ESHRE Campus 2017
Effects of ART and endometriosis on pregnancy outcome

THE UNIVERSITY OF TOKYO

Endometriosis and miscarriage risk

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disclosure

I have nothing to disclose on this presentation.

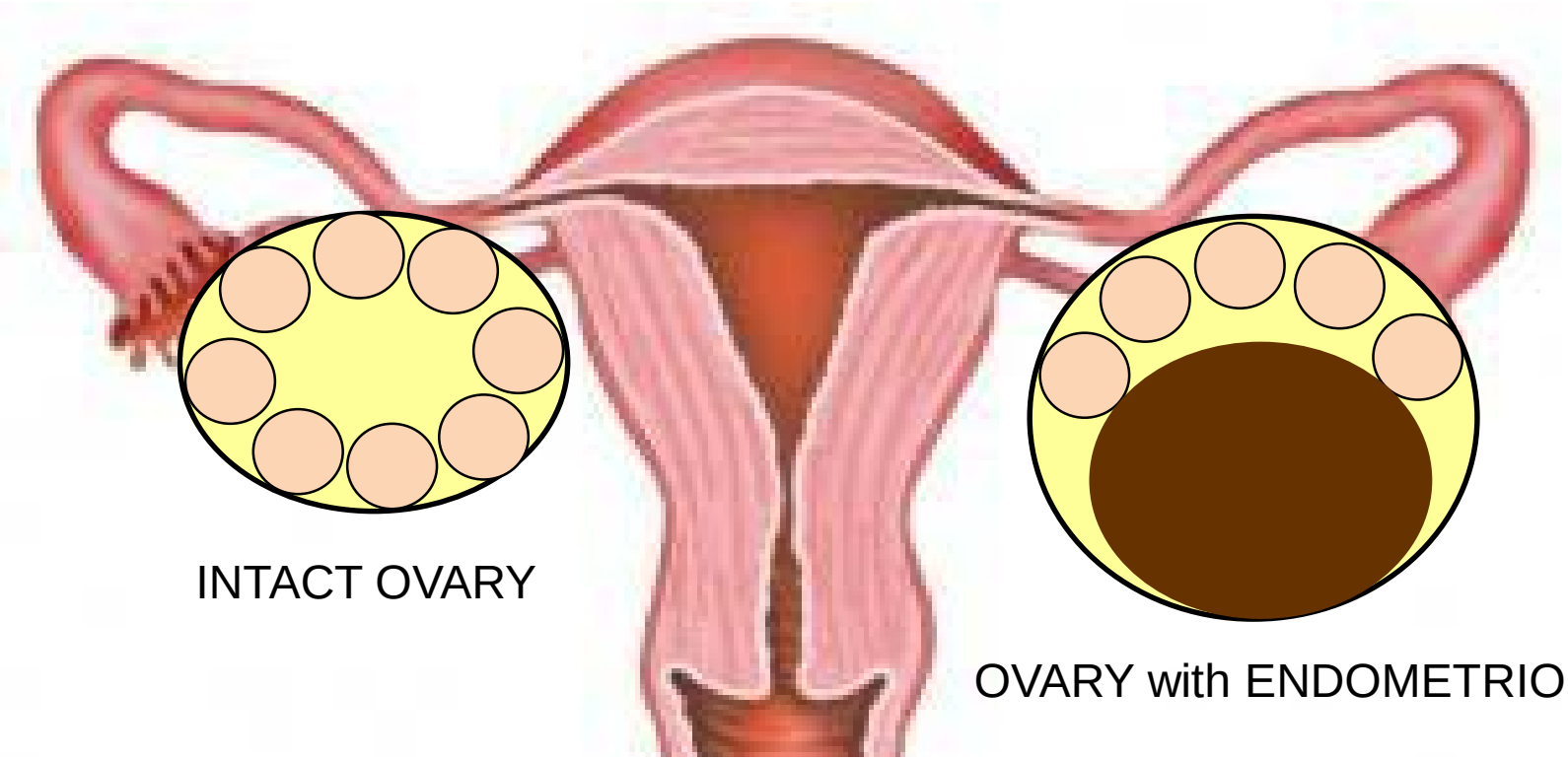
Contents

Contents (PART 1)

Possible causes of miscarriage associated with endometriosis

- The ovary
  - Quality of oocytes in ovary with endometrioma or operated ovary ?
- The endometrium
  - Gene expression
  - Hypercoagulation
  - Progesterone resistance
  - Uterine movement
  - Bacterial infection
- Association of adenomyosis

Is the quality of retrieved oocytes decreased in the ovary with endometrioma?



