# Hormone und Schwangerschaft als Thromboserisikofaktoren, Therapie der schwangerschaftsassoziierten Thrombose

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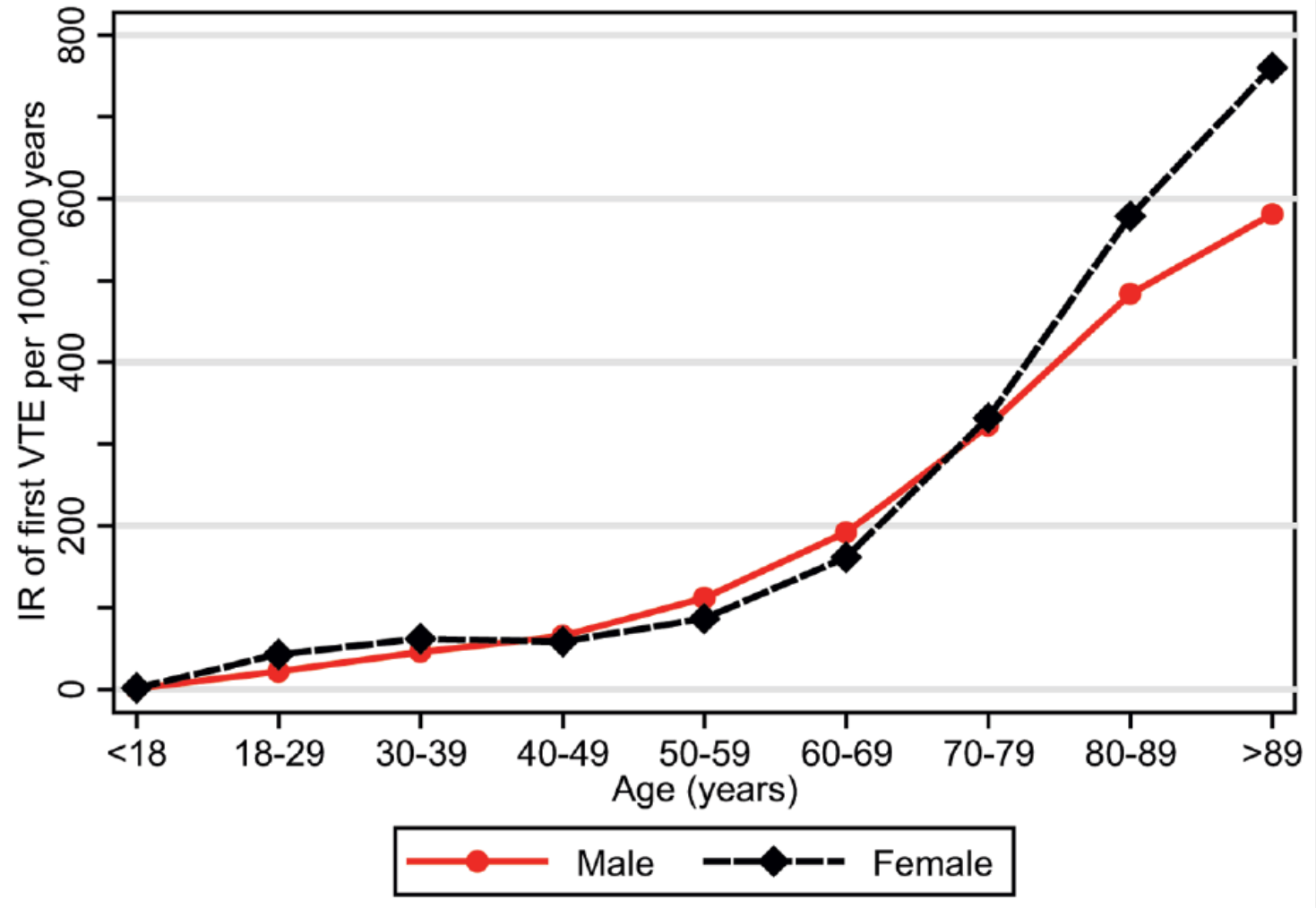
# Incidence of first VTE




