/1000
Sweden	20/1000
UK	17/1000
Holland	7/1000

Methods of Induced Abortion Vary with length of gestation

Surgical

- Menstrual regulation < 3 weeks
- Vacuum curettage < 13 weeks
- Dilatation and curettage (D & C) < 13 weeks
- Dilatation & Evacuation (D & E) 13 - 20 weeks
- Hysterotomy / hysterectomy > 20 weeks
- Dilatation and Extraction > 20 weeks
- (Partial birth abortion)

Medical Induced Abortion

- Antiprogestins (RU486) and prostaglandin (<7 weeks, can be up to 20 weeks)

- Instillation < 20 weeks (saline, urea)

Clinical Trials of Medical Induced Abortion

	RU 486, Oral Misoprostol < 49 days (rates)[1]	RU 486, Oral Misoprostol < 63 days (rates)[2]	Methodtexate and Misoprostol < 56 days (rates)[3]
N	505	133	31
Complete Abortion	96.9%	95.0%	90.3%
Failures			
Persistent pregnancy	0.8%	1.0%	6.5%
Incomplete explusion	1.8%	4.0%	3.2%
Excess bleeding	0.4%		

1 Women < 49 days pregnant. RU 486 600 mg orally followed in 48 hours by Misoprostol 400 ug orally (Peyron. NEJM 1993;328:1509)

2 Women < 63 days pregnant. RU 486 600 mg, viginal misprostol 800 ug orally (El Refaey. NEJM 1995;332:963

3 Women < 56 days pregnant. Methotrexate injection followed 3 days later by 800 ug of misoprostol vaginal suppository (Creinin 1994;272:1190)

Mortality from Induced Abortions

Mortality

- Abortion related deaths approximately 60-120,000 per year (10 to 20% of maternal deaths)

Measurement

- Abortion mortality ratio per 100,000 live births and abortions
- Abortion mortality rate per 100,000 women between the ages of 15 - 45 years
- Abortion case-fatality ratio per 100,000 procedures

Mortality from Induced Abortions

- **Mortality Rates vary by:**
  - Legal status (increased if illegal)
  - Type of procedure
  - Length of gestation
  - Facilities and training of personnel (“unsafe abortion” WHO classification based on anesthesia, back up emergency care, skill and experience of personnel)
  - Estimate 20,000,000 “unsafe abortions”/year, approximately 78,000 deaths