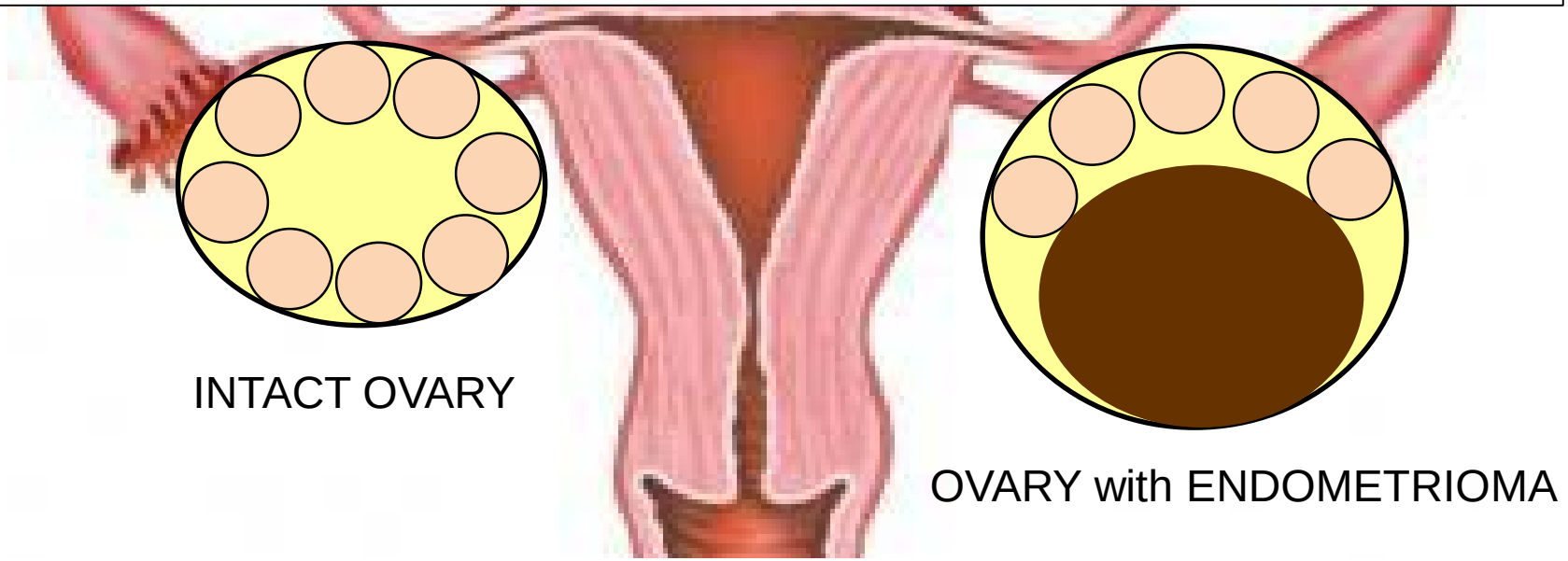
Is the quality of retrieved oocytes decreased in the ovary with endometrioma?

Number of oocytes retrieved, MII oocytes retrieved and total embryos formed were not statistically different between ovaries with endometriomas and healthy ovaries of the same individuals.

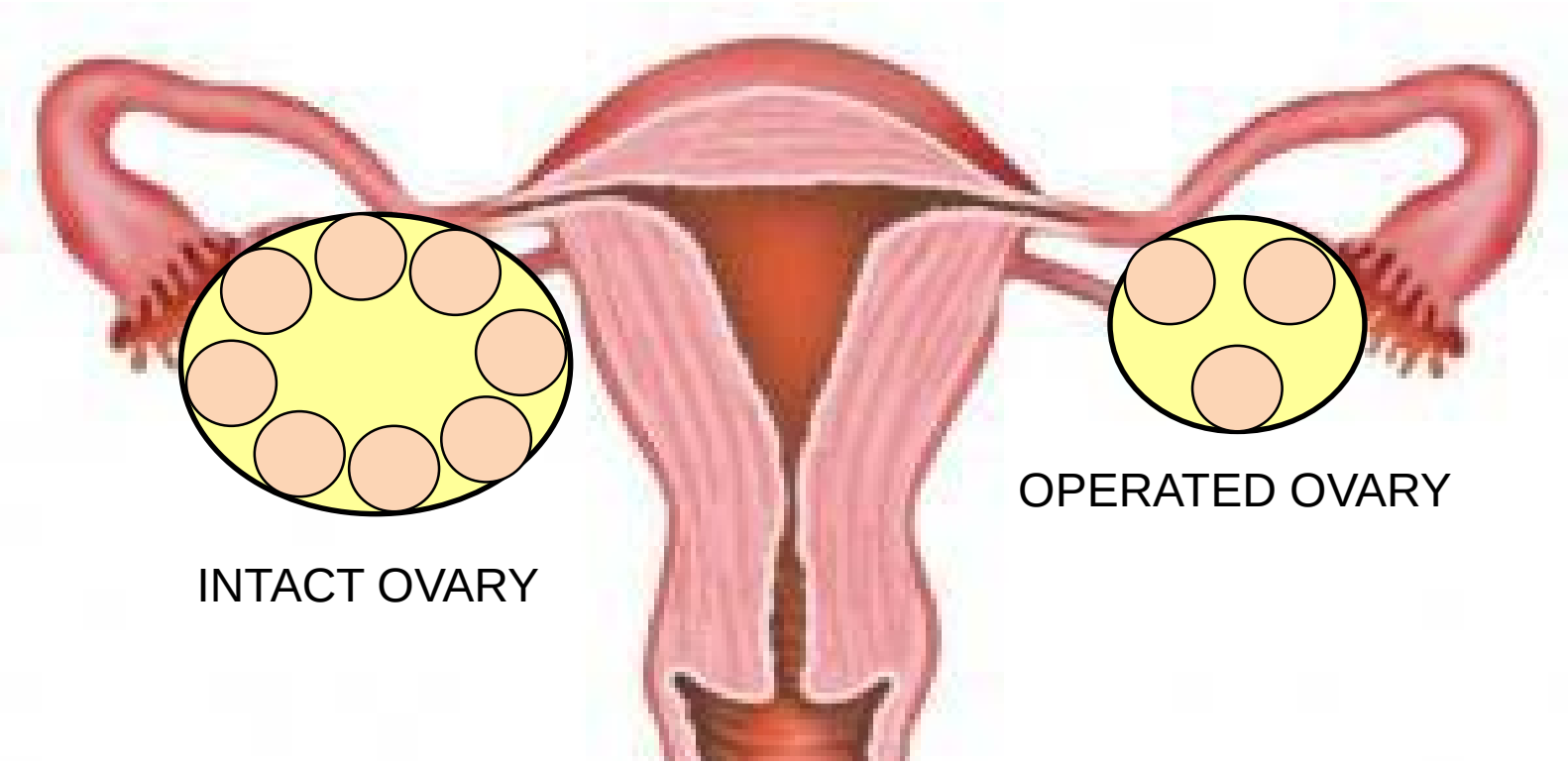
Yang C, et al. Reproductive BioMedicine Online. 31: 9-19. 2015

Is the quality of retrieved oocytes decreased in the ovary with endometrioma?

