ISSN : 2149-9322
E-ISSN : 2149-9330

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

Clinical Investigations

TURKISH SOCIETY OF OBSTETRICS AND GYNECOLOGY

galenos yayınevi

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

Contact
¬FUJO &NFÉ #VMWBS•)ÛSSJZFU $BEEFTJ)BSCJZF .BIBMMFTJ ¸WFÉ
1IPOF 'BY & NBJM FEJUPS!UKPE PSH

(BMFOPT 1VCMJTIJOH)PVTF
Owner and Publisher
%FSZB .PS
&SLBO .PS
1VCMJDBUJPO $PPSEJOBUPS
#VSBL 4FWFS
Web Coordinators
'VBU)PDBMBS
5VSHBZ "LQ•OBS
(SBQIDT %FQBSUNFOU
"ZEB "MBDB
¬J EFN #JSJODJ
(ÛM BI ¸[HÛM
'JOBODF $PPSEJOBUPS
4FWJOÉ ¬BLNBL
1FSPKFDU $PPSEJOBUPS
%VZHV :•ME•S•N
(BN[F "LTPZ
)BUJDF 4FWFS
.FMJLF &SFO
1•OBS "LQ•OBS
(ÛMBZ "L•O
¸[MFN ¬FMJL
3BCJB 1BMB[P MV
3FTFBSDI & Development
.FSU $BO ¸ÕTF
.FWMÛEF ¸[MFN "LHÛOFZ
1VCMJTIFS $POUBDU
Address: .PMMB (ÛSBOJ .BI ¸BÉBNBL 4L /P
TUBOCVM 5VSLFZ
Phone:
Fax:
E-mail: JOGP!HBMFOPT DPN US ZBZJO!HBMFOPT DP
Web: XXX HBMFOPT DPN US
1VCMJTIFS $FSUJÛDBUF /VNCFS
0OMJOF 1VCMJDBUJPO %BUF
ISSN: E-ISSN:
*OUFSOBUJPOBM TDJFOUJàD KPVSOBM QVCMJTIFE RV

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

AIMS AND SCOPE

5VSLJTI +PVSOBM PG 0CTUFUSJDT BOE (ZOFDPMPHZ JT JOEFYFE JO $FOUSBM 1.$ 8FC PG 4DJFODF &NFSHJOH 4PVSDFT $JUBUJPO *OEFY &4$* &#4$0 %0"+ *OEFY $PQFSOJDVT 4DPQVT $*/")- (PPHMF 4DIPMBS 5ÇCJUBL 6MBLCJN 5VSLJTI .FEJDBM %BUBCBTF 5VSL .FEMJOF and Turkiye Citation Index.

Open Access Policy

5IJT KPVSOBM QSPWJEFT JNNFEJBUF PQFO BDDFTT UP JUT DPOUFOU PO UIF QSJODJQMF UIBU NBLJOH SFTFBSDI GSFFMZ BWBJMBCMF UP UIF QVCMJD TVQQPSUJOH B HSFBUFS HMPCBM FYDIBOHF PG LOPXMFEHF

0QFO "DDFTT 1PMJDZ JT CBTFE PO SVMFT PG #VEBQFTU 0QFO "DDFTT *OJUJBUJWF #0"* IUUQ XXX CVEBQFTUPQFOBDDFTTJOJUJBUJWF PSH #Z iPQFO BDDFTTu UP <QFFS SFWJFXFE SFTFBSDI MJUFSBUVSF> XF NFBO JUT GSFF BWBJMBCJMJUZ PO UIF QVCMJD JOUFSOFU QFSNJUUJOH BOZ VTFST UP SFBE EPXOMPBE DPQZ EJTUSJCVUF QSJOU TFBSDI PS MJOL UP UIF GVMM UFYUT PG UIFTF BSUJDMFT DSBXM UIFN GPS JOEFYJOH QBTT UIFN BT EBUB UP TPGUXBSF PS VTF UIFN GPS BOZ PUIFS MBXGVM QVSQPTF XJUIPVU àOBODJBM MFHBM PS UFDIOJDBM CBSSJFST PUIFS UIBO UIPTF JOTFQBSBCMF GSPN HBJOJOH BDDFTT UP UIF JOUFSOFU JUTFMG 5IF POMZ DPOTUSBJOU PO SFQSPEVDUJPO BOE EJTUSJCVUJPO BOE UIF POMZ SPMF GPS DPQZSJHIU JO UIJT EPNBJO JT HJWFO UP BVUIPST UP SFUBJO DPOUSPM PWFS UIF JOUFHSJUZ PG UIFJS XPSL BOE UIF SJHIU UP CF QSPQFSMZ BDLOPXMFEHFE BOE DJUFE

5IJT KPVSOBM JT MJDFOTFE VOEFS B $SFBUJWF $PNNPOT *OUFSOBUJPOBM -JDFOTF

Permission

1FSNJTTJPO SFRVJSFE GPS VTF BOZ QVCMJTIFE VOEFS $$ #: /$ MJDFOTF XJUI DPNNFSDJBM QVSQPTFT TFMMJOH FUD UP QSPUFDU DPQZSJHIU PXOFS BOE BVUIPS SJHIUT 3FQVCMJDBUJPO BOE SFQSPEVDUJPO PG JNBHFT

INSTRUCTIONS FOR AUTHORS

Peer-review

Authorship

Phone number:
E-mail:

.BOVTDSJQUT TVCNJUUFE GPS QVCMJDBUJPO

INSTRUCTIONS FOR AUTHORS

5JUMF 1BHF

" TFQBSBUF UJUMF QBHF TIPVME MJTU

5IF NBOVTDSJQU UJUMF XIJDI TIPVME DPOUBJO OP NPSF UIBO DIBSBDUFST DPVOUJOH MFUUFST BOE TQBDFT BOE TIPVME OPU DPOUBJO BOZ BCCSFWJBUJPOT PS DPNNFSDJBM OBNFT

" TIPSU UJUMF PG OP NPSF UIBO DIBSBDUFST BT B SVOOJOH GPPU

"MM BVUIPST OBNF T JOTUJUVUJPOBM BGGJMJBUJPOT BOE VQ UP UXP NBKPS EFHSFF T

$PSSFTQPOEJOH BVUIPS T OBNF BEESFTT UFMFQIPOF JODMVEJOH UIF NPCJMF QIPOF OVNCFS GBY OVNCFS BOE FNBJM BEESFTT 5IF DPSSFTQPOEJOH BVUIPS XJMM CF SFTQPOTJCMF GPS QPTUJOH BOE UIF PUIFS NBUUFST SFMBUJOH UP UIF NBOVTDSJQU

1SFDJT

5IF QSFDJT JT B POF TFOUFODF TZOPQTJT PG OP NPSF UIBO XPSET UIBU EFTDSJCFT UIF CBTJD àOEJOHT PG UIF BSUJDMF 1SFDJT NBZ CF TFFO CFMPX

A6TJOH B QPJOU RVFTUJPOOBJSF XF IBWF FWBMVBUFE UIF USFOE PG 3PCPUJD TVSHFSZ USBJOJOH JO UIF HZOFDPMPHJD TVSHFSZ GFMMPXTIJQ QSPHSBNT BDSPTT UIF OBUJPO

"CTUSBDU

"MM NBOVTDSJQUT TIPVME CF BDDPNQBOJFE CZ BO BCTUSBDU 5IF BCTUSBDU TIPVME CF JO UIF BCTUSBDU TIPVME CF DPOTJTUFOU XJUI UIF NBJO UFYU BOE UBCMFT PS àHVSFT "WPJE VTF PG BCCSFWJBUJPOT 0SJHJOBM SFTFBSDI SFQPSUT TIPVME IBWF B TUSVDUVSFE BCTUSBDU PG OP NPSF UIBO XPSET VTJOH UIF GPMMPXJOH IFBEJOHT

p0CKFDUJWF .BJO RVFTUJPO PCKFDUJWF PS IZQPUIFTJT TJOHMF QISBTF TUBSUJOH XJUI GPS FYBNQMF i5P FWBMVBUF u PS i5P FTUJNBUF u <OFWFS TUBSU XJUI i5P EFUFSNJOF u>

p.BUFSJBMT BOE .FUIPET 4UVEZ EFTJHO NBUFSJBMT BOE TUBUJTUJDBM BOBMZTFT NFBTVSFT BOE JO UIF DBTF PG B OFHBUJWF TUVEZ TUBUJTUJDBM QPXFS

p3FTVMUT .FBTVSFNFOUT FYQSFTTFE JO BCTPMVUF OVNCFST BOE QFSDFOUBHFT BOE XIFO BQQSPQSJBUF JOEJDBUF TFMBUJWF SJTLT PS PEET SBUJPT XJUI DPOàEFODF JOUFSWBMT BOE MFWFM PG TUBUJTUJDBM TJHOJàDBODF BOZ SFTVMUT DPOUBJOFE JO UIF BCTUSBDU TIPVME BMTP CF QSFTFOUFE JO UIF CPEZ PG UIF NBOVTDSJQU UBCMFT PS àHVSFT

p$PODMVTJPO %JSFDUMZ TVQQPSUFE CZ EBUB BMPOH XJUI DMJOJDBM JNQMJDBUJPOT

"VUIPST GSPN 5VSLFZ PS 5VSLJTI TQFBLJOH &VSPQFBO DPVOUSJFT TIPVME BMTP TVCNJU B 5VSLJTI BCTUSBDU JODMVEJOH UIF 5VSLJTI UJUMF XIJDI XJMM CF :ÕOUFNMFS #VMHVBMBS 4POVÉu 5IF BCTUSBDU PG "VUIPST XIPTF OBUJWF MBOHVBHF JT OPU 5VSLJTI XJMM CF QSPWJEFE GSFF PG DIBSHF CZ 5VSLJTI MBOHVBHF TFSWJDFT JOUP 5VSLJTI MBOHVBHF

" TUSVDUVSFE BCTUSBDU JT OPU SFRVJSFE XJUI SFWJFX BSUJDMFT BOE DBTF SFQPSUT

Keywords

#FMPX UIF BCTUSBDU QSPWJEF UP LFZXPSET CZ VTJOH .FEJDBM 4VCKFDU)FBEJOHT .F4) MJTU CF VTFE BT LFZXPSET ,FZXPSET TIPVME CF QJDLFE GSPN .F4) MJTU

4VCKFDU)FBEJOHT .F4) MJTU XXX OMN OJI HPW NFTI .F4)IPNF IUNM

5VSLJTI BCTUSBDUT TIPVME IBWF LFZXPSET i"OBIUBS #JMJNMFSu GSPN XXX CUJGEJ[JO DPN VOEFS i5ÛSLJZF #JMJN 5FSJNMFSJu

4FWFSBM UZQFT PG NBOVTDSJQUT TIPVME DPOUBJO VQ UP UIF GPMMPXJOH OVNCFS PG XPSET SFGFSFODFT BOE BVUIPST BT TVNNBSJ[FE JO 5BCMF

$PQZSJHIU USBOTGFS GPSNT UIF DPWFS MFUUFS

Table 1. .BOVTDSJQU MFOHUI BOE BVUIPS MJNJUT

"SUJDMF UZQF	5FYU -FOHUI Count*	Maximum Number of Authors	Maximum Number of 3FGFSFODFT
0SJHJOBM 3FTFBSDI	XPSET	XPSET QBHFT	NA
$BTF 3FQPSU	XPSET	XPSET QBHFT	
4ZTUFNBUJD 3FWJFX	XPSET	XPSET QBHFT	
$VSSFOU $PNNFOUBSZ	XPSET	XPSET QBHFT	
1SPDFEVSF BOE *OTUSVNFOU	XPSET	XPSET QBHFT	
-FUUFST	NA	XPSET	

.BOVTDSJQU MFOHUI JODMVEFT BMM QBHFT JO B NBOVTDSJQU JF CPEYT àHVSFT MFHFOET BOE BDLOPXMFEHFNFOUT DPNQPOFOUT TIPVME CF FYDMVEFE GSPN XPSE DPVOUJOH
–BQQSPYJNBUFMZ /" OPU BQQMJDBCMF

0SJHJOBM SFTFBSDIFT TIPVME IBWF UIF GPMMPXJOH TFDUJPOT

*OUSPEVDUJPO

4UBUF DPODJTFMZ UIF QVSQPTF BOE SBUJPOBMF GPS UIF TUVEZ BOE DJUF POMZ UIF NPTU QFSUJOFOU SFGFSFODFT BT CBDLHSPVOE "WPJE B EFUBJMFE MJUFSBUVSF SFWJFX JO UIJT TFDUJPO

Materials and Methods

%FTDSJCF UIF QMBO QBUJFOUT FYQFSJNFOUBM BOJNBMT NBUFSJBM BOE DPOUSPMT NFUIPET BOE QSPDFEVSFT VUJMJ[FE BOE UIF TUBUJTUJDBM NFUIPE T FNQMPZFE JO TVGàDJFOU EFUBJM TP UIBU PUIFS JOWFTUJHBUPST DPVME SFQSPEVDF UIF XPSL *EFOUJGZ NFUIPET PG TUBUJTUJDBM BOBMZTFT VTFE BOE BQQMJDBCMF DMJOJDBM USJBMT BOE SFHJTUSBUJPO GPS UIFJS TFMFDUJPO $JUF BOZ TUBUJTUJDBM TPGUXBSF VTFE &YQSFTT Q WBMVFT UP UXP EFDJNBM QMBDFT

$MJOJDBM USJBMT TIPVME CF SFHJTUFSFE JO B QVCMJD USJBMT SFHJTUSZ BDDFQUFE CZ UIF *$.+& "DDFQUFE SFHJTUSJFT BSF MJTUFE JO UIF 3#" SFTPVSDFT BOE QBSUJDJQBOU JOGPSNFE DPOTFOU NVTU CF PCUBJOFE