Martinez, Thromb Haemost 2014

# Frau, 16 Jahre

- Bisher gesund, sehr sportlich, BMI 19 $kg/m^2$
- Mutter Pulmonalembolie mit 46 Jahren
- Frage hormonelle Verhütung

# Hormonal contraceptives

| Hormonal contraceptive method | VTE risk (RR, 95% CI), compared with non-users |
|---|---|
| Does not increase VTE risk | |
| Levonorgestrel-releasing intrauterine device | 0.6 (0.2-1.5) |
| Low-dose progestin pill | 0.9 (0.6-1.5) |
| Uncertain VTE risk | |
| Etongestrel birth control implant | 1.4 (0.6-3.4) |
| Increases VTE risk | |
| Combined oral contraceptives | |
| Ethinylestradiol/levonorgestrel | 2.9 (2.2-3.8) |
| Ethinylestradiol/desogestrel | 6.6 (5.6-7.8) |
| Ethinylestradiol/drospirenone | 6.4 (5.4-7.5) |
| Progestin-only injections (DMPA) | 2.7 (1.3-5.5) |
| High dose progestin pills[a] | 5.9 (1.2–30.1) |

Bistervels, J Thromb Haemost 2019

| Hormone preparations | Progesterone | Estrogen (mcg) (multiple numbers indicate multiphasic/extended formulations) | Effectiveness* | VTE risk |
|---|---|---|---|---|
| Progestin only pills | Norethindrone | None | 93.0% | No increased risk |
| | Drospirenone | None | | |
| LNG IUD | Levonorgestrel | None | 99.7% | No increased risk |
| Implant† | Etonogestrel | None | 99.9% | No increased risk |
| Injectable ("Depo") | Medroxyprogesterone | None | 96.0% | OR 2.2 (1.3-4.0)‡ |
| Vaginal ring | Segesterone | Ethinyl estradiol (13 mcg/day) | 93.0% | 6.5-fold (4.7-8.9) increased risk compared to non hormone users (mixed data compared to oral preparations)§ |
| | Etonogestrel | Ethinyl estradiol (15 mcg/day) | | |
| Transdermal patch¶ | Levonorgestrel | Ethinyl estradiol (30 mcg/day) | 93.0% | 7.9-fold (3.5-17.7) increased risk compared to non hormone users (mixed data compared to oral preparations)§ |
| | Norelgestromin | Ethinyl estradiol (30 mcg/day) | | |
| 4th Generation Progesterone COC | Dienogest | Estradiol valerate (3,2,2,1 mg) | 93.0% | Similar/improved risk as 2nd generation progesterone COC |
| 2nd Generation Progesterone COC | Levonorgestrel | Ethinyl estradiol (20, 10) | 93.0% | OR 2.38 (2.18-2.59)** |
| | | Ethinyl estradiol (20) | | |
| | | Ethinyl estadiol (30) | | |
| | | Ethinyl estradiol (20, 25, 30,10) | | |
| | | Ethinyl estradiol (30, 10) | | |
| 1st Generation Progesterone COC | Norethindrone acetate | Ethinyl estradiol (10,10) | 93.0% | No data comparing 1st and 2nd generation, recommend lowest dose of estrogen for lowest risk of VTE |
| | | Ethinyl estradiol (20) | | |
| | | Ethinyl estradiol (30) | | |
| | | Ethinyl estradiol (20,30,35) | | |
| | Norethisterone†† | - | | |
| | Norethindrone | Ethinyl estradiol (35) | | |
| | Ethynodiol diacetate | Ethinyl estradiol (35) | | |
| | | Ethinyl estradiol (50)‡‡ | | |
| | Norgestrel | Ethinyl estradiol (30) | | |
| | | Ethinyl estradiol (50)‡‡ | | |
| | Medroxyprogesterone†† | - | | |
| 3rd Generation Progesterone COC | Norgestimate | Ethinyl estradiol (35) | 93.0% | OR 2.53 (2.17-2.96)** |
| | Desogestrel | Ethinyl estradiol (20,0,10) | 93.0% | OR 3.64 (3.00-4.43)** |
| | | Ethinyl estadiol (30) | | |
| | Gestodene†† | - | | OR 4.28 (3.66-5.01)** |
| 4th Generation Progesterone COC | Drospirenone | Ethinyl estradiol (20) | 93.0% | Similar risk as 3rd generation progesterone COC |
| | | Ethinyl estradiol (30) | | |
| | | Estetrol (14.2 mg) | | |