The quality of oocytes from the ovary with endometrioma is not inferior to that recovered from contra-lateral healthy ovary.



Is the quality of retrieved oocytes decreased in the operated ovary for endometrioma?



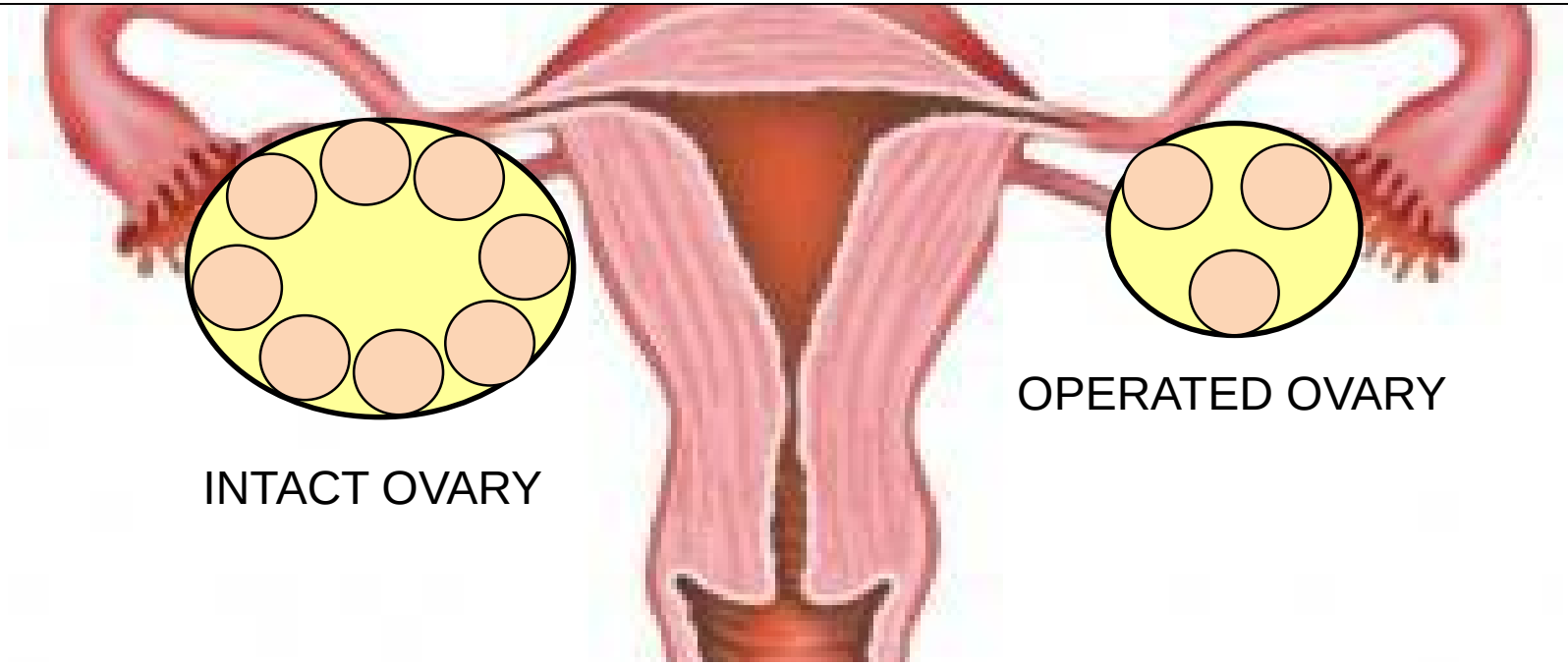
Is the quality of retrieved oocytes decreased in the operated ovary for endometrioma?

- Mean number of oocytes from ovaries with a history of excision of endometrioma (E-Ov) was significantly smaller than that from contra-lateral healthy ovaries (H-Ov) (2.2±2.0 vs. 5.1± 3.3, P=0.009).
- There was no difference between oocytes from E-Ov and H-Ov in terms of normal fertilization rate (63.6 % vs.69.5 %, P=0.43) and the rate of top-quality embryos (40.0 % vs. 49.0 %, P=0.34).
- Clinical and on-going pregnancy rates per embryos were also similar (40.0 % vs. 25.0 %, P= 0.39 and 20.0 % vs. 20.8 %, P=0.96).

Harada M, et al. J Assist Reprod Genet. 32: 685-9. 2015

Is the quality of retrieved oocytes decreased in the operated ovary for endometrioma?

The quality of oocytes from the operated ovary is not inferior to that from contra-lateral healthy ovary.



Contents (PART 1)

Aberrant expression of genes in the endometrium at the time of implantation in women with endometriosis

- Fifteen endometrial biopsy samples (obtained during the window of implantation from eight subjects with and seven subjects without endometriosis) were processed for expression profiling on Affymetrix Hu95A microarrays.

- Abnormally expressed genes: genes involved in embryonic attachment, embryo toxicity, immune dysfunction, and apoptotic responses.

- The endometrium of women may be hostile to embryos.

Kao LC, et al. Endocrinology. 144: 2870-81. 2003

Miscarriage might be related to hypercoagulable state in women with endometriomas

- Women with ovarian endometriomas had a significantly shortened APTT and TT and elevated fibrinogen levels as compared with controls.
- No difference was observed in fasting glucose levels, PT, D-dimer, INR, platelet count, and serum cortisol levels between patients with ovarian endometriomas and the controls.