4UBUF UIF HFOFSJD OBNFT PG UIF ESVHT XJUI UIF OBNF PG UIF NBOVGBDUVSFS BOE DPVOUSZ PG PSJHJO

Results

1SFTFOU UIF EFUBJMFE àOEJOHT TVQQPSUFE XJUI TUBUJTUJDBM NFUIPET 'JHVSFT BOE UBCMFT TIPVME TVQQMFNFOU UIF UFYU QSFTFOUFE JO UIF SFTVMUT TFDUJPO BOE UIFSF XJMM CF OP SFQFUJUJPO

INSTRUCTIONS FOR AUTHORS

PVUDPNF EBUB BT CPUI BCTPMVUF BOE
QSFTFOUFE UIJT XBZ JT NVDI NPSF VTF
BOE QFSDFOUBHFT TIPVME CF HJWFO JO
SJTL 8IFO BQQSPQSJBUF OVNCFS OFFEFE
PS IBSN //5I TIPVME CF TVQQMJFE
PCTFSWBUJPOT EP OPU DPNQBSF ZPVS
4VDI DPNQBSJTPOT BOE DPNNFOUT BSF

%JTDVTTJPO

#FHJO XJUI B EFTDSJQUJPO PG XIBU ZP
QVSQPTF PS PCKFDUJWFT BT TUBUFE JO UIF
BOE TJHOJàDBODF PG ZPVS àOEJOHT UP
CVU EP OPU SFQFBU UIF EFUBJMT HJWF
PQJOJPOT UP UIPTF TUSJDUMZ JOEJDBUF
ZPVS àOEJOH XJUI QSFWJPVT TUVEJFT X
EJGGFS BMUIPVHI B DPNQMFUF SFWJFX

Study Limitations

1SPWJEF JOGPSNBUJPO PO UIF MJNJUBU
CF QSFTFOUFE JO UIJT TFDUJPO " àOBM
JOGPSNBUJPO TIPVME CF QSPWJEFE JO
PG UIF %JTDVTTJPO "MUIPVHI UPQJDT
NFOUJPOFE JU JT VOOFDFTTBSZ UP TUBUF

$PODMVTJPO

5IF DPODMVTJPO PG UIF TUVEZ TIPVME
JNQPSUBOU àOEJOHT TIPVME CF IJHIMJHIUFE BOE JOUFSQSFUFE

$POõJDU PG *OUFSFTU

"VUIPST NVTU JOEJDBUF XIFUIFS PS OPU
XJUI UIF PSHBOJ[BUJPO UIBU TQPOTPSFE UIF SFTFBSDI

5IF NBJO UFYU PG DBTF SFQPSUT TIPVME
TVCIFBEJOHT

*OUSPEVDUJPO $BTF 3FQPSU %JTDVTTJPO BOE 3FGFSFODFT

3FGFSFODFT

3FGFSFODFT BSF OVNCFSFE "SBCJD
PSEFS JO XIJDI UIFZ BQQFBS JO UIF
OPU BQQFBS JO UIF BCTUSBDU BOE MJTUFE
NBOVTDSJQU 5IF QSFGFSSFE NFUIPE
VTJOH XJUIJO QBSFOUIFTFT 6TF UIF
GPS .BOVTDSJQUTu IUUQ XXX JDNK
SFDPNNFOEBUJPOT *G OVNCFS PG BVUIPST
BVUIPST GPMMPXFE CZ FU BM

6TF SFGFSFODFT GPVOE QVCMJTIFE JO
BSF HFOFSBMMZ BDDFTTJCMF 6OQVCMJTIFE EBUB
TUBUJTUJDBM QSPHSBNT QBQFST QSFTFOUFE BU NFFUJOHT BOE TZNQPTJB
BCTUSBDUT MFUUFST BOE NBOVTDSJQUT
MJTUFE JO UIF SFGFSFODFT 1BQFST
CVU OPU ZFU QVCMJTIFE iJO QSFTTu

+PVSOBM UJUMFT TIPVME DPOGPSN UP
*OEFY .FEJDVTu

Samples

+PVSOBM ,FZOFMPHMV)# 0OBMBO (3FNFEJ
#PPL DIBQUFS "ZIBO " FEJUPST
"OLBSB 5VSLFZ (VOFT 1VCMJTIJOH Q

#PPL "SJDJ " 4FMJ & /PO JOWBTJWF .BO

%JTTFSUBUJPO 4BUF UIF JNQPSUBODF

Revisions

3FWJTJPOT XJMM CF TFOU UP UIF DPSSFTQPO
SFUVSOFE BT RVJDLMZ BT QPTTJCMF JO PSEFS

XXX UKPEFSHJTJ PSH 5VSLJTI +PVSOBM PG 0

TURKISH JOURNAL OF OBSTETRICS AND GYNECOLOGY

CONTENTS

Clinical Investigations

OBSTETRICS AND GYNECOLOGY

CONTENTS

Hemorrhagic corpu

Endometrial CD56+ natural killer cells in women with recurrent implantation failure: An immunohistochemical study

7HNUDUOD\DQ LPSODQWDV\RQ EDüDU
&' QDW•UHO NLOOHUU K•FUHOHUL þ

*XOFKLQ %DED\HYD[1] (PUH 3XUXDW[2] 6LEHO 2WUDEL[3] $ODNXü
0HKPHW &HQJL][1] dRODNRÿOX

[1]Necmettin Erbakan University Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey
[2]=H\QHS .DPLO :RPHQ DQG &KLOGUHQ 'LVHDVHV 7UDLQLQJ DQG 5HVHDUFK +RVSLWD
[3]Necmettin Erbakan University Meram Faculty of Medicine, Department of Pathology, Konya, Turkey

$EVWUDFW

2EMHFWLYH ,PSODQWDWLRQ IDLOXUH LV D PXOWLIDFWRULDO SUREOHP RI UHSURGXFWLYH
7KHUH LV LQFUHDVLQJ HYLGHQFH WKDW WKHVH FDVHV RI UHFXUUHQW LPSODQWDWLRQ
provide immune-modulation at the interface between maternal decidua and the trophoblast. The aim of this study to evaluate whether there was a significa
difference in the number of endometrial CD56+ NK between women with a history of recurrent implantation failure and women who had a live birth.
0DWHULDOV DQG 0HWKRGV Patients with a history of recurrent implantation failure were included in the study. Twenty-five women with
implantation failure were assigned to the case group, and 25 women who had one or more live births were assigned to the control group. Endometri
biopsies were obtained during the luteal phase on the 21st day of the menstrual cycle.
Results: 7KHUH ZDV D VWDWLVWLFDOO\ VLJQLILFDQW GLIIHUHQFH EHWZHHQ WKH JURXSV
The mean number of uNK was 10.5±10.5 cells/mm² in the case group and 19.2±11.2 cells/mm² in the control group. There was a statistically significant
GLIIHUHQFH EHWZHHQ WKH WZR JURXSV S
&RQFOXVLRQ Implantation failure is a multifactorial problem of reproductive medicine. The results of our study suggest that uterine NK play a
progress of normal pregnancy and reduced uterine NK cell numbers were associated with implantation failure.

.H\ZRUGV CD56, immunohistochemistry, in vitro IHUWLOL]DWLRQ UHFXUUHQW LPSODQWDWLRQ IDLOXU

Öz

$PDo þPSODQWDV\RQ EDüDU×V×]O×NODU× UHSURG•NWLI W×EE×Q PXOWLIDNW|UL\HO EL
\×OODUGD PHNDQL]PDV×QGD LPP•QRORMLN IDNW|UOHULQ HWNLOL ROGXÿXQD GDLU NDQ
DUDV×QGD LPP•Q PRG•ODV\RQX VDÿODU dDO×üPDP×]×Q DPDF× WHNUDUOD\DQ LPSODQWD
X1. K•FUHOHUL Do×V×QGDQ IDUN ROXS ROPDG×ÿ×Q×Q DUDüW×U×OPDV×G×U
*HUHo YH <|QWHPOHU dDO×üPD\D WHNUDUOD\DQ LPSODQWDV\RQ EDüDU×V×]O×ÿ× RODQ
JUXEXQX FDQO× GRÿXP |\N•V• RODQ NDG×Q LVH NRQWURO JUXEXQX ROXüWXUGX (Q
OXWHDO ID]GD DO×QG× +HU LNL JUXS X1. Do×V×QGDQ NDUü×OD üW×U×OG×
%XOJXODU +HU LNL JUXS DUDV×QGD FDQO× GRÿXP S YH G•ü•N VD\×V× S D
10,5±10,5 cells/mm² idi. Kontrol grubunda ise 19,2±11,2 cells/mm² LGL 2OJX JUXEXQGD X1. VD\×V× DQODPO× RODUDN
6RQXo þPSODQWDV\RQ EDüDU×V×]O×NODU× UHSURG•NWLI W×EE×Q PXOWLIDNW|UL\HO EL
URO R\QDG×ÿ× YH VD\×ODU×Q×Q D]DOPDV×Q×Q WHNUDUOD\DQ LPSODQWDV\RQ EDüDU×V×

$QDKWDU .HOLPHOHU &' LPP•QRKLVWRNLP\D in vitro IHUWLOL]DV\RQ WHNUDUOD\DQ LPS

PRECIS: We evaluated whether there was an effect of the number of endometrial CD56+ NK on women with a history of recurrent implantation failure.

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL *XOFKLQ %DED\HYD 0'
Necmettin Erbakan University Meram Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey
Phone: +090 332 223 60 00 (PDLO drgunuvar@gmail.com 25&,' ,' orcid.org/0000-0003-1519-2255

5HFHLYHG *HOLü 7DULKL 24.09.2019 $FFHSWHG .DEXO 7DULKL 18.10.2020

,QWURGXFWLRQ

Accomplished implantation of an eight-cell embryo into the endometrium is mandatory for reproduction. The rate of successful implantation of an embryo is approximately 30% Implantation failure is a multifactorial problem of reproductive PHGLFLQH 5HFXUUHQW LPSODQWDWLRQ as a failure of pregnancy after at least three previous assisted reproductive technique cycles, or implantation failure with a WUDQVIHU RI PRUH WKDQ IRXU HPEU\RV RI +XPDQ 5HSURGXFWLRQ DQG (PE SUHJQDQF\ UHTXLUHV V\QFKURQL]DWLRQ DQG HQGRPHWULXP +RZHYHU WKH still not fully understood.

There is increasing evidence that these cases of RIF might have an immunologic background. The endometrium plays a role in implantation physiology via immune cells, cytokines, and chemokines. Multiple kinds of immune cells are potentially involved in supporting immune tolerance during implantation and successful ongoing pregnancy. Uterine natural killer X1. FHOOV H[SUHVV WKHLU VSHFLILF FHOO VXUIDFH PDUNHU &' differ from blood NK cells. These uNK cells are the dominant OHXNRF\WH SRSXODWLRQ RI X decidua at the time of implantation and early placentation Although the function of uNK cells is uncertain, the regulation of uNK cells at the time of eight-cell embryo implantation is thought to feature in implantation. In a normal pregnancy, uNK cells provide immune-modulation at the interface between decidual tissue and trophoblast. We aimed to evaluate whether there was a significant difference in the count of endometrial CD56+ NK between women with RIF and women who had a live birth.

Materials and Methods

3DUWLFLSDQWV DQG 6WXG\ 'HVLJQ

Twenty-five women with RIF and 25 women who had one or more live births between January 2012 and December 2017 were included in the study. RIF was defined as the failure of good quality embryos to implant after at least 3 cycles of IVF :RPHQ ZLWK SRVLWLYH IRU DQWL S anticardiolipin IgM and IgG, anti-DNA, antiphospholipid IgM DQG ,J* DQWL WR[RSODVPD ,J0 D excluded from the study. Women with abnormal thyroid function tests results, anti-thrombin III deficiency, protein C RU 6 GHILFLHQF\ IDFWRU 9 /HLGHQ mutation, mutation of MTHFR C677T gene, and/or mutation of MTHFR A1298C gene were also excluded from the study +\VWHURVDOSLQJRJUDSK\ ZDV SHUI before the procedure and there were no abnormal findings Twenty-five women who had one or more live births were assigned to the control group. None of the 25 women in the control group received assisted reproduction treatment at any WLPH 7KH ORFDO HWKLFV FRPPLWW QR 7KH SDWLHQWV ZHUH LQ writing.