LaVasseur, RTPH 2022

# Combined oral contraceptives - absolute VTE risk

| | Risk (95 %CI) per 100 pill years | |
|---|---|---|
| **Thrombophilia** | **Carrier** | **Non-carrier** |
| FV Leiden or FII mutation | 0.49 (0.18–1.07) – 2.0 (0.3–7.2) | 0.0 (0–5.5) – 0.19 (0.07–0.41) |
| FV Leiden/FII mutation<br>Double hetero or homo | 0.86 (0.10–3.11) | 0.19 (0.07–0.41) |
| Deficiency of antithrombin, protein C, or protein S | 4.3 (1.4–9.7) – 4.62 (2.5–7.9) | 0.48 (0.1–1.4) – 0.7 (0.0–3.7) |

Simioni, Thromb Haemost 1999; Vlijmen, Arch Int Med 2007; Vlijmen, Blood 2011

# Frau, 16 Jahre

- Bisher gesund, sehr sportlich, BMI 19 kg/m$^2$
- Mutter PE mit 46 J
- Frage hormonelle Verhütung

- KEIN Thrombophiliescreening
- Hormonelle Kontrazeptiva möglich, Thromboserisiko unterschiedlich
- IUD-Mirena® << orale Gestagene << kombinierte Präparate 2.Gen.