Wu Q, et al. Reprod Sci. 22: 1107-14. 2015

Miscarriage might be related to progesterone resistance in women with endometriosis

	Expression of progesterone-induced genes by progesterone stimulus
Endometrium of women without endometriosis	++++++++++
Endometrium of women with endometriosis	++++++++
Endometriotic tissue	+

Bulun SE, et al. Molecular and Cellular Endocrinology. 248: 94-103. 2006

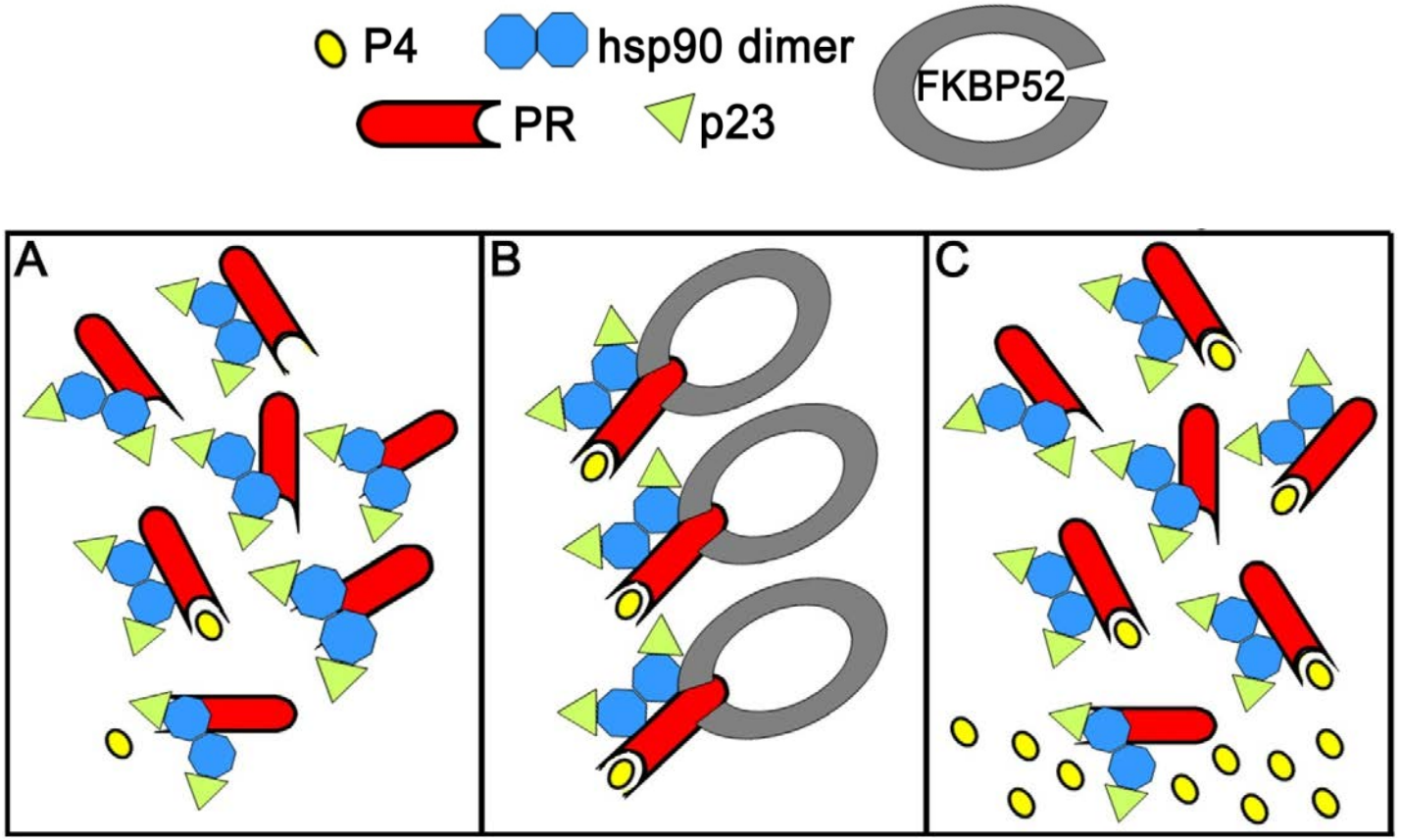
Molecules involved in progesterone-progesterone receptor(PR) signaling