&ROOHFWLRQ RI 7LVVXH 6DPSOHV ([DPLQDWLRQ

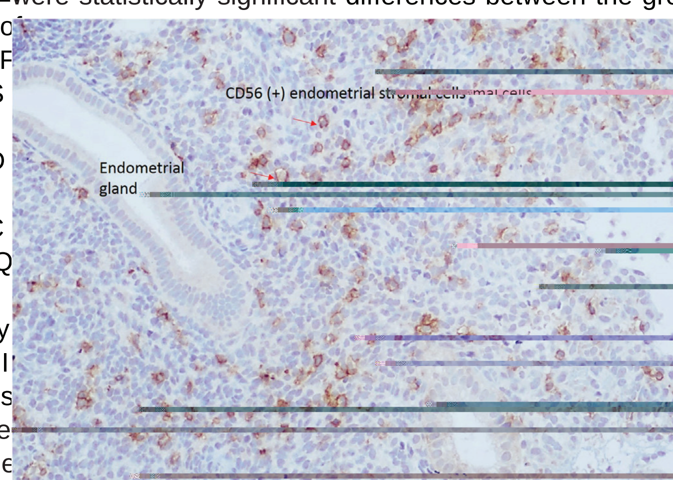
Endometrial biopsies were obtained during the luteal phase on the 21-24th day of the menstrual cycle using the Pipelle device and fixed in 10% formaldehyde. Formalin-fixed and paraffin-embedded tissue samples were incubated for PLQ EXWKH ZLWK SHQ &6 RFLSHULPDU\ %\ RORJ\GLD XWRFKVVPVRXRFDWUD /DER ZLWK EHWZHHQ 'DNR 6$UR $\VWHP +53 ,PPXQRKLVWRFKHPLFDO PDUNHU 6\VWHP +53 'DNR 1RUWK $PHULFD ,QF $PLQRHWK\O chromogen was added for 15 minutes. Paraffin-embedded tissue samples were stained using Mayer's hematoxylin. The same pathologist evaluated all samples using an Olympus BX53 microscope at 400x magnification. CD56+ cell counts were determined as cells/mm²)LJXUH

6WDWLVWLFDO $QDO\VLV

'DWD ZHUH DQDO\]HG XVLQJ WKH 6366 %0 6366 6WDWLVWLFV IRU :LQGRZV +LVWRJUDP QRUPDOLW\ SORWV DQG WHVW ZHUH XVHG WR DQDO\]H GDWD PHDQ VWDQGDUG GHYLDWLRQ PHGL XVHG LQ WKH DQDO\VLV RI TXDQWLWDWLYH RU)LVKHU·V ([DFW WHVW ZDV XVHG W Mann-Whitney U test was used in the analysis of quantitative GDWD 6WDWLVWLFDO VLJQLILFDQFH Z

Results

Twenty-five women with RIF and 25 women as fertile controls were included in the study. The parental chromosomes were normal in all women. The mean ages of the case and control groups were 33.5±5.6 and 34.4±5.3 years, respectively. The WZR JURXSV ZHUH VLPLODU LQ WHUP were statistically significant differences between the groups in



)LJXUH CD56+ cells were shown in the endometrial tissue

WHUPV RI WKH QXPEHU RI GHOLYHULHV S DQG PLVFDUULDJHV S 7DEOH 7KH PHDQ QXPEHU RI X1. ZDV cells/mm² in the case group and 19.2±11.2 cells/mm² in the control group. There was a statistically significant difference EHWZHHQ WKH WZR JURXSV LQ WHUPV RI X1. S 7DEOH 7KHUH ZDV D VLJQLILFDQW SRVLWLYH FRUUHODWLRQ EHWZHHQ the number of uNK cells and the number of miscarriages U S 7KHUH ZDV DOVR D VLJQLILFDQW SRVLWLYH correlation between the number of uNKs and the number of OLYH ELUWK U S &RUUHODWLRQ FRHIILFLHQWV RI parity, live birth, miscarriages, and uNK of the patient group are shown in Table 2.

Discussion

The endometrial leukocyte population consists of T-cells, macrophages, and natural killer cells. T-cells constitute 45% of leukocytes in the proliferative phase. Although their numbers remain constant throughout the cycle, their rate in proliferative phase is higher compared with other types of leukocytes. The most important leukocyte population in the endometrium comprises uNK cells. These lymphocytes contain the NK cell surface antigen CD56. During the implantation, large granular lymphocytes constitute 70-80% of the leukocyte population, and if conception occurs, their number increases more. UNK cells are particularly abundant in the uterus at the time of implantation and are in close contact with placental trophoblast FHOOV 81. FHOOV KDYH D PDMRU UROH LQ WKH LPSODQWDWLRQ DQG GHYHORSPHQW RI WKH SODFHQWD DQG YDVFXODULJDWLRQ ,W OLPLWV WK trophoblast invasion to decidua. In the absence of implantation,

7DEOH Patient demographics and comparison of the number of endometrial CD56+ NK between groups

	,PSODQWDWLRQ IDLOXUH	Controls QQ	p
Age (years)	33.5±5.6	34.4±5.3	0.224
No. of deliveries	0		
1R RI PLVFDUULDJHV	0		
uNK	10.5±10.5	19.2±11.2	

uNK: Uterine natural killer

uNK cells undergo apoptosis and are therefore thought to play a role in the initiation of menstrual bleeding. UNK cells also secrete several growth factors involved in angiogenesis, such as VEGF, placental growth factor, and angiopoietin-2. Giuliani et al. found that the number of endometrial CD56+ cells was not significantly different in women with recurrent pregnancy loss. By contrast, Quenby et al. demonstrated that the mean count of uNK cells was significantly higher in women with recurrent pregnancy loss than women with had a live birth history. Clifford et al. also described increased expression of uNK in 29 women with recurrent pregnancy loss. 6LPLODUO\ in the current study, there was a positive correlation between the number of miscarriages and the amount of endometrial CD56+ cells. There was also a positive correlation between the number of live births and the number of endometrial CD56+ cells. Different etiologies except for reduced uNK, such as chromosomal abnormalities, could be a reason for miscarriage. 6DFNV DQG)LQQ found that uNK numbers increased dramatically from about 5% of stromal cells in the follicular and early luteal phases of the menstrual cycle to 30-40% of stromal cells in the mid and late luteal phases when implantation occurred. Gaynor and Colucci indicated that uNK numbers increased further to as much as 70% of stromal cells if implantation occurred. The current study demonstrated that there was a positive correlation between the number of live births and the number of endometrial CD56+ cells, and there was also a significantly reduced density of CD56+ cells in women with recurrent implantation failure. In contrast, Tuckerman et al. found that the high density of CD56+ cells in the endometrium of women with RIF was directly involved LQ LPSODQWDWLRQ GXUDWLRQ found $GGLWLRQDOO\ a higher density of endometrial CD56+ cells in women with RIF than in controls. They suggested that testing for endometrial NK cells might be helpful in women with idiopathic RIF during the luteal phase.

:H DFNQRZOHGJH WKDW WKH VPDOO nature, and lack of the chromosome analysis of the miscarriage tissues are the main limitations of the study. Increasing the number of patients and including other subgroups of CD 56+ cells to the study may help explain the mechanism.

7DEOH Correlation coefficients of parity, live births, miscarriages, and uNK of the patient group

	3DULW\		/LYH ELUWK		0LVFDUULDJHV		uNK	
	r	p	r	p	r	p	r	p
3DULW\	1		0.870		0.963		0.476	
/LYH ELUWK	0.870		1.000		0.827		0.463	0.001
0LVFDUULDJHV	0.963		0.827		1		0.430	0.002
uNK	0.476		0.463	0.001	0.430	0.002	1	

uNK: Uterine natural killer

Conclusion

Implantation failure is a multifactorial problem of reproductive PHGLFLQH +RZHYHU WKH PHFKDQLVP RI WKLV SURFHVV LV VWLOO QRW fully understood. The results of our study suggest that uNKs play a role in the progress of normal pregnancy and reduced uNK cell numbers were associated with implantation failure. We believe that further studies will explain the role of these cells in the etiology.

(WKLFV

(WKLFV &RPPLWWHH The local ethics committee DSSURYHG WKH VWXG\ DSSURYDO QR

,QIRUPHG &RQVHQW The patients were informed orally and in writing.

3HHU UHYLHZ Externally and internally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

&RQFHSW %* 32 0&d 'HVLJQ <(3 5$ 0&d 'DWD Collection or Processing: P.O., R.A., Analysis or Interpretation: 32 5$ /LWHUDWXUH 6HDUFK 32 5$:ULWLQJ <(3 %* R.A., G.B.

&RQIOLFW RI ,QWHUHVW The authors report no conflict of interest.

)LQDQFLDO 'LVFORVXUH Authors have no financial interests about the research.

References

&RXJKODQ & /HGJHU : :DQJ 4 /LX) 'HPLURO $ *XUJDQ 7 HW DO Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28:14-38.

9DQ 0RXULN 06 0DFNORQ 16 +HLMQHQ &- (RJHUIRQ cytokines, adhesion molecules, and immune cells in establishing an LPSODQWDWLRQ HQYLURQPHQW - /HXNRF %LRO

%ROLV 6 7RPHWWHQ 0 .DQGLO - +DJHQ (,QWHUFHOOXODU DGKHVLRQ PROHFXOH mediator capable of disrupting immune integration and tolerance mechanism at the feto-maternal interface in murine pregnancies. J Immunol 2005;174:1820-9.

.RRSPDQ /$ .RSFRZ +' 5\EDORY % %R\ 6FKDW]) HW DO +XPDQ GHFLGXDO QDW NK cell subset with immunomodulatory potential. J Exp Med 2003;198:1201-12.

1DJOHU $ /DQLHU / &ZLUOD 6 3KLOOLSV human FcRIII-positive and negative natural killer cells. J Immunol 1989;143:3183-91.

*LXOLDQL (3DUNLQ ./ /HVVH\ %$ <RX &KDUDFWHUL]DWLRQ RI XWHULQH 1. FHOO recurrent pregnancy loss and associated endometriosis. Am J Reprod Immunol 2014;72:262-9.

4XHQE\ 6 9LQFH *)DUTXKDUVRQ 5 $SOL D GHIHFW LQ QDWXUH·V TXDOLW\ FRQWURO

&OLIIRUG .)OHDQDJDQ $ 5HJDQ / (QGRPH cells in women with recurrent miscarriage: a histomorphometric VWXG\ +XP 5HSURG

6DFNV *)LQNHOVWHLQ (1DWXUDO NLOOH Am J Reprod Immunol 2020:e13291.

*DLQ RU /0 &ROXFFL) 8WHULQH 1DWXUD 'LVWLQFWLRQV DQG ,QIOXHQFH RQ 3UHJ Front Immunol 2017;8:467.

7XFNHUPDQ (0DULHH 1 3UDNDVK $ /L natural killer cells in peri-implantation endometrium from women with repeated implantation failure after IVF. J Reprod Immunol 2010;87:60-6.

6DQWLOODQ , /R]DQR , /R]DQR 0 0DQQ - 9HUG Where and when should natural killer cells be tested in women with repeated implantation failure? J Reprod Immunol 2015;108:142-8.

Comparison of intramuscular versus subcutaneous aqueous progesterone for luteal phase support in artificially prepared frozen embryo transfer cycles

+RUPRQ UHSODVPDQ× LOH KD]×UODQP× VLNOXVODU×QGD LQWUDPXVN•OHU SUR SURJHVWHURQXQ OXWHDO ID] GHVWHÿL

(PUH 1L\D]L 7XUJXW .•EUD % RQXU 0•IWý =DIHU ÿDQL .DUD <DUN×QHU 0XVWDID %DKoHFL

[1]%DKoHFL +HDOWK *URXS)XO\D ,9) &HQWHU þVWDQEXO 7XUNH\
[2]Cyprus Science University, Fakulty of Medrome, Department of Statistics, Kyrenia, Cyprus

$EVWUDFW

2EMHFWLYH Cryopreservation of embryos for future transfer attempts has noticeably increased in the last decade, especially due to the developments in in vitro IHUWLO]DWLRQ ,9) ODERUDWRULHV ,Q SDUDOOHO GLIIHUHQW SURJHV HPEU\R WUDQVIHU $&)(7 DWWHPSWV HVSHFLDOO\ ZLWK UHVSHFW WR WKH URXWH RI SURYLGH PRUH LQIRUPDWLRQ DERXW WKH HIILFDF\ SURILOH RI QRYHO VXEFXWDQHRXV 0DWHULDOV DQG 0HWKRGV This retrospective, single-centre cohort study included a total of 507 AC-FET cycles performed betwe 7KUHH KXQGUHG IRUW\ QLQH SDWLHQWV UHFHLYHG PJ RI LQWUDPXVFXODU DV WZLFH GDLO\ 2QO\ WKH ILUVW DQG VLQJOH EODVWRF\VW WUDQVIHUV IURP WKH VD \HDUV ERG\ PDVV LQGH[NJP FRQFHQWUDWLRQ JHQHWLF WHVWLQJ F RXWFRPH ZDV WKH OLYH ELUWK UDWH /%5
Results: 7KH QXPEHU RI SUHYLRXV ,9) DWWHPSWV W\SH RI LQIHUWLOLW\ SHDN HVWUDGLR QXPEHU RI 31 ZDV VLJQLILFDQWO\ GLIIHUHQW EHWZHHQ WKH JURXSV 3RVLWLYH SUHJQ PLVVHG DERUWLRQ UDWHV S ZHUH FRPSDUDEOH EHWZHHQ WKH JURXSV 7KH WRWD LQWHUYDO &, S @ HQGRPHWULDO WKLFNQHVV $25 &, &, S DFKLHYHG VWDWLVWLFDO VLJQLILFDQFH IROORZLQJ ELQDU\ ORJLVW VWDWLVWLFDO VLJQLILFDQFH S
&RQFOXVLRQ $V D QRYHO RSWLRQ 63 KDV FRPSDUDEOH HIILFDF\ LQ SUHJQDQF\ RXWFR FET cycles.

.H\ZRUGV 6XEFXWDQHRXV DTXHRXV SURJHVWHURQH LQWUDPXVFXODU SURJHVWHURQH

Öz

$PDo 6RQ RQ \×OGD in vitro IHUWLOL]DV\RQ ,9) ODERUDWXYDU×QGD PH\GDQD JHOHQ WHNQR EX HPEUL\RODU×Q JHOHFHNWHNL WUDQVIHU LüOHP VD\×ODU× IDUN HGLOLU ELU üHNLOG o|]•OP•ü HPEUL\R WUDQVIHUL +5 'd(7 |QFHVL X\JXODQDQ SURJHVWHURQ 3 \HULQH NR oRN WDUW×ü×OPD\D EDüODQP×üW×U %X oDO×üPDGD \HQL ELU IRUP•ODV\RQ RODQ VX ED GDKD ID]OD ELOJL HGLQPH\L DPDoODG×N

PRECIS: 6XEFXWDQHRXV DTXHRXV SURJHVWHURQH LV DQ HIIHFWLYH DOWHUQDWLYH transfer cycles.