# Hormone contraceptives and arterial thrombosis

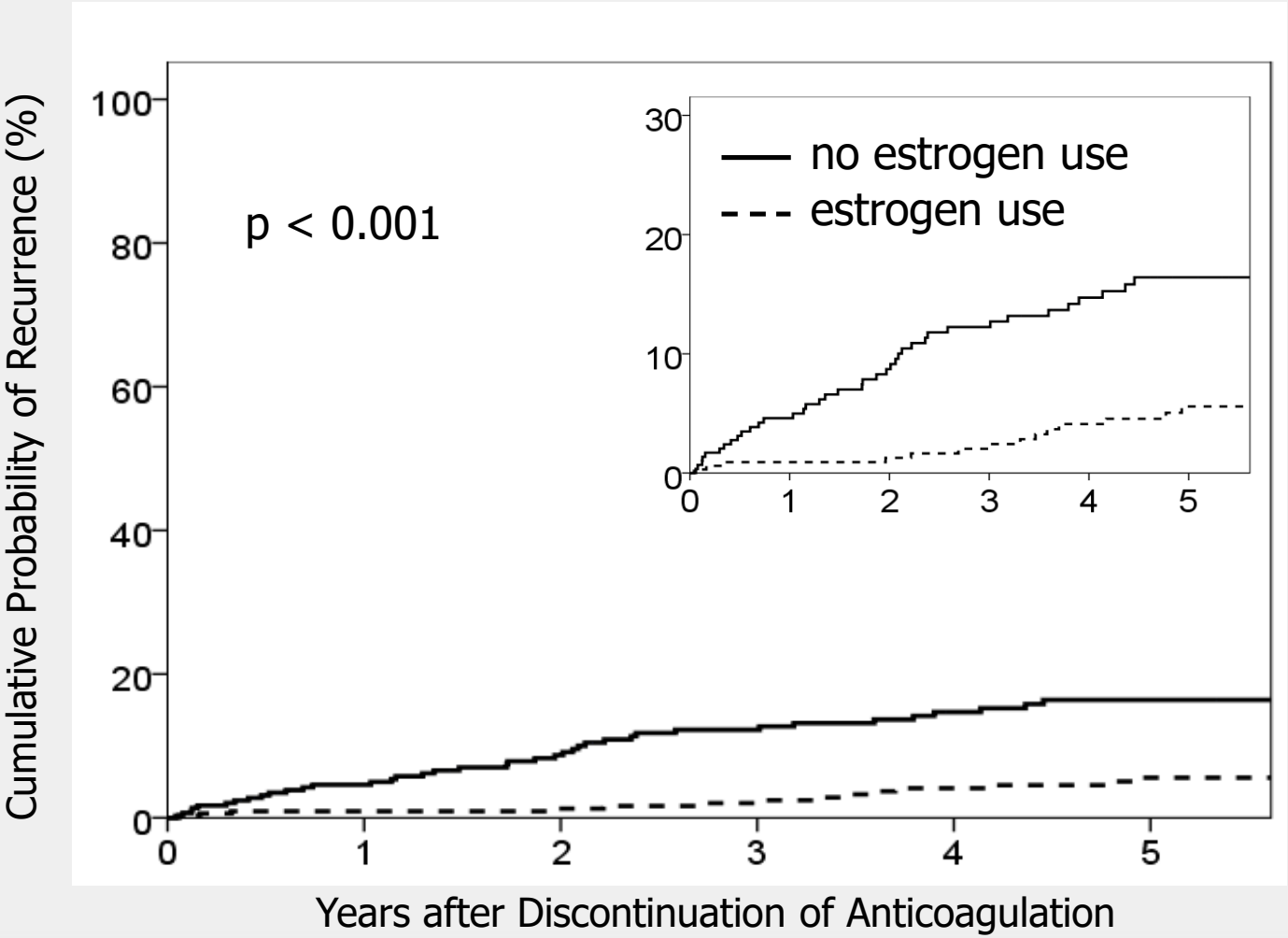
- 1.5 – 2-fold increased RR of thrombotic stroke and MI among users of combined OC (ethinyl estradiol 30-40 µg)
- ~3-fold increased RR with vaginal ring or patch
- Desogestrel/ethinyl estradiol 20 µg for 1 year
  - arterial thrombosis: 2.0/10 000 women
  - venous thrombosis: 6.8/10 000 women

Lidegaard, N Engl J Med 2012

# Frau, 26 Jahre

- Akute tiefe Beinvenenthrombose, sekundär während Einnahme hormoneller Kontrazeptiva
- Frage Dauer Antikoagulation/Verhütung?