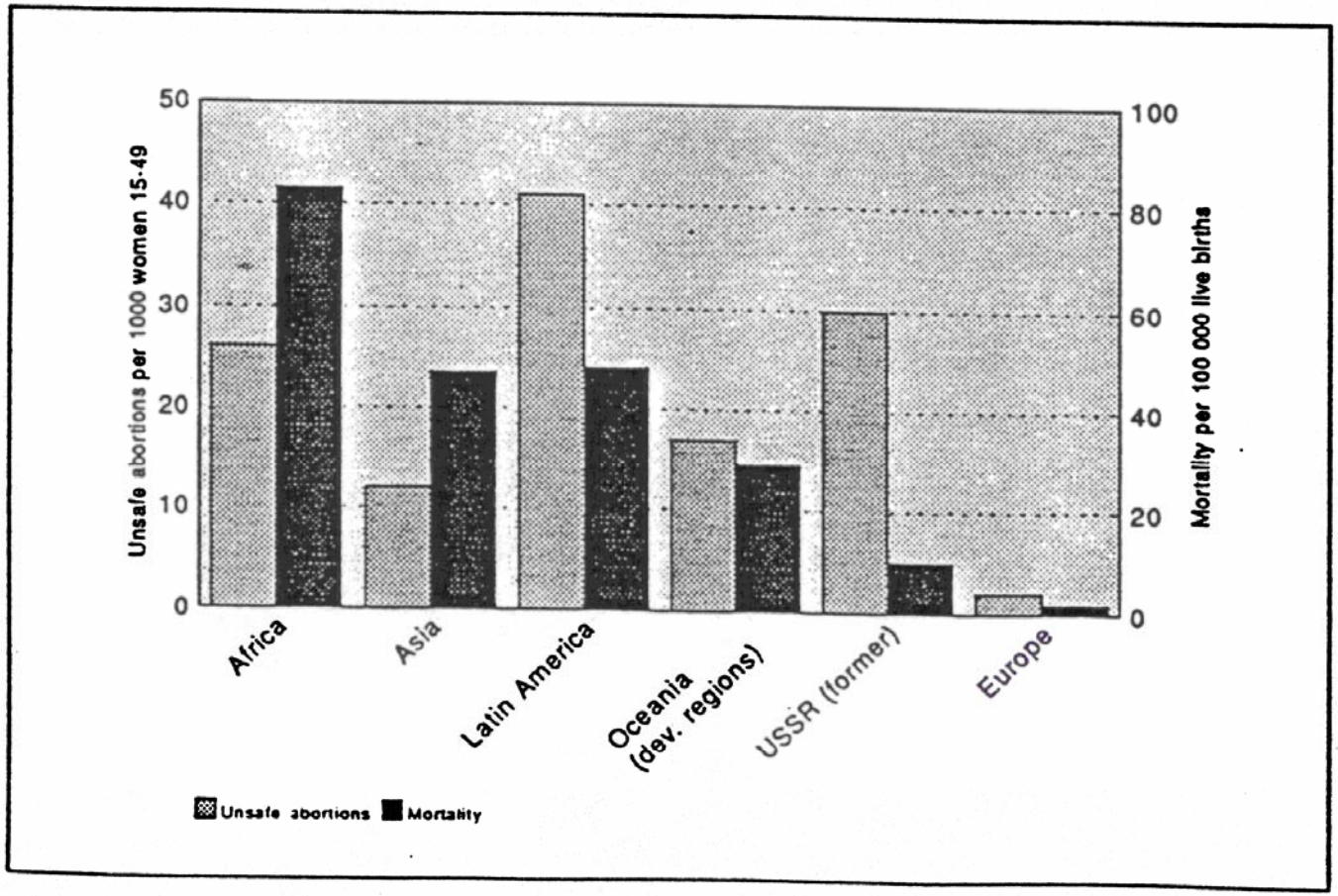
US. Abortion case-fatality ratios

Procedure	Rate Per 100,000	Relative Risk
Curettage	0.5	1.0
Evacuation	3.7	6.8
Instillation	7.1	13.0