$GGUHVV IRU &RUUHVSRQGHQFH (PUH 1L\D]L 7XUJXW 0'
%DKoHFL +HDOWK *URXS)XO\D ,9) &HQWHU þVWDQEXO 7XUNH\
Phone: +90 533 641 20 10 (PDLO dremreturgut@gmail.com 25&,' ,' orcid.org/0000-0002-5986-3121
5HFHLYHG *HOLü 7DULKL 17.06.2020 $FFHSWHG .DEXO 7DULKL 18.10.2020

*HUHo YH <|QWHPOHU 5HWURVSHNWLI WHN PHUNH]OL NRKRUW oDO×üPDV× RODUDN GL]
WDQH +5 'd(7 VLNOXVXQX LoHUPHNWHGLU +DVWDODU×Q ·XQGD PJ LQWUDP
63 J•QGH LNL GHID NXOODQ×OG× $\Q× WHGDYL VLNOXVXQGD HOGH HGLOHQ YH GRQDGXU
KDVWDQ×Q WHNUDUOD\DQ WHGDYL VLNOXVODU× oDO×üPD\D GDKLO HGLOPHGL 2 VpHUP 2 LO HG
NRQVDQWUD6VRRQ•D[UDN NDEXO HGLOGL 3UHLPSODQWDV\RQ JHQHWLN WDQ× X\JXODQDQ
RUDQODU× /%5 HOH DO×QG×
%XOJXODU gQFHNL ,9) GHQHPH VD\×V× LQIHUWLOLWH WLSL]LJRW VHUXP HVWUDGLRO
IDUNO×O×N J|VWHUGL 3R]LWLI JHEHOLN S NOLQLN JHEHOLN S YH /%5 S
EHQ]HUGL þNLOL ORMLVWLN UHJUHV\RQ DQDOL]LQGH WRSODQDQ RRVLW VD\×V× >D\DU
HQGRPHWUL\DO NDO×QO×N $25 &, S YH NUL\RSUH]HUYDV\RQ J•Q
RODUDN DQODPO× EXOXQGX)DNDW NXOODQ×ODQ 3 WLSL /%5 VRQXoODU×QGD DQODPO×
6RQXo 63 HQMHNVL\RQODU× JHEHOLN VRQXoODU× •]HULQGH NDUü×ODüW×U×ODELOLU EL
$QDKWDU .HOLPHOHU 6XEN•WDQ|] SURJHVWHURQ LQWUDP•VN•OHU SURJHVWHURQ GRQ

Introduction

Almost 37 years ago, the first human pregnancy was reported IROORZLQJ IUR]HQ HPEU\R WUDQVIHU)(7. Following the developments in the in vitro IHUWLOL]DWLRQ ,9) ILHOG WKH cryopreservation of embryos and subsequent FET strategy has doubled in the last decade. Artificial endometrial preparation is one of the methods used for FET cycles and has been found as successful as the other approaches. In these cycles, minimal monitoring is required, and the timing of embryo transfer and LQLWLDWLRQ RI SURJHVWHURQH. Therefore, 3 LV PRUH IOH[LEOH it allows both the physicians and embryology staff to easily RUJDQL]H GDLO\ EXVLQHVV SODQQLQJ.

Exogeneous P replacement is preceded by estrogen supplementation and its use is mandatory to prepare the endometrium for successful implantation and the survival of the pregnancy. Exogeneous P can be administered by different routes: intramuscular, vaginal, oral, rectal, and recently, subcutaneous. Oral micronised P formulations are exposed to the first-pass effect within the liver, hence they have a low effect profile. Vaginal formulations such as capsules, gels or suppositories showed a similar efficacy profile when compared with each other or by the intramuscular route. +RZHYHU GHEDWHV UHJDUGLQJ WKH WLPH RI LQLWLDWLRQ ... WLPLQJ IRU OXWHDO SKDVH VXSSRUW /36 ... 2LO EDVHG LQWUDPXVFXODU SURJHVWHURQH ... painful and may cause serious adverse effects such as skin inflammation and sterile abscesses, but they have been found to decrease subendometrial uterine contractility better than YDJLQDO SURJHVWHURQH 93 DQG WKLV SRVLWLYH HIIHFW KDV EHHQ related to increased pregnancy outcomes and decreased rates of embryo displacement following the attachment process.

In the light of new technological developments, subcutaneous DTXHRXV SURJHVWHURQH 63 KDV ... and absorbable state by the addition of `-cyclodextrin. Two UDQGRPL]HG FRQWUROOHG WULDOV 5&7 ... F\FOHV FRPSDUHG WKH HIILFDF\ RI 63 ... RQJRLQJ SUHJQDQF\ UDWHV 235V ... . Regarding the degree of acceptance and satisfaction, the authors found significantly increased acceptance rates for the 63 URXWH FRPSDUHG ZLWK 93

7KH XVH RI 63 FRQWLQXHV WR JDLQ SR...

Today, most physicians use VP or IMP regimens, alone or in FRPELQDWLRQ IRU /36 &XUUHQWO\ ... the effectiveness of the new formulation in artificially prepared)(7 $&)(7 F\FOHV 7KHUHIRUH LQ R... to contribute to the literature by comparing two different P UHSODFHPHQW UHJLPHQV 63 YV ,03 L... AC-FET cycles.

Materials and Methods

'HVLJQ

In this retrospective, single-center cohort study, we reviewed the pregnancy outcomes of 507 AC-FET cycles, performed between June 2018 and April 2020 in Bahceci Fulya IVF centre. The reason for choosing the time interval in this way was the LQWURGXFWLRQ RI WKH 63 IRUPXODWLRQ... Ethics approval was obtained from the institutional review ERDUG DSSURYDO QXPEHU GDWH ... experience and reports in the literature, we switched to the IUHH]H DOO DQG VXEVHTXHQW)(7 VWU... due to its superior reproductive outcomes compared with fresh transfer. Only the first single blastocyst transfers from the same cohort were included in the study. The eligibility criteria IRU WKH FRXSOHV ZHUH DV IROORZV IH... LQGH[%0, [2]•DQG ... ,03 SUHSDUDWLRQV DUH ... Sperm concentration •[[6]. Couples with a history of repeated implantation IDLOXUH ! UHFXUUHQW PLVFDUULD... for intrauterine adhesions, submucosal fibroids and mullerian DQRPDOLHV XQLFRUQXDWH ELFRUQX... excluded from the study. Also, couples carrying chromosomal abnormalities and preimplantation genetic testing cycles were not included.

2YDULDQ 6WLPXODWLRQ 3URWRFRO 6HOHFWLRQ

7KH JRQDGRWURSLQ UHOHDVLQJ KRU... protocol was the preferred method for ovarian stimulation. On the 2nd or 3rd day of the menstrual cycle, gonadotrophin LQMHFWLRQV ZHUH VWDUWHG /%5 ... KRUPRQH *RQDO) 0HUFN 6HURQR *H... highly purified KXPDQ PHQRSDXVH JRQDGRWU... ,8 0HULRQDO ,%6$ SUHSDUDWL...

were designated at the physician's preference. When the
OHDGLQJ IROOLFOH H[FHHGHG PP
DQWDJRQLVW &HWURWLGH 6HURQR
of maturation trigger. Maturation of the oocytes was induced either with the use of 250 µg of human chorionic gonadotropin
K&* 2YLWUHOOH 6HURQR RU
)HUULQJ 7UDQVYDJLQDO VRQRJUDSK\ 79 86* JXLGHG RRF\WH
retrieval was performed 35-36 hours later.

/DERUDWRU\ 3URFHVV

After the denudation process, each metaphase II oocyte
ZDV LQMHFWHG ZLWK VSHUP XVLQ
LQMHFWLRQ WHFKQLTXH DQG FXOW
HTXLOLEUDWHG FXOWXUH GLVK $
KRXUV DIWHU LQVHPLQDWLRQ
6FLHQWLILF &$ 86$ ZDV XVHG WKU
period. Blastocyst quality assessment was performed on day 5 or 6 by two senior embryologists, with the aid of a morphology-based three-part scoring system as described previously. Once the embryo reached the expansion degree of at least 3,
YLWULILFDWLRQ ZDV SHUIRUPHG IRU
RI EODVWRF\VWV ZDV DV IROORZV
RU DQG $% $& %$ %% SRRU
RU &$

$UWLILFLDO 3UHSDUDWLRQ RI)(7 &\FOH

Endometrial preparation was started on day 2 or 3 of menstrual
EOHHGLQJ ZLWK HVWUDGLRO YDOHU
'HQPDUN DW D GRVDJH RI PJ GD\
implemented. Follow-up visits were performed between day 10 and 14 of treatment. Endometrial thickness was measured
XVLQJ 79 86* DQG EORRG ZDV GUDZQ
(DQG 3 OHYHOV 7KH GRVDJH RI (
GD\ LI WKH WKLFNQHVV ZDV PP DQG
visit was planned within the next seven days for confirmation.
$FFRUGLQJ WR WKH SDWLHQW·V DQG SK\VLFLDQ·V SUHIHUHQFH /36 ZDV
LQLWLDWHG HLWKHU ZLWK PJ ,03
)DUPD 7XUNH\ RQFH SHU GD\ RU ZLWK
,%6$ 6ZLW]HUODQG LQMHFWLRQV
ZDV LQMHFWHG EHWZHHQ DQG SP
UHSHDWHG HYHU\ KRXUV DW WKH
LQMHFWLRQ WKH ILUVW GRVH ZDV
DQG WKH VHFRQG GRVH ZDV LQMHF
scheme was followed every day. In our daily routine, all transfers are performed between 4 pm and 7 pm. Accordingly, FET was performed following the 5th dose of IMP and the 11th GRVH RI 63
DGPLQLVWUDWLRQ 6HUXP
β-hCG levels were measured 12 days after
)(7 DQG OHYHOV • ,8 ZHUH DFFHSWHG DV SRVLWLYH $IWHU ZDUGV (
replacement was stopped at the 6th week of pregnancy, whereas P was continued until 10 weeks in both arms.

2XWFRPHV

3ULPDU\ RXWFRPH ZDV WKH /%5 SHU
SUHJQDQF\ &3 ZDV GHILQHG DV

intrauterine gestational sac at 6-7 weeks of pregnancy. Missed
DERUWLRQ ZDV GHILQHG DV D &3
gestation.

6WDWLVWLFDO $QDO\VLV

)RU WKH ILUVW VWHS WKH .ROPRJRURY
PJ WULSWRUHOLQ *RQDSHSW\O
tests were performed to understand whether the continuous variables followed a normal distribution. Accordingly, the
PHGLDQ TXDUWLOH TXDUWLOH YD
reported in the tables. Afterwards, the independent samples median test was run to determine if there were differences in continuous parameters between patients in the two treatment groups. The chi-square test was performed to test the significance of each categorical parameter and the results were reported as percentages.
A binary logistic regression model was performed regarding outcomes to determine whether a patient was having a live birth. In this model, female age, duration of infertility, sperm concentration, type of infertility, total number of retrieved
RRF\WHV HQGRPHWULDO WKLFNQHVV
HQ(7 DQG WKH ,$ RI 3 DGPLQLVWUDWLRQ
as independent variables. The backward conditional procedure was used and variables that were not statistically significant were removed from the model. The final binary logistic model reported only the statistically significant parameters. To
PHDVXUH WKH HIIHFW RI HDFK VLJQLILFDQW
DQG DGMXVWHG RGGV UDWLRV ZHUH
8$25 LQGLFDWHG WKH HIIHFW RI HDFK
other factors were eliminated and only the specific variable
ZDV WDNHQ LQWR FRQVLGHUDWLRQ $G
calculated when all the significant independent variables were taken into account, simultaneously.

Results

All 507 patients in our study were assigned to one of the two
/36 DOWHUQDWLYHV 03 ZDV XVHG LQ
DQG 63 ZDV XVHG LQ $&)(7 F
were matched, concerning demographics, and embryologic parameters as shown in Table 1. Accordingly, the median values of the number of previous IVF attempts, peak E2 levels, the total number of oocytes, mature oocytes, and the number of
31]\JRWHV ZHUH VLJQLILFDQWO\ GLIIHUHQW
Table 2 displays the characteristics of AC-FET cycles and pregnancy outcomes. As shown, the only parameter to reach statistical significance was the peak E2 levels, which were measured on the day of or one day before the initiation of P
UHSODFHPHQW S 7KHUH ZHUH Q
EHWZHHQ JURXSV UHJDUGLQJ SRVLWLYH
&3 UDWHV S /%5V S DQG 0
Binary logistic regression analysis was performed to determine the independent variables, those which had a significant
HIIHFW RQ OLYH ELUWK RXWFRPH 7DE

7DEOH Demographics, clinical and embryologic parameters

	,03 Q	63 Q	S YDOX
Female age			0.305
%0, NJ P			0.073
Duration of infertility			0.913
Previous IVF attempts			0.003*
6SHUP FRQFHQWUDWLRQ			0.475
Type of infertility Female Male 8QH[SODLQHG 8(, Combined			0.017*
7RWDO GRVH RI JRQDGRWURSLQV ,8			0.850
3HDN (OHYHOV SJ P/			
Total number of oocytes			0.002*
No. of mature oocytes			0.003*
No. of 2PN			0.001*
)HUWLOL]DWLRQ UDWH)5			0.843
%ODVWXODWLRQ UDWH SHU 31			0.687

9DOXHV DUH UHSRUWHG DV PHGLDQ 4 4
,QGHSHQGHQW VDPSOHV PHGLDQ WHVW ZDV XVHG WR WHVW WKH PHGLDQ YDOXH EHWZHHQ WKH ,03 DQG 63
*statistically significant p-value at the _ OHYHO ,03 ,QWUDPXVFXODU SURJHVWHURQH %0, %RG\ PDVV LQGH[,9)

7DEOH Properties of FET cycles and pregnancy outcomes

	,03	SP	S YDOX
(QGRPHWULDO WKLFNQHVV PP			0.224
Cryopreservation day			
Day 5			0.907
Day 6			
Blastocyst Quality			
Excellent			
Good			0.301
Poor			
3HDN (OHYHOV LQ)(7 SJ P/			0.025*
3RVLWLYH SUHJQDQF\			0.474
&OLQLFDO SUHJQDQF\			0.979
0LVVHG $ERUWXV			0.144
/LYH ELUWK			0.404

r² WHVW ZDV XVHG WR WHVW WKH SURSRUWLRQV EHWZHHQ WKH ,03 DQG 63 JURXSV IRU FDWHJRULFDO YDU
*statistically significant p-value at the _ OHYHO
,QGHSHQGHQW VDPSOHV PHGLDQ WHVW ZDV XVHG WR WHVW WKH PHGLDQ YDOXH IRU FRQWLQXRXV YDOXH
progesterone

statistically significant, r² S 7KH PRGHO correctly classified 62.1% of cases. As shown in Table 3, H[SODLQHG ²1DJHONHUNH 5 DQ LQFUHDVH LQ and RYHUDOO concluded that variables such as the total