# Estrogen use

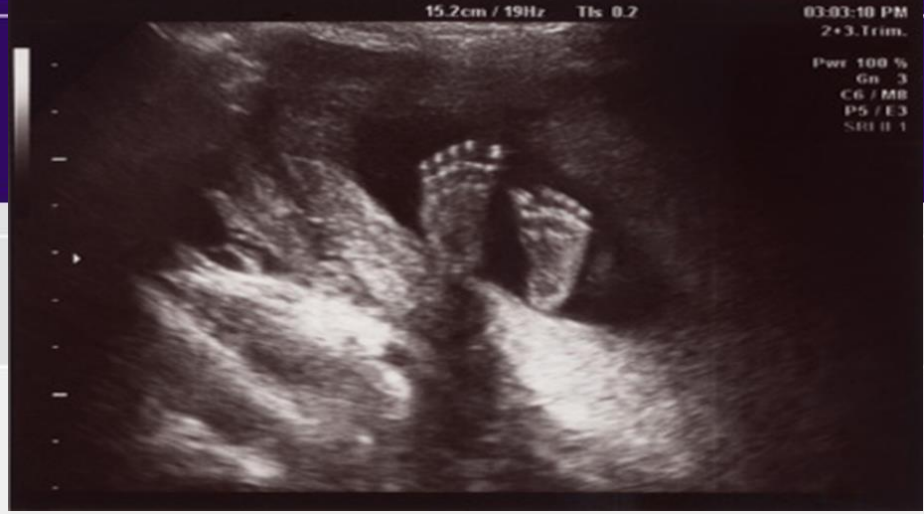



Eischer, J Thromb Haemost 2014

# Recommendations to a woman with VTE

- After a first VTE provoked by hormones or pregnancy stop anticoagulation after 3 months.
- Fully anticoagulated: safe use of combined hormonal contraceptives.
- Anticoagulation stopped: no combined hormonal contraception or depot medroxyprogesteronacetate.
- IUD-Mirena®, etonogestrel (progestin) subdermal implant, and the copper IUD should be considered first-line contraceptive options.

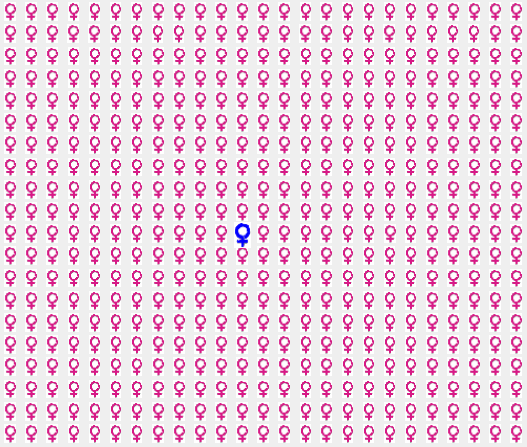
# Frau, 30 Jahre




- 26. SSW, 1. SS
- Schmerzen und Schwellung im linken Bein
- Kompressionsultraschall → Thrombose V. poplitea

# Pregnancy associated VTE

- VTE rates (/1000 pt yrs)
  - Antepartum 1.0
  - Postpartum 5.0
  - Not pregnant 0.5
- Increased risk throughout pregnancy
- Pulmonary embolism major cause of maternal death (fatal PE 2-3/100 000 births)
- Risk after cesarean section >> vaginal delivery
- Isolated iliac vein thrombosis relatively frequent
- Risk persists until 12 wks postpartum (max first 6 wks)



1 of 500 women has a VTE during pregnancy or after delivery

# Which anticoagulants can safely be used during pregnancy?

| Anticoagulant | Acceptability in Pregnancy | Comments |
|---|---|---|
| **LMWH** | **Yes** | • Does not cross the placenta<br>• LMWH preferred over UFH due to maternal safety profile (likely lower risk of HIT, reduced bone mineral density) |
| **UFH** | **Yes** | • Does not cross the placenta |
| **Danaparoid** | **Yes** | • Does not cross the placenta |
| **Fondaparinux** | **No** | • Reported to cross placenta in small amounts<br>• Clinical experience with fondaparinux very limited |
| **Vitamin K antagonist** | **No** | • Crosses the placenta<br>• Potential for teratogenicity, pregnancy loss, fetal bleeding, neurodevelopmental deficits |
| **Direct oral anticoagulants** | **No** | • Likely cross the placenta<br>• Reproductive effects in humans are unknown |

Modified after ASH guidelines, Bates et al, Blood advances 2018; Middeldorp, Blood 2020

# LMWH once or twice daily?

- Very limited data in pregnant women
- Low overall incidence of VTE or bleeding (<1%), no difference between the two dosing schedules (observational studies)

**Guideline:** For pregnant women with acute VTE treated with LMWH, the panel suggests **either once-daily or twice-daily dosing** regimens.

ASH guidelines, Bates et al, Blood advances 2018

# LMWH anti-Xa monitoring?

- Very limited data
- No established therapeutic range for LMWH in pregnancy
- Absence of evidence of benefit
- Drawbacks of testing: frequent blood tests, clinic visits, costs

**Guideline:** For pregnant women with acute VTE treated with therapeutic LMWH, the panel suggests **against routine monitoring of anti-Xa levels** to guide dosing.

