Divergent Roles of Peripheral Leukocytes Before Preparing for Pregnancy and Before Conception in Spontaneous Abortion: A Population-based Retrospective Cohort Study

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BACKGROUND

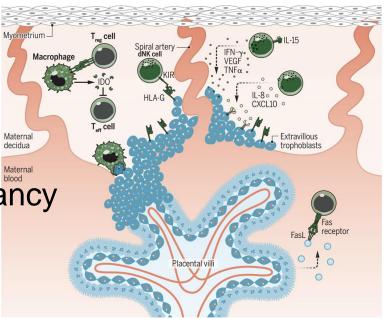
Spontaneous abortion (SAB)

The most common complication of early pregnancy

- Pathogenesis: fetal factors + maternal factors
- + paternal factors

Immunity

- One of the most booming fields in reproduction
- Leukocytes at the maternal-fetal interface
 - Maintaining placental development and function
 - Fighting against infection
 - Minimizing the risk of fetal attack by maternal immune system
- No lab-based evidence of peripheral leukocytes (PLs)





BACKGROUND

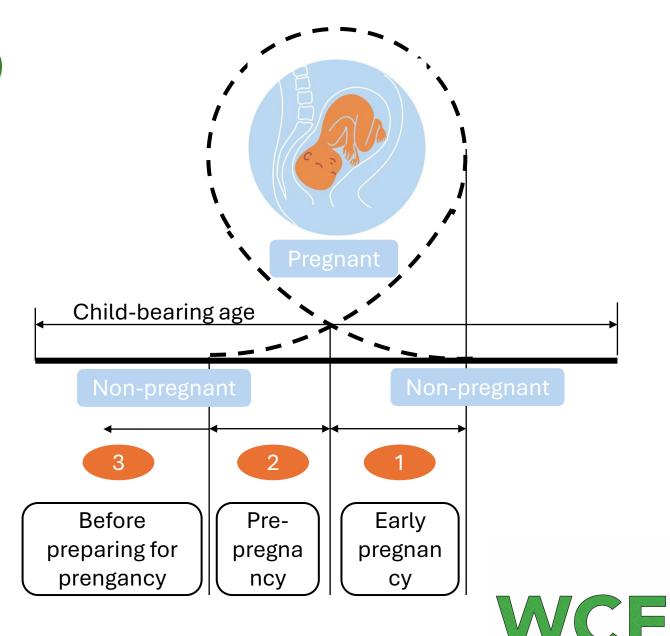
- Problem Formation
 - Low pre-pregnancy PLs were associated with increased risk of SAB
 - Increased risk of periconceptional infection
 - Inadequate recruitment at the maternal-fetal interface during and after embryo implantation.
 - Others mechanism?
 - Shared immunogenetic basis between mother and fetus?
 - Innate and adaptive immunity memory?



BACKGROUND

Problem Formation

- Is PLs before preparing for pregnancy associated with the risk of SAB?
 - Before preparing for pregnancy ≠ Before conception
 - Immunological preparation for maternal and fetal functioning after conception



METHODS

- Study design: retrospective cohort study
- Data sources and collection
 - National Free Pre-pregnancy Checkups Project
 - Preconception health examination
 - Early-pregnancy follow-up
 - Outcome follow-up
 - 238 716 women who had participated the project twice



METHODS

- Exposure and Outcome
 - Exposure
 - PLs before preparing for pregnancy: PLs determined at the prepregnancy health examination of the first participation
 - Pre-pregnancy PLs: PLs determined at the second participation
 - Outcome
 - SAB at the second participation: fetal death occurring before the 28th week of gestation