7DEOH /RJLVWLF UHJUHVVLRQ PRGHO RQ OLYH ELUWK RXWFRPH

					&, IRU 25	
	%	Wald	S YDOXH	OR	/RZHU	Upper
Total no. of oocytes	0.024	4.715	0.030	1.024	1.002	1.047
Endometrial thickness	0.114	4.040	0.044	1.121	1.003	1.253
Cryopreservation day						
Day 5	Reference	----	----	-----	-----	-----
Day 6	-0.864	7.338	0.007	0.421	0.226	0.788

A binary logistic regression model was used with a backward conditional procedure. The outcome variable was taken as having a live birth or not. References category on the cryopreservation day was taken as day 5.
*statistically significant p-value at the _ OHYHO &, &RQILGHQFH LQWHUYDO 25 2GGV UDWLR

number of retrieved oocytes, endometrial thickness, and cryopreservation day were statistically significant both when considered separately and when taken into analysis at the same time. AC-FET cycles using day 6 cryopreserved blastocysts resulted in a 57.9% less likely live births compared with day EODVWRF\VW WUDQVIHUV > $25 &, S @ ,W LV DOVR total number of retrieved oocytes increased by one unit, patients were 1.024 times more likely to have a live birth, and similarly, when the endometrial thickness increased by one unit, patients ZHUH WLPHV PRUH OLNHO\ WR KDYH D OLYH ELUWK $25 &, S DQG $25 S UHVSHFWLYHO\ 3 DGP DFKLHYH VWDWLVWLFDO VLJQLILFDQFH S

Discussion

As far as we know, this is the first study to compare the clinical HIILFLHQF\ SURILOHV RI WKH QRYHO IMP in AC-FET cycles. The results of our study showed non-LQIHULRU SUHJQDQF\ RXWFRPHV RI in women undergoing AC-FET compared with IMP.

For many years, owing to its insoluble properties, the only way to administer the synthetic progesterone hormone was WKURXJK LQWUDPXVFXODU LQMHFWLRQ adverse effects and causes discomfort, most studies used IMP as a reference when comparing other formulations due to its reliable contributions to pregnancy outcomes. The aim RI SURGXFLQJ D QHZ LQMHFWDEOH WKH DGYDQWDJH RI H[LVWLQJ SDU results, and to eliminate its adverse effects, complications, and negative effects on patient comfort)RU WKLV SXU et al. DVVHVVHG WKH ELRDYDLODELOL in comparison with oil-based IMP among postmenopausal and reproductive-aged women. Irrespective of the route of DGPLQLVWUDWLRQ LP DQG VF &max RI 63 SURGXFW ZHUH WLPH RI WKH RLO\ ,03 S 0RUHRYHU Cmax ZDV WLPHV VKRUWHU LQ WK safety profiles, the authors reported lower frequency and shorter duration of adverse effects, those related to hormonal FKDQJHV DQG LQMHFWLRQ VLWH UHDFW histologic changes caused by two different dosing regimens, PJ GDLO\ DQG PJ GDLO\ RI 63 Z endometrial sampling. The authors reported adequate pre-decidual transformation within the endometrial specimens of the entire cohort and concluded that the new formulation ZDV D YDOLG RSWLRQ IRU /36)URP WK QDUURZ %0, UDQJH ² LQ WKH VWXG\ be interpreted with caution and further well-designed studies could give more accurate information especially in overweight and obese women.

There is still no consensus on the best route of administration for replacement in AC-FET cycles. According to a Cochrane review, there was no significant difference between VP and IMP LQ WHUPV RI &3 0$ UDWHV DQG /%5 declared that the results were insufficient to draw a definite conclusion due to the heterogeneity between the included studies. In a more recent analysis in which VP and IMP were compared in FET cycles, similar pregnancy outcomes were reported. By contrast, Devine et al. reported decreased OPRs only in the VP group when compared with VP plus IMP DQG ,03 RQO\ DQG WKH\ WHUPLQDWH GLXP WR $ LQ WKH 7KH EURDG UDQJH RI DJH VH \HDUV DQG WKH QLQH GD\ XVH RI 93 E into account. In another study, significantly lower rates of CP and live births were reported in the VP group following day-3 FET. WHUDO LQMHFWLRQ RQ SUHJQDQF\

The main limitations of the study were the use of the slow SUHVHUYDWLRQ WHFKQLTXH IRU FU\RSUHVH WR\ RI WKH QRYHO 63 LQ VPDOO VRI to the inconsistent results mentioned in the above studies, using oral dydrogesterone for FET cycles also needs further investigation.

$V WKH ,9) SUDFWLFH LV PRYLQJ WRZDUGV NQRZ are made throughout the stimulation phase of IVF treatments. 7KH 63 IRUPXODWLRQ SURYLGHV SDWLHQWV ZLWK IDPLOLDU attempts and feel safe ZKLOH VHOI DGPLQLVWHULQJ Moreover,

WKH OHVVHU LQMHFWLRQ VLWH SDLQ related to its water-soluble content. Another advantage of 63 XVH LV SUHYHQWLQJ WKH PHVV\ GLVFKDUJH UHSRUWHG ZLWK 93 application.

6WXG\ /LPLWDWLRQV

7KH PDMRU ZHDNQHVVHV RI RXU VWXG\ DUH LWV UHWURVSHFWLYH GHVLJQ DQG ODFN RI UDQGRPL]DWLRQ IRU WKH W\SH RI 3 IRUPXODWLRQV ,WV retrospective nature is also the greatest obstacle to reaching information about patient comfort. The main reason for the VPDOO VDPSOH VL]H LV WKDW WKH 63 IRUP VWDUWHG WR EH XVHG LQ RXU country approximately two years ago. We designed this study in patients who were aged younger than 37 years to alleviate the risk of aneuploidy, which might give rise to increased rates RI DERUWLRQV)RXU KXQGUHG HLJKW\ RQH SDWLHQWV in the study were aged younger than 37 years. Due to the legal restrictions in our country, we included only single blastocyst transfers. We believe that the strict inclusion and exclusion criteria helped us to generate homogenous groups and detailed analysis of the variables added strength to our work.

Conclusion

This study provides clinical evidence that the newly developed 63 IRUPXODWLRQ KDV D FRPSDUDEOH HIILFLHQF\ SURILOH RQ SUHJQDQF\ RXWFRPHV DQG LV D VWURQJ FDQGLGDWH IRU /36 LQ $&)(7 F\FOHV Future prospective studies and RCT are needed to clarify the best way regarding various P replacement regimens.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO Ethics approval was obtained IURP WKH LQVWLWXWLRQDO UHYLHZ ERDUG 6XSSO DSSURYDO QXPEHU GDWH

,QIRUPHG &RQVHQW Retrospective study.
3HHU UHYLHZ Externally and internally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV 0 % &RQFHSW 0 % 'HVLJQ 0 % 'DWD &ROOHFWLRQ RU 3URFHVVLQJ (1 7 $QDO\VLV RU ,QWHUSUHWDWLRQ = < /LWHUDWXUH 6HDUFK (1 7 :ULWLQJ E.N.T.

&RQIOLFW RI ,QWHUHVW The authors report no conflict of interest.
)LQDQFLDO 'LVFORVXUH Authors have no financial interests about the research.

References

1. 7URXQVRQ $ 0RKU / +XPDQ SUHJQDQF\ IROORZLQJ FU\RSUHVHUYDWLRQ thawing and transfer of an eight-cell embryo. Nature 1983;305:707-9.
2. &HQWHUV IRU 'LVHDVH &RQWURO DQG 3UHYHQWLRQ $6505 6RFLHW\ IRU Assisted Reproductive Technology 2016 Assisted Reproductive 7HFKQRORJ\ 1DWLRQDO 6XPPDU\ 5HSRUW 86 'HSDUWPHQW RI +HDOWK DQG +XPDQ 6HUYLFHV KWWSV ZZZ FGF JRY DUW UHSRUWV $57 1DWLRQDO 6XPPDU\ 5HSRUW SGI
3. Ghobara T, Gelbaya TA, Ayeleke RO. Cycle regimens for IUR]HQ WKDZHG HPEU\R WUDQVIHU &RF 2017;7:CD003414.
4. 2UWHJD , 9HODVFR -$* 3URJHVWHURQH V embryo transfer cycle. Curr Opin Obstet Gynecol 2015;27:253-7.
5. 6KDSLUR ' %RRVWDQIDU 5 6LOYHUEHUJ . WKH HYLGHQFH SURJHVWHURQH VXSSOHP HPEU\R WUDQVIHU 5HSURG %LRPHG 2QOL TXL] 6
6. 9DLVEXFK (/HRQJ 0 6KRKDP = 3URJHVW evidence-based medicine translated to clinical practice? A worldwide webbased survey. Reprod Biomed Online 2012;25:139-45.
7. .OHPHQW $+ 6DPDUD 1 :HLQWUDXE $ 0L et al. Intramuscular Versus Vaginal Progesterone Administration in 0HGLFDWHG)UR]HQ (PEU\R 7UDQVIHU &\F 7ULDO $VVHVVLQJ 6XE (QGRPHWULDO &R Invest 2018;83:40-4. SDWLHQWV
8. 6KDSLUR '% 3DSSDGDNLV -$ (OOVZRUWK 3URJHVWHURQH UHSODFHPHQW ZLWK YDJ cycle and pregnancy outcomes in ivf patients receiving vitrified EODVWRF\VWV +XP 5HSURG
9. 6KLED 5 .LQXWDQL 0 2NDQR 6 .DZDQR 5)RXU 9DJLQDO 3URJHVWHURQHV IRU /XWH 7KDZHG (PEU\R 7UDQVIHU &\FOHV $ 5DQ Reprod Med Biol 2019;19:42-9.
10. *URHQHZRXG (5 &DQWLQHDX $(3 .ROOHQ BJ. What is the optimal means of preparing the endometrium in IUR]HQ WKDZHG HPEU\R WUDQVIHU F\FOH PHWD DQDO\VLV +XP 5HSURG 8SGDWH
11. &DVSHU 5) /XWHDO SKDVH VXSSRUW IRU LQWUDPXVFXODU RU YDJLQDO SURJHVWHU 8.
12. Cometti B. Pharmaceutical and clinical development of a QRYHO SURJHVWHURQH IRUPXODWLRQ 6
13. %DNHU 9/ -RQHV &$ 'RRG\ .)RXON 5 <H $ UDQGRPL]HG FRQWUROOHG WULDO FRP of aqueous subcutaneous progesterone with vaginal progesterone IRU OXWHDO SKDVH VXSSRUW RI LQ YLW 2014;29:2212-20.
14. /RFNZRRG * *ULHVLQJHU * &RPHWWL % 6 versus vaginal progesterone gel for luteal phase support in vitro IHUWLOL]DWLRQ D QRQLQIHULRULW\ UDQ 6WHULO
15. 9HQWXUHOOD 5 9DLDUHOOL $ %XIIR / 3HGUL 6 HW DO 3URJHVWHURQH IRU SX IRU IUR]HQ WKDZHG EODVWRF\VW WUDQV a prospective study on patients' opinions on a new subcutaneous formulation. Gynecol Endocrinol 2018;34:766-71.
16. 6KDSLUR %6 'DQHVKPDQG 67 *DUQHU)& 7KRPDV 6 (YLGHQFH RI LPSDLUHG HQGRPH VWLPXODWLRQ IRU LQ YLWUR IHUWLOL]D WULDO FRPSDULQJ IUHVK DQG IUR]HQ WK UHVSRQGHUV)HUWLO 6WHULO
17. 6KDSLUR %6 'DQHVKPDQG 67 *DUQHU)& 7KRPDV 6 (YLGHQFH RI LPSDLUHG HQGRPH VWXG\ HYDOXDWLQJ HQGRPHWULDO PRUSKRORJ\ LQ IUHVK DQG IUR]HQ WKDZHG H UHVSRQGHUV)HUWLO 6WHULO

Gardner DK, Schoolcraft WB. Culture and transfer of human blastocysts. Curr Opin Obstet Gynecol 1999;11:307-11.

Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril

Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M. Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study. Fertil Steril

Polyzos NP, Messini CI, Papanikolaou EG, Mauri D, Tzioras S, Badawy A, et al. Vaginal progesterone gel for luteal phase support in IVF/ICSI cycles: a meta-analysis. Fertil Steril

Silverberg KM, Vaughn TC, Hansard LJ, Burger NZ, Minter T. Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial. Fertil Steril

Kaser DJ, Ginsburg ES, Missmer SA, Correia KF, Racowsky C. Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day cryopreserved embryo transfer. Fertil Steril 2012;98:1464-9.

24. Zoppetti G, Puppini N, Ospitali F, Fini A. Pharmaceutics, preformulation and drug delivery. J Pharm Sci 36.

Zoppetti G, Puppini N, Pizzutti M, Fini A, Giovani T, Comini S. Water soluble progesterone-hydroxypropyl-cyclodextrin complex for injectable formulations. J Incl Phenom Macrocycl Chem 2007;57:283-8.