PR isoforms

PR co-regulators
- Co-activator
- Co-repressor

PR chaperone complex
- Hsp90
- p23
- FK506 binding protein (FKBP)52

FKBP52 potentiates the responses of PR

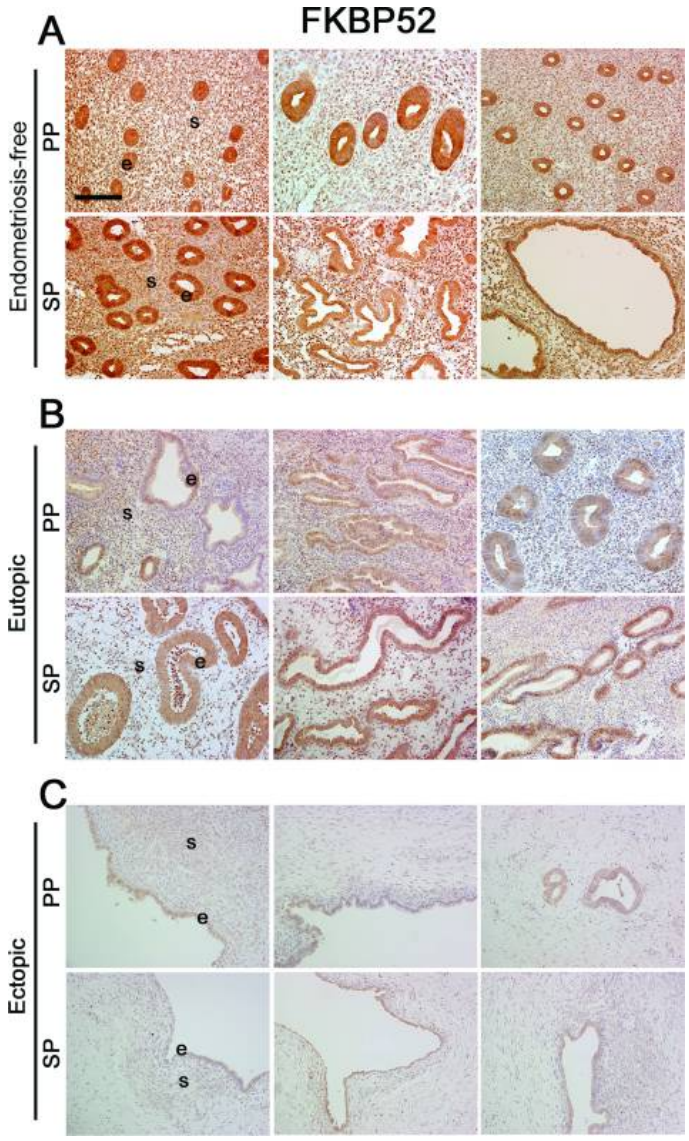


FKBP52 -/-

WT

FKBP52 -/-
+ abundant P_4

FKBP52 expression in the human endometrium and the endometriotic tissue



endometrium

Hirota Y, et al. Am J Pathol. 173: 1747-57. 2008

Function of FKBP52 in pregnancy

- Implantation failure is the major phenotype found in *Fkbp52*$^{-/-}$ CD1 female mice.

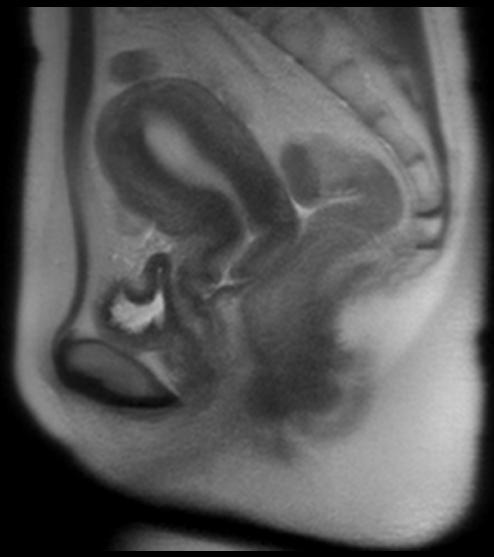
- P_4 at higher than normal pregnancy levels conferred PR signaling sufficient for implantation in *Fkbp52*$^{-/-}$ CD1 female mice, but these levels were inefficient in maintaining pregnancy to full term.

- However, elevating P_4 levels further restored PR signaling for successful term pregnancy with normal litter size.