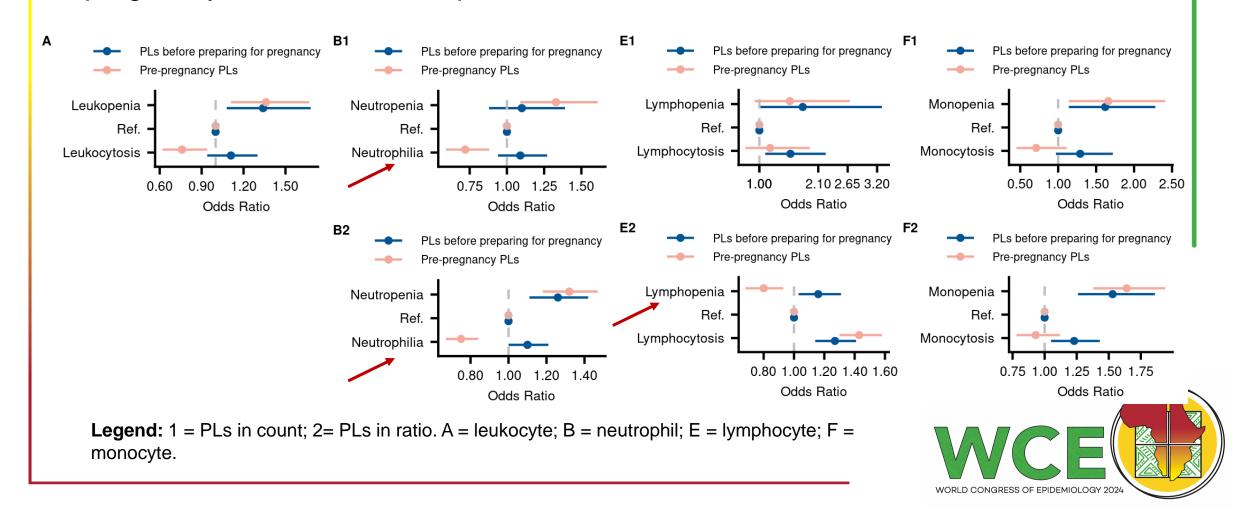
METHODS

- Statistical methods
 - Odds ratio (OR) with 95% confidence interval (CI)
 - Logistic regression
 - Adjusted for the imbalance caused by baseline characteristics via inverse probability weighting (IPW)
 - Non-linear dose-response relationship
 - Restricted cubic splines
 - Data analysis software: R



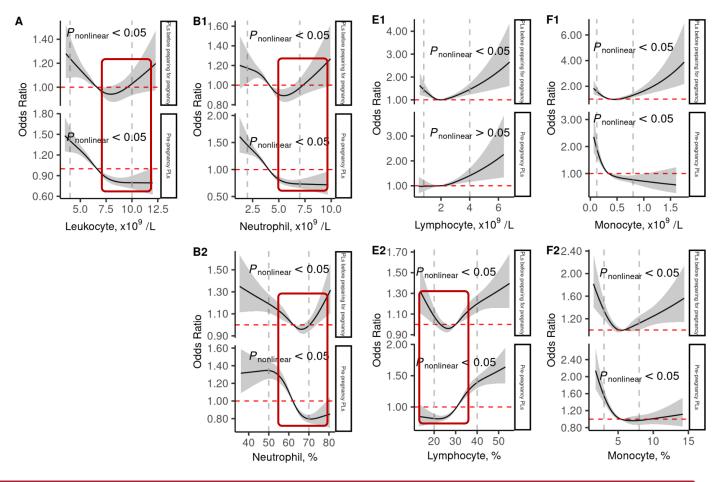
RESULTS

• **Figure 1.** Inverse-probability weighted ORs of PLs before preparing for pregnancy and before conception for the risk of SAB.



RESULTS

 Figure 2. Exposure-response relationship between PLs before preparing for pregnancy and before conception and the risk of SAB



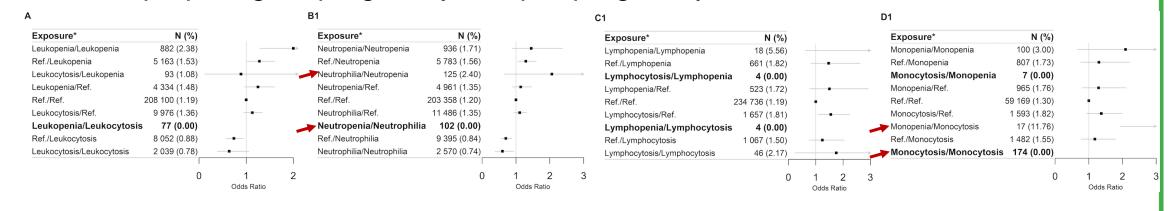
Legend:

1 = PLs in count; 2= PLs in ratio. A = leukocyte; B = neutrophil; E = lymphocyte; F = monocyte



RESULTS

 Figure 3. Inverse-probability weighted ORs for the risk of SAB according to PLs before preparing for pregnancy and pre-pregnancy PLs



Legend:

1 = PLs in count; 2= PLs in ratio. A = leukocyte; B = neutrophil; C = lymphocyte; D = monocyte.