Hysterectomy/hysterotomy	51.6	95.0

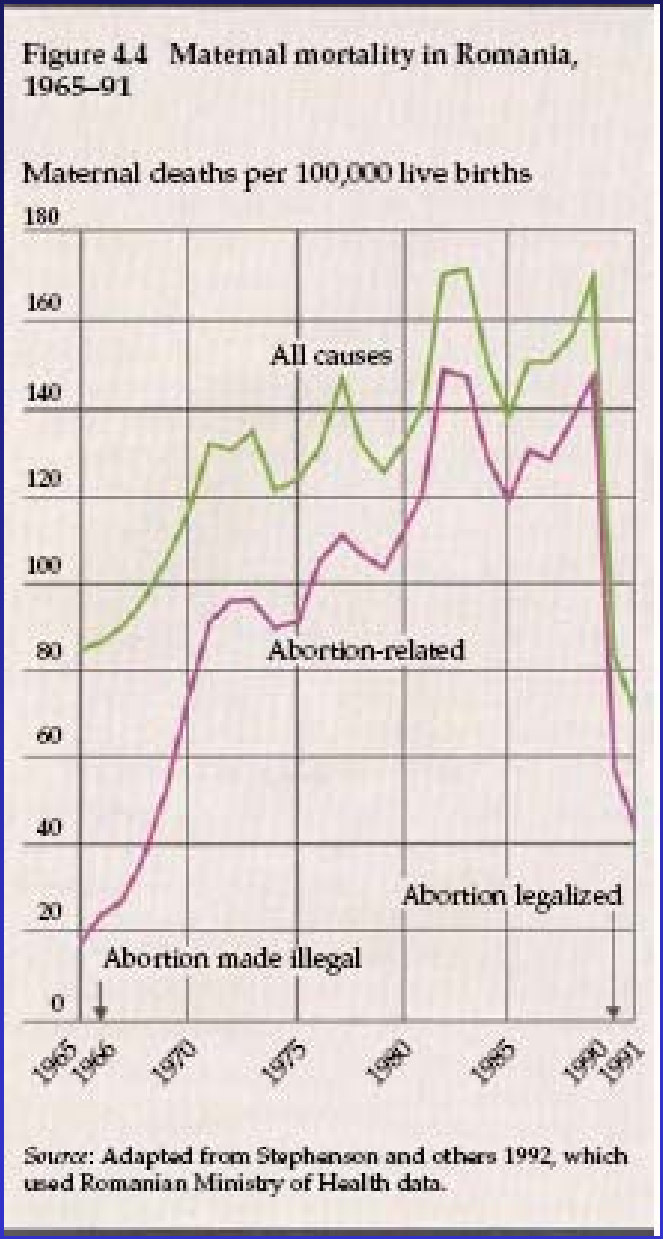
Data Source: Lawson HW, et al. Abortion mortality, United States, 1972 through 1987. Am J Obstet Gynecol 1994;171:1365-72