Tranguch S, et al. J Clin Invest. 117: 1824-34. 2007

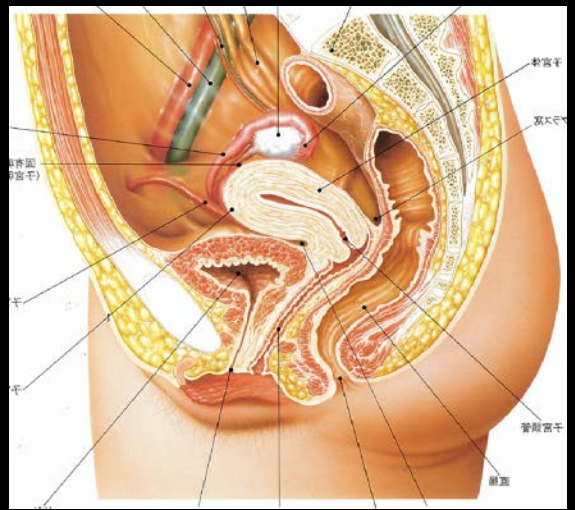
Uterine peristalsis

menstruation
Fundus ⇒Cervix

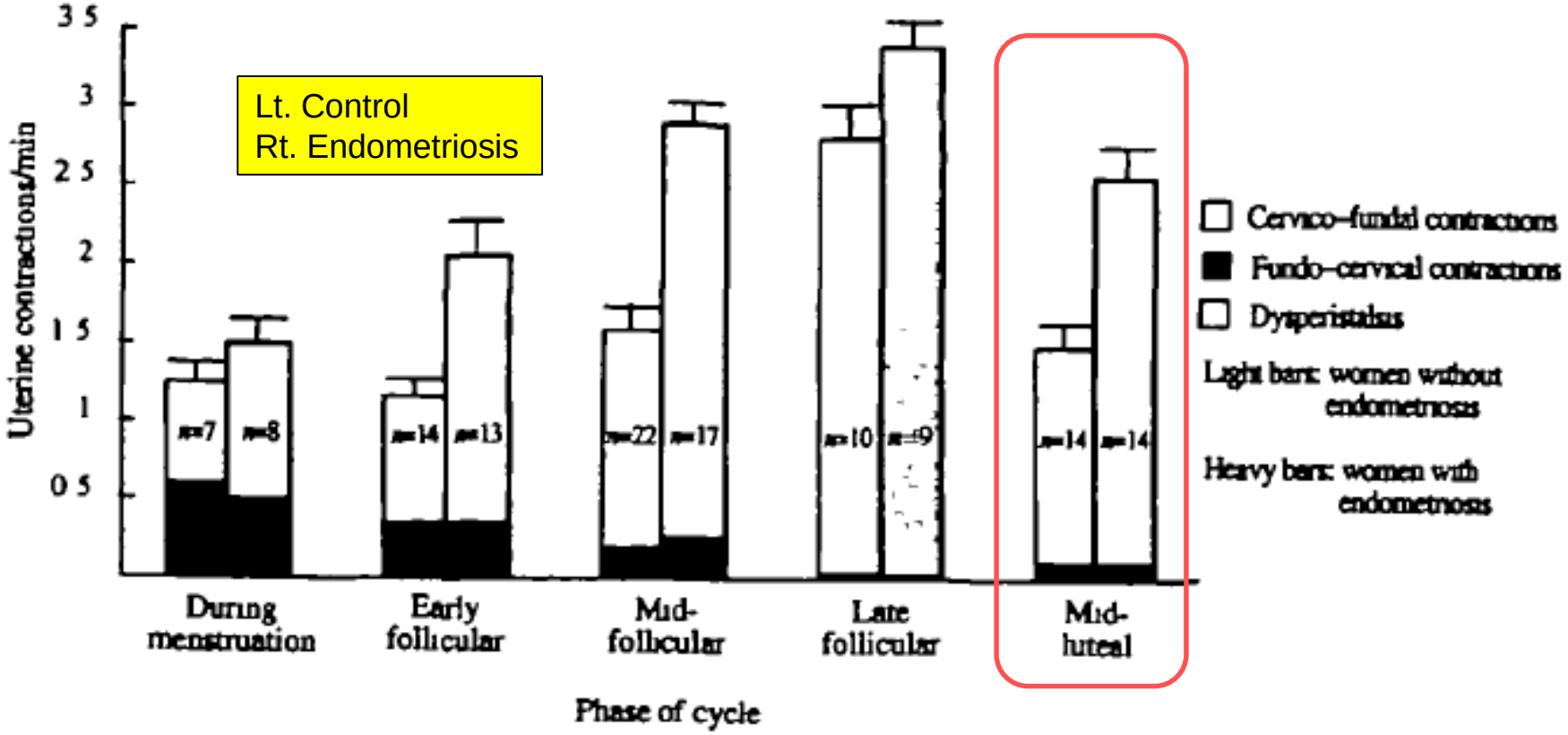


ovulation
Cervix ⇒ Fundus

implantation
no movement

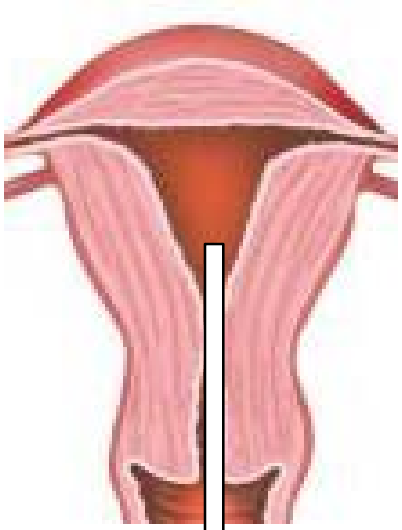


Uterine contraction is more active in women with endometriosis at mid-luteal phase

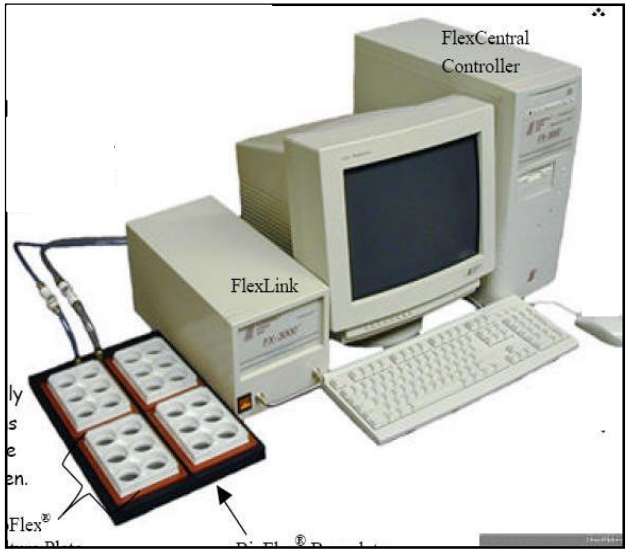


Leyendecker G, et al. Hum Reprod. 11: 1542-51. 1996

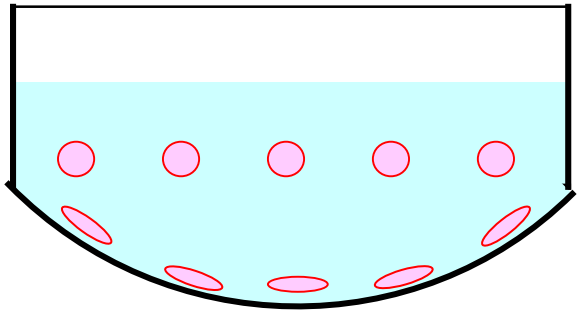
Mechanical stretch was added to cultured endometrial cells.



