Pathogenesis of Endometriosis in Non-Human Primates: A Critical Literature Review

Ferheen Abbasi, MS[1] and Frederick J. Meyers, MD, MACP[2]

[1]University of California, Davis, School of Medicine [2]University of California, Davis Health, School of Medicine, Department of Internal Medicine, Division of Hematology and Oncology

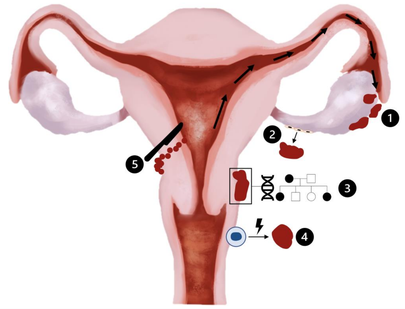
Retrograde menstruation and inoculation is necessary but may not be sufficient for the development of endometriosis in non-human primates.

INTRODUCTION

- Endometriosis: ectopic endometrial tissue that responds to cyclical hormonal changes during a normal menstrual cycle, becoming trapped in an endometrioma and causing pain [1, 2].
- NHPs have been used to study endometriosis: baboons, cynomolgus, rhesus, and marmoset monkeys.

Five hypotheses of endometriosis:

1. **Retrograde menstruation**: menstrual blood flows backwards into the pelvis via the fallopian tubes, leading to endometrial cells being transplanted from the uterus [3, 4].
2. **Coelomic metaplasia**: epithelium tissue in the pelvis transforms via metaplasia into endometrial tissue [5].
3. **Hereditary**: similar age of onset is seen in sisters, incidence increases if endometriosis is seen in first degree relatives. The 10q26 chromosome locus has been implicated for endometriosis, specifically CYP2C19 [6].
4. **Embryonic rest theory**: Presence of cells originating from the Mullerian duct and form endometrial tissue when induced [7].
5. **Surgery**: Endometrial cells seed into abdomen following surgery, linked to the development of endometriosis later in life [8].



OBJECTIVE

We examined data derived from NHPs to assess the different hypotheses in the pathogenesis of endometriosis.

METHODS

- Using the PubMed database, we searched for literature describing endometriosis in different non-human primates: baboon, cynomolgus, rhesus, and marmoset.
- Article titles and abstracts for studies on endometriosis in NHPs were screened.
- Studies not specific to non-human primates or other narrative review articles were manually excluded.
- After initial screening, a further manual search was conducted via citations as well as in the "similar articles" section in PubMed.

RESULTS

Table 1. Inducing Endometriosis in NHPs

Article	Methods	Animal	N	Rate of Endometriosis (%)
Te Linde and Scotto, 1950 [9]	Endometrial tissue transplant	Rhesus	6	6 (100)
Scott et al., 1953 [10]	Cut and tie uterine cervix	Rhesus	10	5 (50)
Splitter et al., 1972 [11]	Irradiation	Rhesus	4	4 (100)
Schenken et al., 1987 [12]	Surgically induced	Cynomolgus	16	16 (100)
Fanton et al., 1991 [13]	Irradiation	Rhesus	128	74 (58)
Rier et al., 1993 [14]	TCDD	Rhesus	14	8 (57)
D'Hooghe et al., 1994 [15]	Cervical obstruction	Baboons	5	1 (20)
D'Hooghe et al., 1995 [16]	Intraperitoneal inoculation of endometrium	Baboons	17	17 (100)
D'Hooghe et al., 1996 [17]	Intraperitoneal inoculation of endometrium	Baboon	113	25 (100)
Sillem et al., 1996 [18]	Intraperitoneal inoculation of endometrium	Cynomolgus	30	23 (76)
Yang et al., 2000 [19]	Endometrial tissue transplant + TCDD	Cynomolgus	23	23 (100)
Baskin et al., 2002 [20]	Estrogen implants	Rhesus	6	6 (100)
Zong et al., 2003 [21]	Endometrial tissue transplant	Rhesus	5	3 (60)
Fazleabas et al., 2003 [22]	Intraperitoneal inoculation of endometrium	Baboons	13	13 (100)
Hastings et al., 2006 [23]	Intraperitoneal inoculation of endometrium	Baboons	24	24 (100)
Jones et al., 2006 [24]	Intraperitoneal inoculation of endometrium	Baboons	8	8 (100)
Gashaw et al., 2006 [25]	Intraperitoneal inoculation of endometrium	Baboons	6	6 (100)
Einspanier et al., 2006 [26]	Endometrial reflux - non-invasive vs invasive	Marmoset	29	19 (66)
Defrere et al., 2008 [27]	Endometrial tissue transplant	Rhesus	3	0 (0)
Dehoux et al., 2011 [28]	Endocervical canal and horn resection	Baboons	29	8 (30)
Hey-Cunningham et al., 2011 [29]	Intraperitoneal inoculation of endometrium	Baboons	11	11 (100)
Afshar et al., 2013 [30]	Intraperitoneal inoculation of endometrium	Baboons	4	4 (100)
Donnez et al., 2013 [31]	Intraperitoneal inoculation of endometrium	Baboons	10	10 (100)
Langoi et al., 2013 [32]	Intraperitoneal inoculation of endometrium	Baboons	16	16 (100)
Kyama et al., 2014 [33]	Intraperitoneal inoculation of endometrium	Baboons	5	5 (100)
Donnez et al., 2015 [34]	Intraperitoneal inoculation of endometrium	Baboons	10	N/A
Orellana et al., 2017 [35]	Intraperitoneal inoculation of endometrium	Baboons	3	3 (100)
Le et al., 2022 [36]	Intraperitoneal inoculation of endometrium	Baboons	8	N/A

- Endometriosis was induced in 28 of the articles using various laboratory techniques.
- The main methods used to induce endometriosis included:
  - endometrial tissue transplant (4)
  - intraperitoneal inoculation of endometrium (15)
  - irradiation (2)
  - TCDD (dioxin) (2)
- 19 of the studies induced endometriosis using the retrograde menstruation hypothesis via directly inoculating the abdomen with endometrium or closing the cervix such that endometrial fluid traveled through the fallopian tubes into the abdomen.
  - A majority (12) of those studied had a 100% success rate.

CONCLUSIONS & IMPLICATIONS

- Intraperitoneal inoculation of endometrium has become the method to induce endometriosis [16].
- Retrograde menstruation cannot fully explain the development of endometriosis. 90% of human menstruators have been found to retrograde menstruate, but most do not have endometriosis.
  - Endometriosis lesions can also be found in sites outside of the pelvis (bone, lung), locations where menstrual fluid cannot reach [37, 38].
- NHPs provide an established model to characterize endometriosis due to retrograde menstruation. We hypothesize that the absence of allelic diversity in NHP facilitates the induction of endometriosis. Additional alterations or co-factors are necessary for the multi-step pathogenesis of endometriosis.

Contact

Ferheen Abbasi, MS
University of California, Davis
School of Medicine
ferabbasi@ucdavis.edu

Acknowledgments

We thank Dr. Melody Hou, Amy Studer, and Dr. Peter Katz for critical reading.

References