*: Exposure is arranged as PLs before preparing for pregnancy first and pre-pregnancy PLs second.

_										
Exposure*	N (%)					Exposure*	N (%)			
Neutropenia/Neutropenia	5 142 (1.52)					Lymphopenia/Lymphopenia	4 336 (0.67)			
Ref./Neutropenia	14 826 (1.63)					Ref./Lymphopenia	13 687 (0.87)	-		
Neutrophilia/Neutropenia	2 223 (1.53)	-		_		Lymphocytosis/Lymphopenia	1 304 (1.00)	_	-	
Neutropenia/Ref.	13 392 (1.43)					Lymphopenia/Ref.	15 277 (1.32)		-	
Ref./Ref.	139 666 (1.17)		•			Ref./Ref.	155 975 (1.12)		+	
Neutrophilia/Ref.	25 403 (1.37)					Lymphocytosis/Ref.	17 754 (1.49)			
Neutropenia/Neutrophilia	1 978 (1.37)		-	_		Lymphopenia/Lymphocytosis	1 515 (1.85)			
Ref./Neutrophilia	24 931 (0.87)	-				Ref./Lymphocytosis	20 489 (1.68)			
Neutrophilia/Neutrophilia	11 155 (0.81)					Lymphocytosis/Lymphocytosis	8 379 (1.47)			
	0	1	1	2	3		0		1	2
			Odds R	atio					Odds Rat	io

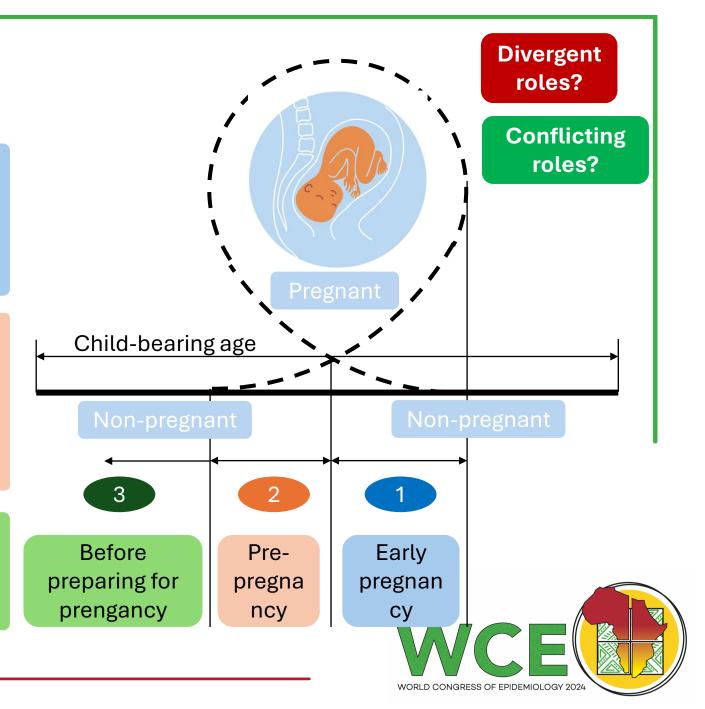
C2

Exposure*	N (%)	
Monopenia/Monopenia	1 368 (1.46)	
Ref./Monopenia	3 283 (1.74)	
Monocytosis/Monopenia	348 (2.30)	-
Monopenia/Ref.	2 904 (1.58)	-
Ref./Ref.	41 410 (1.23)	•
Monocytosis/Ref.	6 312 (1.76)	
Monopenia/Monocytosis	321 (4.36)	
Ref./Monocytosis	5 825 (1.13)	
Monocytosis/Monocytosis	2 543 (0.98)	-
	0	1 2
		Odds

D2

CONCLUSIONS

- Maintaining placental development and function
- Fighting against infection
- Minimizing the risk of fetal attack by maternal immune system
- Providing sufficient leukocytes needed by maternal-fetal interface to maintain placental development and function
- Fighting against periconceptional infectior
- Ability to shift the Th1/Th2/Th17 and Treg paradigms
- Indicating exposure possibility to environmental pathogens
- Immunogenetic basis?
- Immunological memory?



CONCLUSIONS



 PLs before preparing for pregnancy and before conception have divergent roles in the development of SAB.



 More efforts is needed to forward the immune window of pregnancy from periconception to a period before preparing for pregnancy.





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