ASH guidelines, Bates et al, Blood advances 2018

# Acute VTE and pregnancy – how I do it

- LMWH at therapeutic dose based on actual body weight
- Once daily dosing
  - Considering feasibility and acceptability of daily injections*
  - Skin reactions (20-40% of women type IV hypersensitivity)*
- No anti-Xa monitoring except for extreme body weights/severe renal function impairment/antithrombin deficiency
- Duration:
  - At least 3 months
  - Throughout pregnancy and until 6 weeks after delivery (8 after caesarean section)

*Bank, Thromb Res 2004, Schindewolf J Allergy Clin Immunol 2013, Schultinge Neth J Med 2013

# Management of anticoagulation around the time of delivery

- Mode of delivery based on obstetric considerations/patient preference
- Caesarean section:
  - Stop LMWH 24 hours before surgery
- Vaginal delivery:
  - Scheduled (induced) delivery, discontinue LMWH 24 hours before
- Respect neuraxial anaesthesia timelines
- Restart LMWH after 6-8 hours at prophylactic dose
- Full therapeutic dose not before 12-24 hours

Modified after ASH guidelines, Bates et al, Blood advances 2018; Middeldorp, Blood 2020

# Frau, 34 Jahre, 4 Jahre später

# Risk factors for recurrent VTE in pregnancy

- Personal history of VTE (up to 10% without prophylaxis)
- Thrombophilia
- Strong family history
- BMI ≥ 30 kg/$m^2$

Brill-Edwards, New Engl J Med 2000; Pabinger, J Thromb Haemost 2005; De Stefano, Br J Haematol 2006; de Moreuil, JTH 2022

# Prophylaxis in pregnant women with prior VTE

| Prior VTE History | Antepartum Prophylaxis | Postpartum Prophylaxis |
|---|---|---|
| **Unprovoked VTE** | Yes | Yes |
| **Provoked VTE, Hormonal risk factor** | Yes | Yes |
| **Provoked VTE, Non-hormonal risk factor** | No* | Yes |

*as long as no current additional risk factors for VTE

ASH guidelines, Bates et al, Blood advances 2018

Position paper GTH, Hart et al, Haemostaseologie 2020

# Prophylaxis in pregnant women without prior VTE

| Hereditary Thrombophilia | Family History of VTE | Antepartum Prophylaxis | Postpartum Prophylaxis |
|---|---|---|---|
| Heterozygous PGM ***or*** Heterozygous factor V Leiden | (+) | No | No/consider* |
| | (-) | No | No/consider* |
| Protein S deficiency ***or*** Protein C deficiency | (+) | No/Yes | Yes |
| | (-) | No/Yes | No/Yes |
| Antithrombin deficiency | (+) | Yes | Yes |
| | (-) | No/Yes | No/Yes |

* in case of additional risk factors for VTE

ASH guidelines, Bates et al, Blood advances 2018

Position paper GTH, Hart et al, Haemostaseologie 2020

# Prophylaxis in pregnant women without prior VTE

| Hereditary Thrombophilia | Family History of VTE | Antepartum Prophylaxis | Postpartum Prophylaxis |
|---|---|---|---|
| Homozygous PGM | (+) | Yes* | Yes |
| | (-) | No/Yes | Yes |
| Homozygous factor V Leiden | (+) | Yes | Yes |
| | (-) | Yes | Yes |
| Combined thrombophilia | (+) | Yes | Yes |
| | (-) | Yes | Yes |

*in the absence of family studies not a formal recommendation

ASH guidelines, Bates et al, Blood advances 2018

Position paper GTH, Hart et al, Haemostaseologie 2020

# Prevention of VTE in pregnancy – how I do it

No long-term anticoagulation prior to pregnancy

- History of VTE:
  - LMWH prophylactic dose antepartum until 6-8 weeks postpartum
  - Homozygous/compound heterozygous FVL/PGM
    LMWH intermediate dose antepartum until 6-8 weeks postpartum
- No history of VTE, thrombophilia:
  - Heterozygous FVL/PGM → LMWH prophylactic dose postpartum for 2 weeks in case of additional risk factors (e.g. caesarean section)
  - Major thrombophilia → LMWH prophylactic dose antepartum until 6 weeks postpartum