Sator M, Radicioni M, Cometti B, Loprete L, et al. Pharmacokinetics and safety profile of a novel progesterone aqueous formulation administered by the s.c. route. Gynecol Endocrinol 2013;29:205-8.

de Ziegler D, Sator M, Binelli D, Leuratti C, Cometti B, Bourgain C, et al. A randomized trial comparing the endometrial effects of daily subcutaneous administration of 25 mg and 50 mg progesterone in aqueous preparation. Fertil Steril

Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar AM, Hart RJ, Ciapponi A. Endometrial Preparation for Women Undergoing Embryo Transfer with Frozen Embryos or Embryos Derived from Donor Oocytes. Cochrane Database Syst Rev CD

29. Berger BM, Phillips JA. Pregnancy outcomes in oocyte donation recipients: vaginal gel versus intramuscular oil progesterone replacement. J Assist Reprod Genet 2012;29:237-42.

Devine K, Richter KS, Widra EA, McKeeby JL. Vitrified blastocyst transfer cycles with the use of only vaginal progesterone replacement with Endometrin have inferior ongoing pregnancy rates: results from the planned interim analysis of a three-arm randomized controlled noninferiority trial. Fertil Steril

Rashidi BH, Ghazizadeh M, Tehrani Nejad ES, Bagheri M, Gorginzadeh M. Oral dydrogesterone for luteal support in frozen-thawed embryo transfer artificial cycles: a pilot randomized controlled trial. Asian Pac J Reprod 2016;5:490-4.

Zarei A, Sohail P, Parsanezhad ME, Alborzi S, Samsami A, Azizi M. Comparison of four protocols for luteal phase support in frozen-thawed embryo transfer cycles: a randomized clinical trial. Arch Gynecol Obstet 2017;295:239-46.

Turk J Obstet Gynecol 2020;17:247-252

In vitro maturation with letrozole priming: Can it be a solution for patients with cancerophobia? A pilot study

/HWUR]RO LOH LQ YLWUR PDWXUDVíRQ .DQVHU IRELVL ROODQ KDVWDODUGD ELU o|]•P RODELOLU PL

ýDIDN +DWíUDQ (UR]6D\QXU[1], -$WWSHUQDQ%D0EXLH .DQDW 3HUNEWDü
0LFKDHO[2], 6KHDQ[6] 7DQ

[1]Medicana Samsun International Hospital, Samsun, Turkey
[2]McGill University Faculty of Medicine, Department of Obstetrics and Gynecology, Montreal, Quebec, Canada
[3]Düzce University Faculty of Medicine, Department of Obstetrics and Gynecology, Düzce, Turkey
[4]Afyon Health Sciences University Hospital, Clinic of Obstetrics and Gynecology, Afyonkarahisar, Turkey
[5]Antalya Training and Research Hospital, Clinic of Obstetrics and Gynecology, Antalya, Turkey
[6]Originelle Women's Health and Fertility Center, Montreal, Quebec, Canada

$EVWUDFW

2EMHFWLYH 7R LQYHVWLJDWH ZKHWKHU OHWUR]ROH *in vitro* SULPLQJ FRXOG EH ,90 DV D FRPSOHPHQW
VWLPXODWLQJ KRUPRQH)6+ SULPLQJ
0DWHULDOV DQG 0HWKRGV 7KLV LV D UHWURVSHFWLYH DQDO\VLV RI SDWLHQWV ZKR
2+66 Q FDQFHURSKRELD Q DQG GHVLUH IRU ,90 DIWHU IDLOHG LQ YLWUR IHU
SDWLHQWV UHFHLYHG OHWUR]ROH SULPLQJ
Results: 7KH SDWLHQWV ZKR KDG)6+ RU OHWUR]ROH SULPLQJ ZHUH VWDWLVWLFDOO\ VLPL
IROOLFOH FRXQW VHUXP DQWL 0•OOHULDQ KRUPRQH OHYHOV DQG ,90 LQGLFDWLRQV
JHUPLQDO YHVLFOH RRF\WHV PHWDSKDVH ,, DQG IHUWLOL]HG RRF\WHV ZHUH VLJQLILF
PHWDSKDVH , RRF\WHV ZDV VLJQLILFDQWO\ ORZHU LQ WKH OHWUR]ROH SULPLQJ JURXS
VLPLODU UDWHV RI LPSODQWDWLRQ YV S FOLQLFDO SUHJQDQF\ YV
YV S
&RQFOXVLRQ 3RWHQWLDO LQGLFDWLRQV IRU ,90 LQFOXGH SDWLHQWV ZLWK LQFUHDVHG
FDQ EH XVHG WR SUHVHUYH WKH IHUWLOLW\ RI SDWLHQWV ZLWK HVWURJHQ VHQVLWLY
XQGHUJR ,90 ZLWK OLNHO\ OHVV FRVW WKDQ)6+ SULPLQJ

.H\ZRUGV Cancerphobia, *in vitro* PDWXUDWLRQ WHFKQLTXHV OHWUR]ROH RRF\WHV 2YDULDQ +\

Öz

$PDo %X *in vitro* FDOÕüPDGD \ND VXUDV\RQD ,90 JLUHQ KDVWDODUGD OHWUR]RO NXOODQ×P×Q×Q HWNL
LOH NDUü×ODüW×U×OPDV×Q× DUDüW×UPD\× DPDoODPDNWDG×U
*HUHo YH <|QWHPOHU %X UHWURVSHNWLI oDO×üPD \•NVHN <XPXUWDO×N +LSHUVWLP•
W•S EHEHN WHGDYLVL VRQUDV× ,90 GHQHPN LVWH\HQ Q ,90·\H JLUHQ KDVWDQ×Q
|QF•OOHQPLüWLU
%XOJXODU)6+ YH\D OHWUR]RO |QF•OOHQPLü RODQ KDVWDODU \Dü Y•FXW NLWOH LQGH
VHYL\HOHUL YH ,90 HQGLNDV\RQODU× Do×V×QGDQ LVWDWLVWLNVHO RODUDN EHQ]HUGL
JUXSWD JHUPLQDO YH]LN•O RRVLWOHUL 0HWDID] ,, YH G|OOHQPLü RRVLWOHULQ VD\×V
0HWDID] , RRVLWOHULQLQ VD\×V× OHWUR]RO |QF•OOHQPLü JUXEXQGD DQODPO× RODUD

PRECIS: /HWUR]RO *in vitro* PDWXUDWLRQ SURWRFRO KDV SURPLVLQJ UHVXOWV LQ FDVHV Z
RXWFRPHV DUH FRPSDUDEOH ZLWK)6+ SULPLQJ ,90

$GGUHVV IRU &RUUHVSRQGHQFH ýDIDN +DW×UQD] $VVRF 3URI
0HGLFDQD 6DPVXQ ,QWHUQDWLRQDO +RVSLWDO 6DPVXQ 7XUNH\
Phone: +90 362 311 05 05 (PDLO VDIDNKDWLUQD]#JPDLO FRP 25&,' ,' orcid.org/0000-0001-8859-0639
5HFHLYHG *HOLü 7DULKL 25.06.2020 $FFHSWHG .DEXO 7DULKL 04.10.2020

RODUDN EHQ]HU LPSODQWDV\RQ UDQODU× ·H NDUü× S NOLQLN JHEHOL
S YH FDQO× GRÿXP ·H NDUü× S J|]OHQPLüWLU
6RQXo ,90 LoLQ SRWDQVL\HO HQGLNDV\RQODU DUWP×ü 2+66 ULVNL YH KLSHULQVXOLQ
NDQVHUOHUGH IHUWLOLWH NRUXPD DPDoO× NXOODQ×ODELOPHNWHGLU /HWUR]RO LOH
)6+ |QF•OOHQPLü WHGDYLGHQ RODV×O×NOD GDKD X\JXQ PDOL\HWWH ROPDNWDG×U
$QDKWDU .HOLPHOHU Kanserfobi, in vitro PDWXUDV\RQ WHNQLNOHUL OHWUR]RO RRVLWOHU 2Y

Introduction

In vitro PDWXUDWLRQ ,90 UHIHUV WR WKH UHWULHYDO RI immature oocytes from antral follicles, with the final stages of meiosis completed during in vitro culture. Potential indications for IVM include patients with increased risk for 2YDULDQ +\SHUVWLPXODWLRQ V\QGURPH 2+66 SDWLHQWV ZLWK limited time for ovarian stimulation, and patients with a contraindication for elevated concentrations of estradiol. The primary benefits of IVM are the reduction in gonadotropin H[SRVXUH WKH VXEVHTXHQW GHFUHDVH LQ WKH ULVN RI 2+66 DQG facilitation of oocyte retrieval in oncology patients who need to undergo gonadotoxic treatment without adequate time for ovarian stimulation. Another benefit of IVM is the avoidance from ovarian stimulation-related hyperestrogenism in oncology patients with hormone-sensitive tumors.

/HWUR]ROH LV DQ DURPDWDVH LQKLELWRU WKDW EORFNV WKH FRQYHUVLRQ of androgens into estrogens in the ovarian milieu /HWUR]ROH exerts its primary action by increasing endogenous secretion RI IROOLFOH VWLPXODWLQJ KRUPRQH)6+ DQG D VHFRQGDU\ DFWLRQ by giving rise to a hyperandrogenic microenvironment, which triggers the development of primordial follicles. Therefore, it KDV EHHQ K\SRWKHVL]HG WKDW OHWUR]ROH FRXOG EH XVHG WR DFKLHYH ovarian stimulation in women with hormone-sensitive tumors without exposing them to sustained elevated estrogen levels. The avoidance from hyperestrogenism might also help to relieve the anxiety of infertile women who might be concerned about the long-term probability of developing estrogen-sensitive cancers while they are undergoing an assisted reproductive cycle. On the other hand, the emergence of a hyperandrogenic microenvironment might be beneficial in cases of oocyte maturation arrest.

7KLV VWXG\ DLPHG WR LQYHVWLJDWH ZKHWKHU OHWUR]ROH SULPLQJ could be used efficiently for patients who were to undergo IVM WUHDWPHQW GXH WR D KLJK ULVN RI 2+66 GHVLUH IRU ,90 RU IHDU IRU estrogen-sensitive cancers.

Materials and Methods

This is a retrospective analysis of 63 patients who underwent ,90 WUHDWPHQW GXH WR WKH KLJK ULVN RI 2+66 Q IHDU IRU HVWURJHQ VHQVLWLYH FDQFHUV Q DQG GHVLUH 90 DIWHU 9) IDLOXUH Q DW 6DPVXQ 0HGLFDQD QWHUQDWLRQDO +RVSLWDO EHWZHHQ 6HSWHPEHU DQG -DQXDU\ 7KH SULPDU\ ULVN IDFWRUV IRU 2+66 LQFOXGHG \RXQJ DJH RQ WUDQVYDJLQDO XOWUDVRQRJUDSK\ DQWUDO IROOLFOHV SUHYLRXV 2+66 The women with cancerophobia were those ZLWK 3RO\F\VWLF 2YDU\ V\QGURPH breast disease Q D IDPLO\ KLVWRU\ RI E DQG IDPLO\ KLVWRU\ RI HQGRPHWULXP RI approved by the Institutional Review Board of the study center DSSURYDO QR DQG FRQGXFWHG HWKLFDO SULQFLSOHV RXWOLQHG LQ participants gave written informed consent.

)RUW\ WZR SDWLHQWV ZLWK UHFHLYHG) JRQDGRWURSLQ K&* SULPLQJ DQG OHWUR]ROH K&* SULPLQJ &DQFHURSKRELF JURXS ZDV UHODWHG WR ILEURF\VWLF IDPLO\ KLVWRU\ RI EUHDVW FDQFHU Q 3DWLHQWV ZLWK K\SHUSURODFW non-classic congenital adrenal hyperplasia, adrenal and ovarian androgen-secreting tumors were excluded. Women whose SDUWQHUV KDG D]RRVSHUPLD F\SW ROLJRDVWKHQRWHUDWR]RRVSHUPLD Z *RQDGRWURSLQ DQG /HWUR]ROH 3ULPLQJ

7KH VWDQGDUG SURWRFRO IRU ,90 LQ the study center, as previously described ,90 ZLWK OHWUR priming was used only for the aforementioned indications. Beginning on the 3rd day of a spontaneous or an induced PHQVWUXDO F\FOH SDWLHQWV KDG)HPDUD® %DVHO 6ZLW]HUODQG SDWLHQWV UHFHLYHG UHFRPELQDQW *HQHYD 6ZLW]HUODQG DW D GDLO\ GR ,8 RI XULQDU\®, Organon, Amsterdam, 1HWKHUODQGV RU —J UHFRPELQDQW *HQHYD 6ZLW]HUODQG ZDV DGPLQLV IROOLFOH VL]H ZDV WR PP DQG HQ least 8 mm on transvaginal ultrasonography in the mid-sagittal plane. Under the guidance of transvaginal ultrasonography, oocyte pickup was performed using a 17-gauge double-lumen DVSLUDWLRQ QHHGOH ZLWK DSSOLFDWLRQ 38 hours after hCG administration.

In Vitro 0DWXUDWLRQ

)ROOLFXODU DVSLUDWHV ZHUH FROOH)DOFRQ &RGH ZKLFK ZHUH NHS XVLQJ D VWUDLQHU)DOFRQ —P SRUH D VWHUHRPLFURVFRSH 2O\PSXV 6= oocytes were isolated into the perimeter of a Falcon center-well dish containing flushing medium without heparin and subsequently incubated for two to three hours in IVM media. Upon completion of oocyte collection, the final medium was SUHSDUHG XVLQJ FRPPHUFLDOO\ DYD 0HGL &XOWXUH ,90 6\VWHP /DQG)6+ SUHSDUHG IURP D VWRFN VROXWL *2866 IRU GLOXWLRQ ZLWK P/ ,90 PH

DQG WKHQ LQFXEDWHG and 5% O_2. After DQ
LQFXEDWLRQ LQ /$* PHGLXP RRF\WHV ZHUH SODFHG
ZHOOV RI D IRXU ZHOO GLVK 1XQF
P/ RI ILQDO ,90 PHGLXP FRYHUHG ZLWK OLTXLG SDUDIILQ DQG
incubated for 26-28 hours. Nuclear maturity of oocytes was not assessed any further.