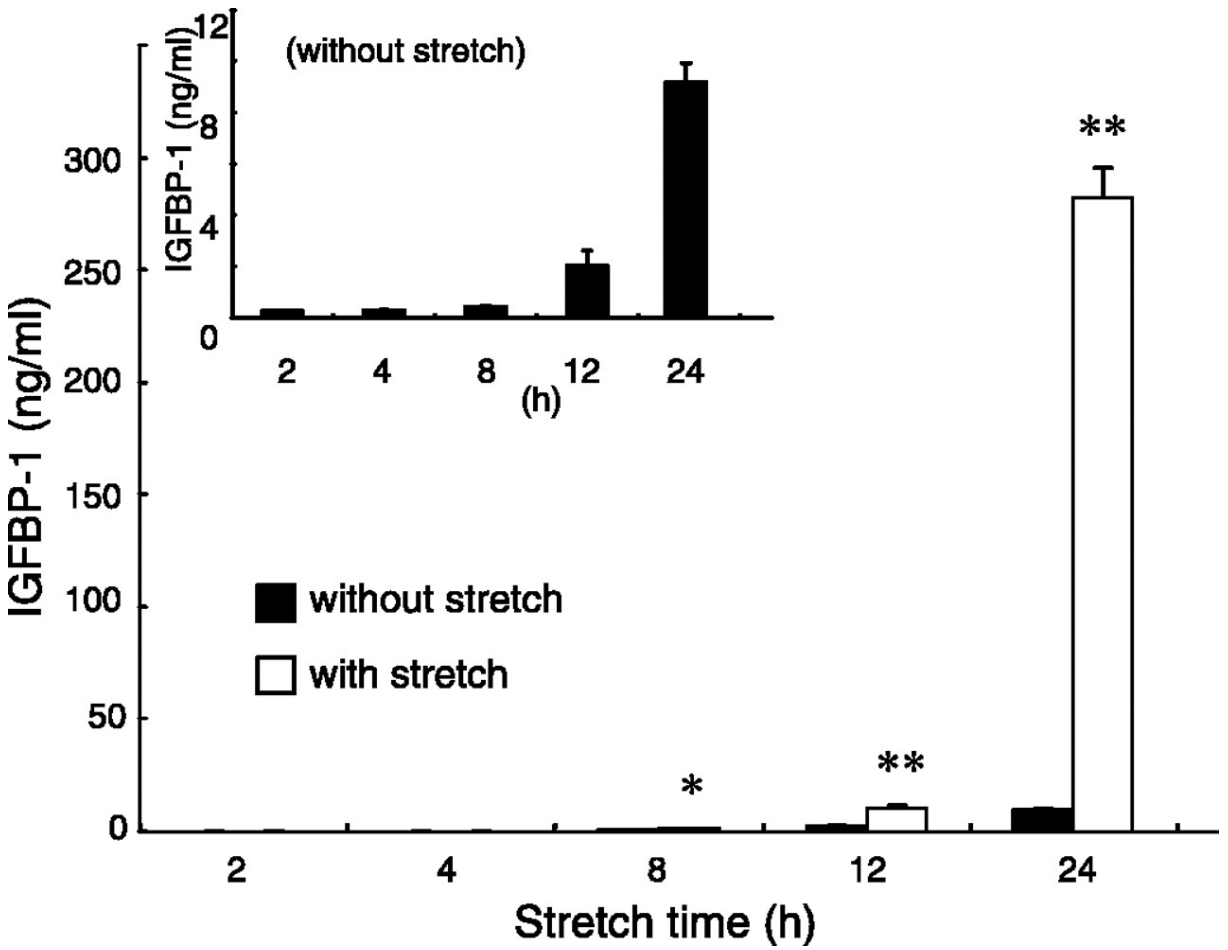
a computer-regulated bioreactor that applies cyclic or static tensile strains to cells cultured in vitro.



Isolated and purified endometrial stromal cells



Effects of cyclic stretch on the secretion of insulin-like growth factor-binding protein-1 (IGFBP-1) from decidualized endometrial stromal cells.



Miyuki Harada et al. Am J Physiol Endocrinol Metab 2006;290:E268-E272

The effect of cyclic stretch on the endometrium

Cyclic stretch upregulates IGFBP-1 secretion from decidualized endometrial stromal cells.
Harada M, et al. Am J Physiol Endocrinol Metab. 2006 Feb;290(2):E268-72

Cyclic stretch stimulates interleukin-8 production in endometrial stromal cells: possible implications in endometrium-related events.
Harada M, et al. J Clin Endocrinol Metab. 2005 Feb;90(2):1144-8

Cyclic stretch augments production of neutrophil chemokines and matrix metalloproteinase-1 (MMP-1) from human decidual cells, and the production was reduced by progesterone.
Zhao Y, et al. Am J Reprod Immunol. 2013 May;69(5):454-62.

Effects of increased peristalsis on the endometrium

Speculated mechanism

↑ IGFBP-1 ⟹ disorganized decidualization

↑ Interleukin-8
↑ Neutrophil chemokines ⟹ inflammation

↑ MMP-1 ⟹ tissue degradation

⇩

ABNORMAL IMPLANTATION and
ADVERSE PREGNANCY OUTCOME

Bacterial infection might be involved in miscarriage in women with endometriosis

- Menstrual blood of women with endometriosis is more contaminated with E. coli than that of control women.

  Khan KN, et al. Fertil Steril. 94: 2860-3.e1-3. 2010

- A shifting of intra-vaginal pH to ≥4.5 was observed in women with endometriosis compared with control women.

  Khan KN, et al. Hum Reprod. 29: 2446-56. 2014

- The number of colony forming units (CFU/ml) of Gardnerella, α-Streptococcus, Enterococci and Escherichia coli was higher in endometrial samples from women with endometriosis than control.

  Khan KN, et al. Hum Reprod. 29: 2446-56. 2014

Association of adenomyosis with endometriosis

- 27-43% of women with endometriosis also have adenomyosis.

  Benagiano G, et al. Hum Reprod Update. 20: 386-402. 2014

- A meta-analysis revealed that miscarriage rates in IVF/ICSI pregnancy were 31.9% (77/241) in women with adenomyosis and 14.1% (97/687) in those without adenomyosis.

  Vercellini P, et al. Hum Reprod. 29: 964-77. 2014

Summary (PART 1)

Possible causes of miscarriage associated with endometriosis

- The ovary
  - Quality of oocytes - unlikely
- The endometrium
  - Aberrant gene expression
  - Hypercoagulation
  - Progesterone resistance
  - Uterine movement
  - Bacterial infection
- Association of adenomyosis

} Possible causes of miscarriage associated with endometriosis

Contents (PART 2)

Clinical data on miscarriage and endometriosis

- Non-ART pregnancy
- ART pregnancy
  - Meta-analysis (Incl. impact of endometrioma)
  - Representative independent studies
- A national cohort study

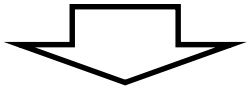
The relationship of endometriosis to miscarriage in non-ART pregnancy (1)

- 226 women with endometriosis
- 34% (77/226) pregnancies ended in first-trimester miscarriage.
  - mild: 49% in 87 pregnancies
  - moderate: 25% in 32 pregnancies
  - severe: 24% in 107 pregnancies
- Following operation, only 9% (7 /76) pregnancies ended in miscarriage.
- The postoperative miscarriage rates were not significantly different according to severity of endometriosis.