# Prevention of VTE in pregnancy – how I do it

## Long-term anticoagulation prior to pregnancy

- Preconception counseling about risks and options
- Counsel women to closely monitor their cycles
- Perform pregnancy test as early as possible (<< 6$^{th}$ week)
- Stop oral anticoagulant when pregnancy test is positive
- Switch to LMWH at once daily therapeutic dose
- Stop LMWH 24 hours before caesarean section or induced vaginal delivery

# VTE in pregnancy – how I do it

## Antithrombin deficiency

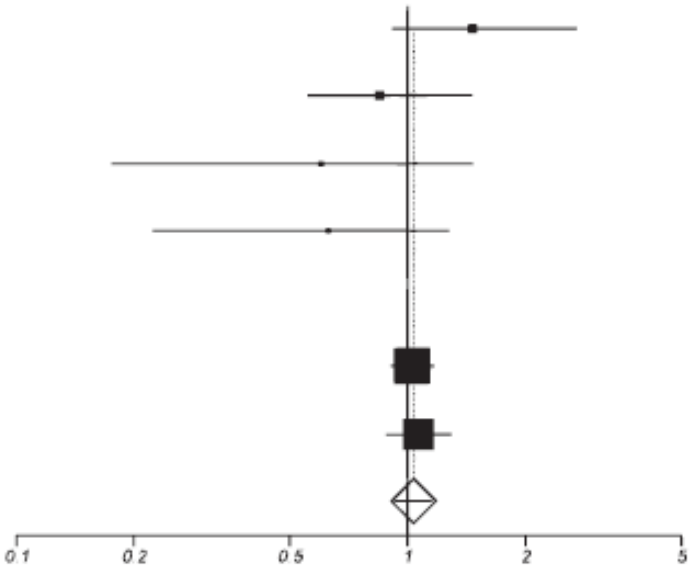
- Individualized approach for treatment and prevention
- Refer to specialized centre, multidisciplinary management
- Preconception counseling about risks and options
- LMWH dosing based on personal and family history of VTE, type of deficiency
- Consider antithrombin concentrate