Unsafe abortion incidence, worldwide

Fig. 4 Incidence of and mortality from unsafe abortion



Source: World Health Organization. *Abortion: A Tabulation of Available Data on the Frequency and Mortality of Unsafe Abortion.* 2nd edition, WHO/FHE/MSM/93.13. Maternal Health and Safe Motherhood Programme. Geneva: WHO Division of Family Health, 1994.



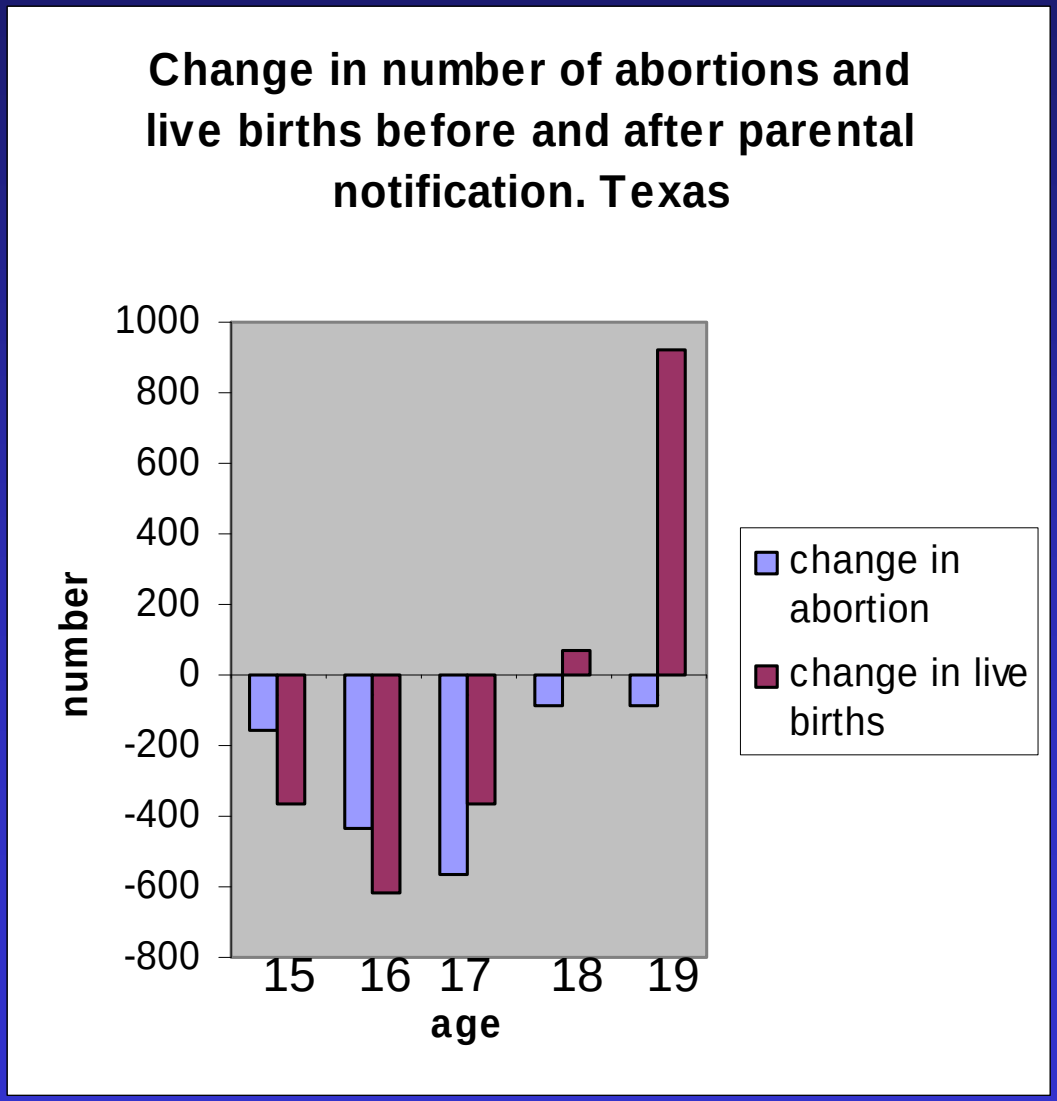
Maternal mortality in legal status of abortion in Romania