,QWUDF\WRSODVPLF 6SHUP ,QMHFWLRQ

,QWUDF\WRSODVPLF VSHUP LQMHFWLRQ ,&6, ZDV SHUIRUPHG LQ DOO
,90 F\FOHV 7KH VSHUPDWR]RD ZHUH SUHSDUHG E\ GHQVLW\
3XUH6SHUP JUDGLHQW &RGHV 36%
*RWKHQEXUJ 6ZHGHQ 5HPRYDO RI WKH FXPXOXV
cells was performed in a hyaluronidase-containing medium using Pasteur pipettes after a 26-28 h incubation period. The oocytes were then transferred to U-IVF medium for culture.
$OO ,&6, SURFHGXUHV ZHUH SHUIRUPHG LQ)DOFRQ 3HWUL GLVK ZLWK
GURSOHWV RI 393 FRQWDLQLQJ PHGLXP IRU VSHUPV 9LWUROLIH &RGH
[P/ DQG GURSOHWV RI IOXVKLQJ PHGLXP ZLWKRXW
heparin for oocytes.
:KHQ WKH ,&6, SURFHGXUH ZDV FRPSOHWHG WKH RRF\WHV ZHUH
SODFHG LQWR ,60 PHGLXP IRU FXOWXUH $IWHU WKH RRF\WH
IHUWLOL]DWLRQ ZDV HYDOXDWHG LQ GURSOHWV RI ,60 PHGLXP
LQFXEDWLRQ RI IHUWLOL]HG RRF\WHV ZDV FRQWLQXHG IRU KRXUV
ZKLFK PDGH XS KRXUV LQ WRWDO
ZKLFK RFFXUUHG K DIWHU ,&6, ZDV GHWHUPLQHG E\ WKH
presence of two distinct pronuclei and two polar bodies within
WKH RRF\WHV LQ ,60 PHGLXP WKURXJK DQ LQYHUWHG PLFURVFRSH
at x200 magnification. This was repeated 24 hours later.

The classification system introduced by Veeck was used for the evaluation of embryo grade on the third day of culture. The embryos were graded as follows: Grade 1 - embryo with
EODVWRPHUHV RI HTXDO VL]H QR F\WRSODVPLF IUDJPHQWV
HPEU\R ZLWK EODVWRPHUHV RI HTXDO VL]H DQG PLQRU F\WRSODVPLF
fragments or blebs: Grade 3 - embryo with blastomeres of
GLVWLQFWO\ XQHTXDO VL]H QRQH RU IHZ F\WRSODVPLF IUDJPHQWV
Embryo transfer was performed using a Wallace embryo transfer
FDWKHWHU :DOODFH 8. XQGHU DEGRPLQDO XOWUDVRQRJUDSK\
guidance and placed 1.5 to 2.5 cm from the fundus. Women aged younger than 35 years could only have a single embryo transferred, and a maximum of two embryos could be transferred to women aged over 35 years. Taking endometrial thickness into consideration, fresh embryo transfers were performed on day 3 or day 5. To prepare the endometrium for embryo transfer, an oral estrogen tablet was administered at a daily dosage of 4
PJ (VWURIHP® 1RYR 1RUGLVN %DJVY UG
IURP WKH WKLUG GD\ RI PHQVWUXDWLRQ /XWHDO SKDVH VXSSRUW
was begun the day following OPU, which was provided with a vaginal progesterone capsule at a daily dosage of 200 mg
3URJHVWDQ® VRIW FDSVXOH 7XUNL\H (VWURJHQ WDEOHWV
and progesterone capsules were continued until the first fetal heartbeat was detected.

Clinical pregnancy was defined as the presence of at least one gestational sac in the uterus. No IVM cycles were cancelled in this study.

6WDWLVWLFDO $QDO\VLV

&ROOHFWHG GDWD ZHUH DQDO\]HG XVLQJ
5RVNLOGH 'HQPDUN FRQWLQJHQF\
IRU WKH 6RFLDO 6FLHQFHV YHUVLRQ
$UPRQN 1< 86$ &RQWLQXRXV YDULDEOHV
as mean ± standard deviation and categorical variables are denoted as numbers or percentages. Continuous variables
ZHUH FRPSDUHG XVLQJ 6WXGHQW·V W
U test, whereas categorical variables were compared using the
)LVKHU·V H[DFW WHVW RU D 7ZR WDLOHG S YDOXH
statistically significant. A post-hoc analysis was performed to
GHWHUPLQH WKH DFKLHYHG SRZHU RI WKH VDPSOH VL]H RI
IRU PLQLPL]LQJ 2+66 ULVN DQG SUHYHQWLQJ PDWXUDWLRQ
DUUHVW KDG SRZHU WR GHWHFW
significance level.

Results

Table 1 compares the baseline characteristics of the 21 patients
ZKR KDG OHWUR]ROH SULPLQJ DQG
priming for IVM treatment. There were no significant group differences in age, body mass index, duration of infertility, basal
DQWUDO IROOLFOH FRXQW DQG VHUXP
DOO 7KH SDWLHQWV ZKR XQGHUZHQW)
DOVR VWDWLVWLFDOO\ VLPLODU LQ WK
7DEOH VXPPDUL]HV WKH ODERUDWRU

7DEOH Baseline characteristics of the patients

	)6+ SULPLQJ	Letrozole SULPLQJ	p
$JH \HDUV	29.2±4.8	31.1±4.2	0.129
%RG\ PDVV LQGH[kg/m²	27.27±6.02	25.16±4.35	0.159
'XUDWLRQ RI LQIHUWLOLW\ \HDUV	8.19	9.14	0.87
$QWUDO IROOLFOH FRXQW	15.7±2.1	17±6.6	0.198
$QWL 0•OOHULDQ KRUPRQH QJ P/	5.56±1.35	6.04±1.36	0.191

9DOXHV DUH JLYHQ DV PHDQ “ 6')6+)ROOLFOH VWLPXODWLQJ KRUPRQH 6' 6WDQGDUG deviation

7DEOH Indications for in vitro maturation

	)6+ SULPLQJ	Letrozole SULPLQJ	p
Oocyte maturation arrest			0.285
3&26 SDWLHQWV ZLWK cancerophobia			0.306
,QFUHDVHG ULVN IRU 2+66			0.099
<RXQJ DJH \HDUV		-	0.209
3RO\F\VWLF RYDULHV RQ 79 86*			0.338
3UHYLRXV 2+66			0.838

9DOXHV DUH JLYHQ DV QXPEHU SHUFHQWDJH)6+)ROOLFOH VWLPXODWLQJ KRUPRQH 3&26 3RO\F\VWLF 2YDU\ V\QGURPH 2+66 2YDULDQ +\SHUVWLPXODWLRQ 6\QGURPH 79 86* Transvaginal ultrasonography

%RWK WKH)6+ DQG OHWUR]ROH SULPLQJ JURXSV ZHUH VWDWLVWLFDOO\ similar concerning the endometrium thickness on the hCG day, time to oocyte pick up, retrieved oocytes counts, and single RU GRXEOH HPEU\R WUDQVIHUV S! IRU DOO :KHQ FRPSDUHG ZLWK WKH)6+ SULPLQJ JURXS D VLJQLILFDQWO\ KLJKHU QXPEHU RI JHUPLQDO YHVLFOH RRF\WHV PHWDSKDVH ,, RRF\WHV S S S UHVSHFWLYHO\ lower number of metaphase I oocytes and grade 3 embryos ZHUH GHWHFWHG LQ WKH OHWUR]ROH SULPLQJ JURXS S S UHVSHFWLYHO\ 7KH QXPEHU RI DOVR VLJQLILFDQWO\ ORZHU LQ WK KHQ FRPSDUHG ZLWK WKH)6+ SULPLQJ JURXS S

Table 4 shows the pregnancy outcomes of the patients. Th SDWLHQWV ZKR UHFHLYHG)6+ DQG OHWUR]ROH SULPLQJ KDG VWDWLVWLFDO VLPLODU UDWHV RI LPSODQWDWLRQ YV S FOLQLFDO SUHJQDQF\ YV S ZLQ SUHJQDQF\ YV S DQG OLYH ELUWK YV S

Discussion

By definition, IVM refers to the maturation of collected immature oocytes under the influence of hormones that exist within the culture media. Thus, hormones are not administered to patients undergoing IVF treatment +RZHYHU WKH JHQH DEHRXW ,90 LV WKDW D VKRUW SULPLQJ increases the chance for oocyte maturation and implantation in SDWLHQWV ZLWK 3&26 7KLV VKRUW SU DGPLQLVWUDWLRQ RI)6+ DW D GRVH R RI WZR WR ILYH GD\V)6+ VWLPXODWL increases the number of immature oocytes retrieved and thus clinical pregnancy rates in IVM cycles . Accordingly, this study adopted an IVM protocol indicating the administration of UHFRPELQDQW)6+ DW D GRVH RI ,8 I ,Q WKLV VWXG\ SDWLHQWV ZLWK 3& priming because they had cancerophobia due to fibrocystic breast disease and a positive family history for breast and endometrium cancer. Therefore, priming was performed using DQ DURPDWDVH LQKLELWRU QDPHO\ O 3&26

In this study, the primary indications for IVM treatment ZHUH WKH DYRLGDQFH IURP 2+66 DQG desiring IVM. It is well known that IVM is the only assisted reproduction technique that has been proved to be devoid of 2+66 ULVN 5HFHQW PHWD DQDO\VHV U with IVM had significantly higher implantation and clinical pregnancy rates, as well as significantly lower miscarriage and cycle cancellation rates . The maturation of human oocytes is naturally arrested at the germinal vesicle stage when the oocytes need gonadotropin stimulation and the metaphase II VWDJH ZKHQ RRF\WHV DUH ZDLWLQJ IR approach for failed IVF could be the IVM of immature oocytes within culture media enriched with factors necessary for oocyte maturation , if compromised in vivo.

Due to the wide variations in priming protocols, varying numbers between 8% and 40% have been specified as the clinical pregnancy rates and live birth rates in IVM cycles . 6LPLODUO\ RXU SUHYLRXV VWXG\ UHS of 44.6% and 44.7% and live birth rates of 34.9% and 34.2% for single-embryo transfer and double-embryo transfers in ,90 F\FOHV ZLWK)6+ SULPLQJ . As for the present study, the clinical pregnancy and live birth rates were respectively 31.5%

7DEOH /DERUDWRU\ ILQGLQJV RI WKH SDWLHQWV

	)6+ SULPLQJ	Letrozole SULPLQJ	p
Endometrial thickness at hCG GD\ PP	9.07±1.25	9.63±1.68	0.138
7LPH WR RRF\WH SLFN XS GD\V	13.2±1.8	14.0±1.3	0.123
5HWULHYHG RRF\WHV Q	12.8±6.8	14.6±3.6	0.273
*HUPLQDO YHVLFOH RRF\WHV Q	3.4±1.0	8.1±6.5	0.003*
0HWDSKDVH , RRF\WHV Q	3.8±1.5	2.6±0.7	0.002*
0HWDSKDVH ,, RRF\WHV Q	6.3±3.1	9.4±2.7	0.001*
)HUWLOL]HG RRF\WHV Q	5.5±2.8	6.8±1.5	0.016*
(PEU\R WUDQVIHU Q			0.621
6LQJOH HPEU\R			-
Double embryo			-
(PEU\R JUDGH Q			0.007*
Grade 1			-
Grade 2			-
Grade 3			-
(PEU\R TXDOLW\ Q			0.007*
One-cell embryo			-
Two-cell embryos			-
Three-cell embryos			-
Four-cell embryos			-

9DOXHV DUH JLYHQ DV PHDQ “ 6' RU QXPEHU SHUFHQWDJH DV LQGLFDWHG)6+)ROOLFOH VWLPXODWLQJ KRUPRQH K&* +XPDQ FKRULRQLF JRQDGRWURSLQ 6WDQGDUG GHYLDWLRQ

7DEOH Comparison of pregnancy outcomes of two groups

	)6+ SULPLQJ	Letrozole SULPLQJ	p
Implantation rate per transfer			0.709
Clinical pregnancy rate per transfer			0.848
6LQJOHWRQ SUHJQDQF\ UDWH SHU transfer			0.688
Twin pregnancy rate per transfer			0.611
/LYH ELUWK UDWH SHU WUDQVIHU			0.682

9DOXHV DUH JLYHQ DV QXPEHU SHUFHQWDJH)6+)R

and 24.1% in IVM cycles with gonadotropin priming. Although clinical pregnancy and live birth rates tended to be higher in IVM cycles with letrozole priming (33.3% and 29.6%), there were no statistically significant differences.

A new indication for IVM has been defined as a convenient therapeutic approach for infertile patients who have been diagnosed as having malignancies and scheduled for oncofertility treatment. The basic rationale for this definition is the feasibility of IVM for preserving oocytes and embryos and thus, future fertility, whenever conventional in vitro fertilization is not an option. A potential factor that might delay the oncology treatment can also be avoided because IVM prevents the risk of OHSS. Additionally, this technique can be used to replace an IVF cycle that would otherwise end up with excessive follicular growth and subsequent cycle cancellation[25,26].

Another advantage of IVM treatment is that it can be started immediately at any time of the menstrual cycle without stimulating ovaries. Therefore, IVM emerges as an appropriate technique for preserving the fertility of oncology patients in whom the initiation of chemotherapy, radiotherapy or surgical treatment cannot be delayed[1,2]. Another advantage of this assisted reproduction technique is that serum estrogen concentrations remain low throughout an IVM cycle. Therefore, IVM has been established as a safe and effective method for fertility preservation in patients with estrogen-sensitive tumors[25,26].

It is also well known that aromatase inhibitors can be used as single agents or adjuncts to FSH-containing ovulation induction regimens for preserving the fertility of patients with estrogen-sensitive breast cancer. Aromatase inhibitors would reduce supra-physiologically serum concentrations of estradiol, suppress local production of estrogen within the tumor tissue, and induce follicular growth in women with estrogen-sensitive malignancies. Combining gonadotropins with aromatase inhibitors would augment the ovarian stimulation without a profound increase in serum estradiol levels[27,28].