# Frau, 41 Jahre

- 2 Schwangerschaften, 1 Kind, 1 Fehlgeburt in 8. SSW

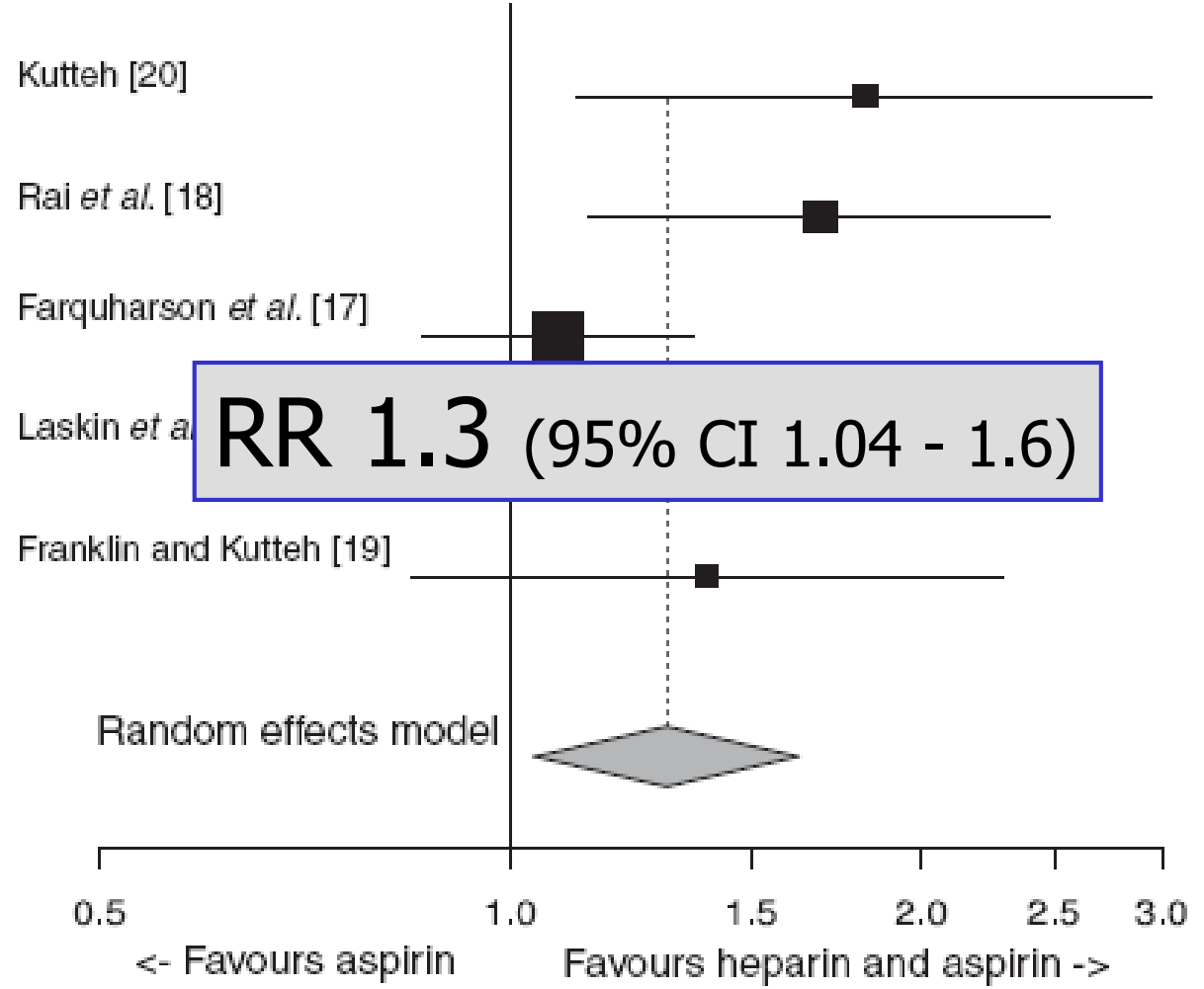
# Women with thrombophilia

| | Event/Total (n/N) | | Relative Risk (95% CI) |
|---|---|---|---|
| | LMWH | No LMWH | |
| HepASA | 6/9 | 10/10 | 1.47 (0.91, 2.71) |
| ALIFE | 9/13 | 20/34 | 0.85 (0.55, 1.47) |
| SPIN | 5/6 | 2/4 | 0.60 (0.17, 1.47) |
| HABENOX | 13/19 | 3/7 | 0.63 (0.22, 1.28) |
| HAPPY | 12/12 | 11/11 | (indeterminate)* |
| TIPPS | 60/69 | 66/74 | 1.03 (0.90, 1.17) |
| ETHIG II | 27/30 | 24/25 | 1.07 (0.88, 1.30) |
| **Combined** | | | **1.04 (0.93, 1.16)** |




Skeith, Blood 2016

# Live births: meta-analysis




Mak, Rheumatology 2010

# Frau, 41 Jahre

- 2 Schwangerschaften, 1 Kind, 1 Fehlgeburt in 8. SSW

→ KEIN Thrombophiliescreening
→ Diagnostik APLA überlegen
→ KEIN niedermolekulares Heparin

# Tender loving care

195 couples with recurrent (≥3) miscarriage

85 without explanation

- Dedicated antenatal care, psychological support: live birth rate 86%
- No specific antenatal care: live birth rate 33%

Stray-Pedersen, Am J Obstet Gynecol 1984