"We cannot ban abortion, we can only ban safe Abortion"

Parental notification law and abortions in Texas (Joyce *et al NEJM* 2006;354:1031)

- Compared abortions and births per 1000 population in teens before (1998-9) and after (2000-02) parental notification
- Assessed ratio of changes in rates 15-17 to changes in 18 year olds (not affected by notification)
- Conclusion: decline in abortion ages 15-17, and increased second trimester abortions in minors 17.50-17.74 years (i.e., caught be change in law)

If abortions and pregnancies decreased in 15-17, is this Due to change in law or a decline in adolescent pregnancy? The denominator should be pregnancies



Risk-Benefit Assessment of Fertility Control

- Compare mortality associated with fertility (i.e., maternal mortality and mortality associated with fertility control (contraception and abortion).

- Data from North America and Europe. Extrapolation to developing countries speculative.

Risk-Benefit Assessment of Fertility Control, cont.

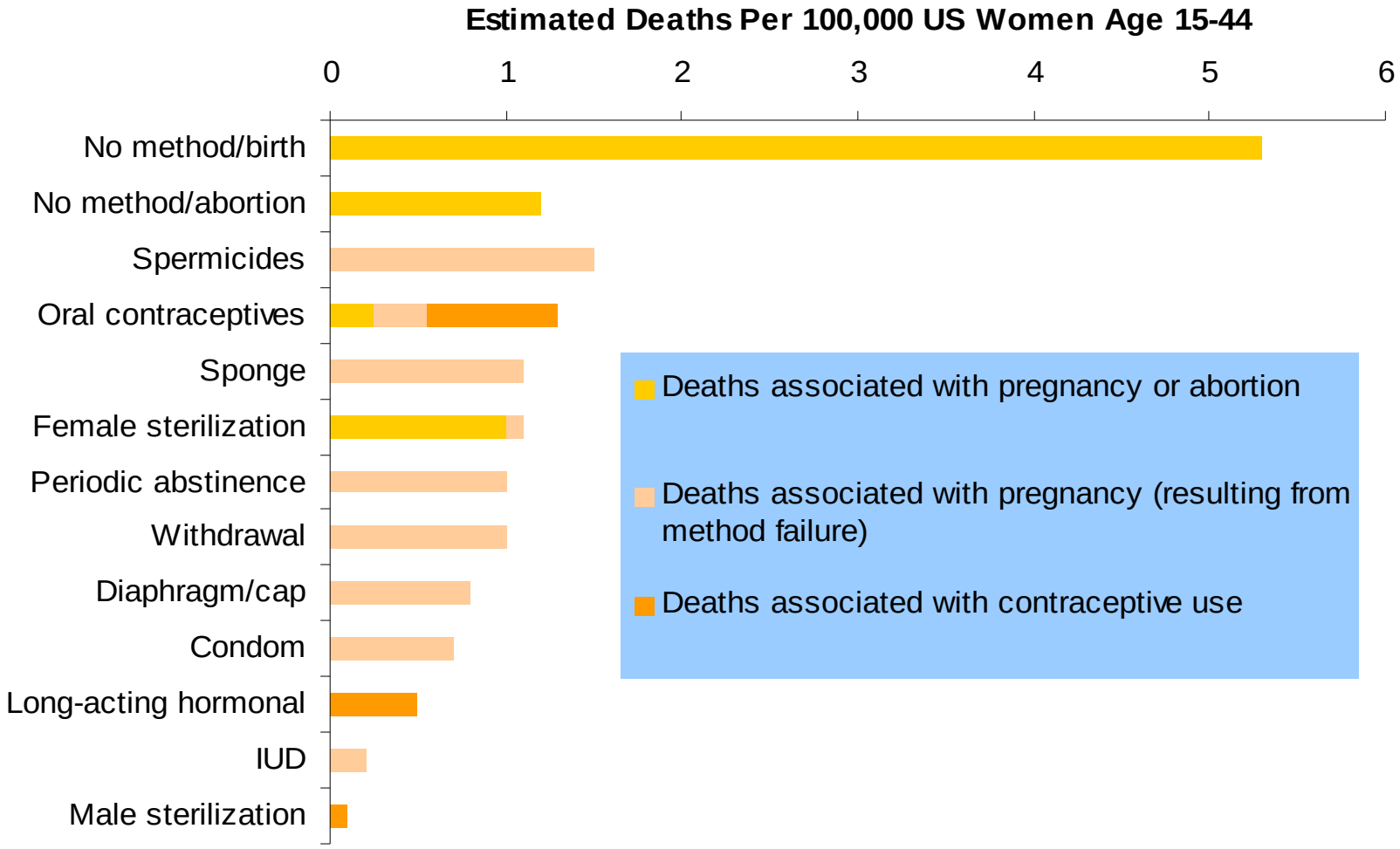
- Mortality associated with fertility control:
  - Deaths due to complications of birth control methods.
  - Deaths due to complications of accidental pregnancies from method failures (including induced abortion)
  - Deaths due to induced abortion at varying stages of gestation

ESTIMATES of MATERNAL MORTALITY
1990

Region	Maternal Mortality Ratio per 100,000 Live Births	Estimated Number of Maternal Deaths	Estimated Lifetime Risk of Maternal Death %
World	430	585,000	
Developed Countries	27	4,000	0.05%
Developing Countries	480	582,000	2.1%
Africa	870	235,000	
South Asia	560	227,000	
East Asia	95	24,000	0.2%
Latin America	190	23,000	
Eastern Europe	62	2,500	
North America	11	500	0.03%

Revised 1990 Estimates of maternal Mortality, A New Approach by WHO and UNICEF, 1996.

Comparison of mortality due to contraception & abortion versus no birth control



Adapted From Harlap S, Kost K and Forrest JD, *Preventing Pregnancy, Protecting Health: A New Look at Birth Control Choices in the United States*, The Alan Guttmacher Institute, New York, 1991

Lifetime Risk of Maternal Deaths

Region	Lifetime Risk/100,000 births
More developed countries	48
Less developed countries	1,800

Based on risk per pregnancy and total number of pregnancies per woman (UNICEF)

Safety of Contraception Summary

- All methods of contraception are safer than child bearing
- Risk/benefit ratio is greatest where maternal mortality is highest or abortion is illegal or unsafe