Wheeler JM, et al. Fertil Steril. 39: 656-60. 1983

The relationship of endometriosis to miscarriage in non-ART pregnancy (2)

- 139 consecutive infertility patients with laparoscopically proven endometriosis (before laparoscopy: miscarriage rate was 63.1%)
  - 95 pts: conservative surgical resection of endometriosis
  - 44 pts: expectant management



  - after surgical treatment, the miscarriage rate was 0% for all stages of endometriosis
  - after expectant management, the miscarriage rate was 16.7% and 21.4% for mild and moderate endometriosis

Metzger DA, et al. Fertil Steril. 45: 18-22. 1986

The relationship of endometriosis to miscarriage in non-ART pregnancy (3)

- 419 women who achieved a first spontaneous singleton pregnancy after surgery for endometriosis

- Miscarriage rate: endometriosis at ovary, 26% (26/100); at ovary and peritoneum, 27.6% (19/69); at rectovaginal, 20.0% (30/150); at peritoneum,12.0% (12/100).

- Miscarriage rate: endometriosis at ovary (26.6%, 45/169) > at rectovaginal or peritoneal endometriosis (16.8%, 42/250). (OR 1.70, 95%CI 1.04-2.81; adjusted for age)

Vercellini P, et al. BJOG. 119: 1538-43. 2012

Miscarriage rate in ART pregnancy: metaanalysis

ART outcomes revealed a small to moderate increase in the risk of miscarriage among pregnant women with endometriosis (RR 1.31, 95%CI 1.07–1.59, 18 studies, 2324 pregnant women, I^2 = 0%).

Barbosa MA, et al. Ultrasound Obstet Gynecol. 44: 261-78. 2014

Women with endometriosis undertaking ART had a similar miscarriage rate compared with women without endometriosis (OR 1.26, 95%CI 0.92–1.70, nine studies, 1259 patients, I^2 = 0%).

Hamdan M, et al. Obstet Gynecol. 125: 79-88. 2015

Miscarriage rate in ART pregnancy: a study from a single center (1990-2002)

- retrospective cohort study in a single center
- a routine infertility workup including laparoscopy/ laparotomy in all patients
- only fresh cycle under long protocol with GnRH-a in all patients
- a serum hCG level >20 IU/L defined as a pregnancy

- The rate of biochemical pregnancies (< 6w) was lower for unexplained (11.7%, 32/274) compared to endometriosis-associated (19.3%, 41/212) and tubal factor (18.0%, 97/540) infertility groups.
- Miscarriage rates between the sixth and 12th week and after the 12th gestational week were similar for all three groups.

Omland AK, et al. Hum Reprod. 20: 722-7. 2005

Miscarriage rate in ART pregnancy: a study from a single center (1996-2011)

- retrospective cohort study in a single center
- a routine infertility workup including laparoscopy/ laparotomy in all patients
- long protocol with GnRH-a in all patients
- from the first treatment cycle
- a serum hCG level >20 IU/L defined as a pregnancy

No differences in the rate of biochemical pregnancies or miscarriages after observation of one or more gestational sacs among the groups.

	ASRM I-II (n=724)	ASRM III-IV (n=350)	Tubal facor (n=1171)
Biochemical preg.	9.6% (25/261)	8.7% (10/115)	14.5% (59/406)
Miscarriage	18.8% (49/261)	17.4% (20/115)	12.6% (51/406)

Opøien HK, et al. Fertility and Sterility. 97: 912-8. 2012

Miscarriage rate in ART pregnancy: a study from two centers

- Singleton pregnancies with ART
- Case: a history of endometriosis surgery or endometrioma (by ultrasound) at the time of ART (n=313)
- Control: matched in 1:1 ratio by age, type of cycle (fresh or frozen), and study period (n=313)

- The miscarriage rate was not different in women with or without endometriosis (15% vs. 19%; OR 0.76, 95%CI, 0.50-1.16).
- No difference between the groups in subgroup analyses according to the type of cycle (fresh and frozen), the number of embryos transferred, the presence of endometriomas, and the history of surgery for endometriosis.

Leonardi M, et al. Fertil Steril. 106: 386-92.e3. 2016

Miscarriage rate in pregnancy: a national cohort study

Cohort study using four national registries
Denmark 1977-2009
24,667 women with endometriosis and 98,668 age-matched control (1:4)

Relative risks (95%CI) of miscarriage for women with endometriosis:

All	1.24 (1.20- 1.29)
Natural	1.21 (1.17- 1.26)
ART	4.34 (3.42- 5.50)

Hjordt Hansen MV, et al. Acta Obstet Gynecol Scand. 93: 483-9. 2014

Summary (2nd part)

In non-ART pregnancy, endometriosis might increase the risk of miscarriage, especially in the case of ovarian endometriosis.

In ART pregnancy, endometriosis might increase the risk of miscarriage.

In ART pregnancy, endometriosis might increase the risk of biochemical pregnancy.

However, well-designed studies are very few.

Future issues

Given that endometriosis is associated with miscarriage,

- ✓ differences in types or status of endometriosis?

  Ovary, peritoneal, deep infiltrating, stage I-IV, pre- or post-surgery, etc.

- ✓ differences in procedures of IVF?

  GnRHa long protocol, antagonist protocol, natural or mild stimulation, frozen cycles, thaw cycles, etc.

- ✓ differences in natural pregnancy and ART pregnancy?
- ✓ differences in chemical pregnancy and miscarriage?
- ✓ the real mechanism by which endometriosis is associated with miscarriage?
- ✓ any measures to prevent miscarriage associated with endometriosis?

Conclusion

There are many potential causes of miscarriage in women with endometriosis.

Overall, endometriosis seems to slightly increase the risk of miscarriage.

However, we don’t have enough data to conclude how endometriosis is associated with miscarriage. Further studies are needed.