Conclusion

The findings of this study suggest that IVM treatment with letrozole priming might be an efficient approach for patients who have a high risk for OHSS or fear for estrogen-sensitive tumors. However, these findings should be interpreted carefully as their power is limited by its retrospective design, small cohort size, technical inadequacy for cryopreservation, and lack of long-term data. Further research is warranted to clarify the clinical implications of letrozole priming in IVM cycles. A prospective study of letrozole-primed IVM should be considered.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board of the study center (approval no: 3/2020).

Informed Consent: All participants gave written informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

[illegible]

M.K.P.

Conflict of Interest: The authors report no conflict of interest.

Financial Disclosure: Authors have no financial interests about the research.

References

1. [illegible]t RJ. In vitro maturation. Best Pract Res Clin Obstet Gynaecol 2018;53:60-72.
2. Sauerbrun-Cutler MT, Vega M, Keltz M, McGovern PG. In vitro maturation and its role in clinical assisted reproductive technology. Obstet Gynecol Surv 2015;70:45-57.
3. Khalili MA, Shahedi A, Ashourzadeh S, Nottola SA, Macchiarelli G, Palmerini MG. Vitrification of human immature oocytes before and after in vitro maturation: a review. J Assist Reprod Genet 2017;34:1413-26.
4. Sonigo C, Grynberg M. In vitro oocyte maturation for female fertility preservation. Gynecol Obstet Fertil 2014;42:657-60.
5. Grynberg M, El Hachem H, de Bantel A, Benard J, le Parco S, Fanchin R. In vitro maturation of oocytes: uncommon indications. Fertil Steril 2013;99:1182-8.
6. Nguyen TT, Doan HT, Quan LH, Lam NM. Effect of letrozole for ovulation induction combined with intrauterine insemination on women with polycystic ovary syndrome. Gynecol Endocrinol 2020;36:860-3.
7. Tanbo T, Mellembakken J, Bjercke S, Ring E, Åbyholm T, Fedorcsak P. Ovulation induction in polycystic ovary syndrome. Acta Obstet Gynecol Scand 2018;97:1162-7.
8. [illegible] Z. Fertility preservation with random-start controlled ovarian stimulation and embryo cryopreservation for early pregnancy-associated breast cancer. Gynecol Endocrinol 2019;35:214-6.
9. Sonigo C, Sermondade N, Calvo J, Benard J, Sifer C, Grynberg M. Impact of letrozole supplementation during ovarian stimulation for fertility preservation in breast cancer patients. Eur J Obstet Gynecol Reprod Biol X 2019;4:100049.
10. [illegible] gonadotropin-releasing hormone agonist combined with aromatase inhibitor as fertility-sparing treatment in obese patients with endometrial cancer. J Gynecol Oncol 2019;30:e61.
11. Sánchez F, Lolicato F, Romero S, De Vos M, Van Ranst H, Verheyen G, et al. An improved IVM method for cumulus-oocyte complexes from small follicles in polycystic ovary syndrome patients enhances oocyte competence and embryo yield. Hum Reprod 2017;32:2056-68.
12. [illegible] Krisher RL. A pre-in vitro maturation medium containing cumulus oocyte complex ligand-receptor signaling molecules maintains meiotic arrest, supports the cumulus oocyte complex and improves

oocyte developmental competence. Mol Hum Reprod 2017;23:594-606.

13. Fiedler K, Ezcurra D. Predicting and preventing ovarian hyperstimulation syndrome (OHSS): the need for individualized not standardized treatment. Reprod Biol Endocrinol 2012;10:32.
14. Hatirnaz S, Hatirnaz E, Dahan MH, Tan SL, Ozer A, Kanat-Pektas M, et al. Is elective single-embryo transfer a viable treatment policy in in vitro maturation cycles? FertilSteril 2016;160:1691-5.
15. Hossain A, Phelps J, Agarwal A, Sanz E, Mahadevan M. A Review of The Society for Assisted Reproductive Technology Embryo Grading System and Proposed Modification. Int J Fertil Steril 2016;10:141-7.

DKDQ07 HDQ6/ &KXQJ-6RQ: &OLQLFDOGHILQLWLRQSDSHU RQ in vitro maturation of human oocytes. Hum Reprod 2016;31:1383-6.

17. De Vos M, Smitz J, Thompson JG, Gilchrist RB. The definition of IVM is clear-variations need defining. Hum Reprod 2016;31:2411-5.

-XQN60 +HDS'PSRUMHG LPSODQWDWLRQ DQGRQJRLQJSUHJQDQF\ rates after single-embryo transfer with an optimized protocol for in vitro oocyte maturation in women with polycystic ovaries and polycystic ovary syndrome. Fertil Steril 2012;98:888-92.

:DOOV 0/ +XQWHU7 5DQ -3 .HHODQ -$ 1DKWDQ (ÐDW/ ,Q vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes. Hum Reprod 2015;30:88-96.

20. De Vos M, Ortega-Hrepich C, Albuz FK, Guzman L, Polyzos NP, Smitz J, et al. Clinical outcome of none hCG-primed oocyte in vitro maturation treatment in patients with polycystic ovaries and polycystic ovary syndrome. Fertil Steril 2011;96:860-4.
21. Lindenberg S. New approach in patients with polycystic ovaries, lessons for everyone. Fertil Steril 2013;99:1170-2.
22. Siristatidis C, Sergentanis TN, Vogiatzi P, Kanavidis P, Chrelias C, Papantoniou N, et al. In vitro maturation in women with vs. without polycystic ovarian syndrome: a systematic review and meta-analysis. PLoS One 2015;10:e0134696.

H HHWL&DOKD]RUH &XSND 06 :QV &RFDQX (Motrenko T, et al. ART in Europe, 2014: results generated from European registries by ESHRE: The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod 2018;33:1586-601.

6KLDVDZD 7HUDGD <Q YLWUR PDWXUDWLRQ RI KXPDQ LPPDWXUH oocytes for fertility preservation and research material. Reprod Med Biol 2017;16:258-67.

6KRKDP /HYROHGDQR 5 /HRQJ 0 :HLVVPDQ $ORQ < Shoham Z. Oncofertility: insights from IVF specialists-a worldwide web-based survey analysis. J Assist Reprod Genet 2019;36:1013-21.

26. Fatum M, McVeigh E, Child T. The case for aromatase inhibitors use in oncofertility patients. Should aromatase inhibitors be combined with gonadotropin treatment in breast cancer patients undergoing ovarian stimulation for fertility preservation prior to chemotherapy? A debate. Hum Fertil (Camb) 2013;16:235-40.
27. Comtet M, Sonigo C, Valdelièvre C, Sermondade N, Sifer C, Grynberg M. Fertility preservation in breast cancer patients: the state of art in 2014? Bull Cancer 2015;102:443-53.

7DNDL 5HFHQWDGYDQFHV LQ RQFRIHUWLOLWFDUH ZRUOGZLGH DQG LQ Japan. Reprod Med Biol 2018;17:356-68.

Introduction

Infertility affects approximately 15% of the general population worldwide and 40-50% is attributed to female infertility. It is caused by many factors, and fallopian tube abnormalities cause about 30-35% of cases of female infertility +\VWHURVDOSLQJRJUDSK\ +6* LV D UHOLDEOH DQG ERWK HUHFWLYH method used in the determination of both tubal pathologies and tubal patency, and uterine and peritoneal pathologies in the investigations into the etiology of infertility. Although +6* LV D SURFHGXUH WKDW GRHV QRW UHTXLUH FHUYLFDO GLODWDWLRQ general anaesthesia, the procedure can be painful. Up to 72% of patients complain of pain from the procedure.

The mechanisms causing pain may include cervical instrumentation, and irritation of contrast medium in uterine cavity distension, and peritoneal irritation of contrast medium that has spread to the abdomen. In addition, taking the uterus into traction by holding the cervix with a tenaculum increases local prostaglandin synthesis and can lead to uterine contractions and pain. Patients think that this procedure will be painful and are reluctant to have the test, which also causes anxiety. Many different randomised controlled studies have investigated many different agents and different application PHWKRGV WR UHGXFH SDLQ DQG DQ[LHW\ GXULQJ +6* in literature that have evaluated these studies. However, the PDMRULW\ RI WKHVH VWXGLHV KDYH OLPLWDWLRQV VXFK DV KHWHURJHQL in the randomisation, lack of blinding, patient selection criteria, differences in drug doses and in the pain score measurements. Therefore, no optimal method has been found as yet, which can EH UHFRPPHQGHG WR DOOHYLDWH SDLQ GXULQJ WKH +6* SURFHGXUH Complementary treatments have started to be more widely used in modern medicine, and of these, acupuncture applications have shown efficacy, especially in acute pain syndromes and chronic pain. Kiran et al. determined that acupuncture DQG QRQ VWHURLG DQWL LQIODPPDWRU\ GUXJV 16$,'V KDYH similar effects in patients with primary dysmenorrhea. In recent UDQGRPLVHG FRQWUROOHG VWXGLHV 6PLWK HW DO reported that acupuncture decreased anxiety and increased quality of life in patients applied with in vitro IHUWLOL]DWLRQ Therefore, the aim of this study was to investigate, for the first time in literature, the effect of acupuncture in reducing pain DQG DQ[LHW\ LQ SDWLHQWV XQGHUJRLQJ +6*

Materials and Methods

Approval for the study was granted by the Clinical Research (WKLFV &RPPLWWHH RI .DKUDPDQPDUDü 6•Wo• þPDP 8QLYHUVLW\ GHFLVLRQ QR VHVVLRQ 3DWLHQWV ZKR DGPLWWHG WR our Assisted Reproductive Techniques clinic with the desire WR KDYH D FKLOG DQG SODQQHG WR in our study. Informed consent was obtained from all the patients. Age, infertility duration, gravida and smoking status of all patients participating in the study were registered. At the beginning of the study, a pilot study was conducted with 10 patients from each group and the minimum number of patients in each group with_ DQG SRZHU ZDV IRX in the power analysis. There with, 133 patients were planned WR EH LQFOXGHG LQ WKH VWXG\ DW I conducted with the remaining 107 patients after excluding WKH RQHV DOOHUJLF WR UDGLRSDTXH Q WKRVH ZLWK FHUYLFDO HQGRPH ZLWK SUHYLRXV\ GHILQHG 16$,' GUXJ WKRVH ZLWK FHUYLFDO VXUJLFDO DO ZHUH IRXQG WR KDYH DFXWH SHOYLF and those who did not want to participate in the study. The UHPDLQLQJ VXEMHFWV ZHUH GLYLGH FRPSXWHU JHQHUDWHG UDQGRPL]DWLR JURXS Q LQWUDPXVFXODU GLFORI Q DQG WKH FRQWURO JURXS Q For the patients in the ACU group, taking anxiety into consideration, the points selected and identified to decrease WKH SDLQ DQG VWUHVV WKDW FDQ GH were those which are most widely used in the treatment of dysmenorrhea and anxiety. All the ACU procedures were DSSOLHG E\ WKH VDPH SK\VLFLDQ $ $&8 SURFHGXUHV IRU PRUH WKDQ WH /LY 3 +7 3& /, /, 63 /5 &3 67 DQG 5HQ SR@ p GVHÀ

vagina, and following observation of the cervix, local cleaning was applied with 3% povidone-iodine. Then, depending on the cervix position, the anterior or posterior cervical lip was held ZLWK D WHQDFXOXP DQG D 5XELQ +6* FDQQXOD ZDV JHQWO\ SODFHG in the cervical canal. The speculum was removed and 10-20 P/ ZDWHU VROXEOH UDGLR RSDTXH VROXWLRQ 8URJUDILQŠ P/ %D\HU $* 7XUNH\ ZDV XVHG DV D FRQWUDVW PHGLXP DQG LQMHFWHG VORZO\ XQGHU VSRW IOXRURVFRS\ $IWHU FRPSOHWLRQ RI WKH procedure, all the instruments were removed and the patient was transferred to a bed.

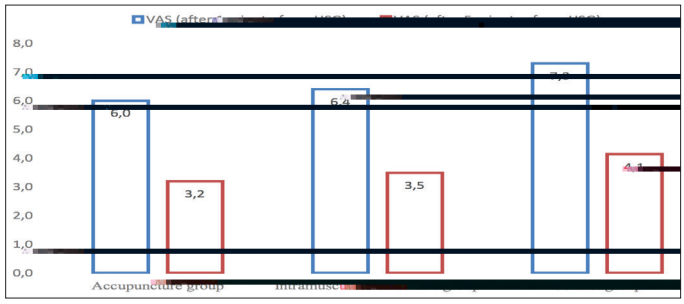
$ 9LVXDO $QDORJ VFDOH 9$6 ZDV XVHG LQ WKH HYDOXDWLRQ RI SDLQ VHYHULW\ DQG WKH 6WDWH WUDLW $Q[LHW\ LQYHQWRU\ VWDWH 67$, 6 LQ WKH HYDOXDWLRQ RI SDWLHQW DQ[LHW\ $OO WKH 9$6 DQG 67$, 6 VFRULQJ ZDV SHUIRUPHG E\ D VLQJOH SK\VLFLDQ $ 8 EOLQGHG WR WKH JURXSV ,Q WKH 9$6 V\VWHP WKH SDWLHQW LV LQVWUXFWHG WR SODFH D PDUN RQ D PP KRUL]RQWDO OLQH FRUUHVSRQGLQJ WR WKH OHYHO RI SDLQ IHOW ZKHUH QR SDLQ DQG LQWROHUDEOH SDLQ 7KH TXHVWLRQV RQ WKH 67$, 6 IRUP ZHUH DVNHG GLUHFWO\ WR WKH patients and the results were recorded. Both evaluations were DSSOLHG DW PLQ DQG PLQ EHIRUH WKH +6* SURFHGXUH DQG DW minutes after the procedure and all the results were recorded. In the evaluation of anxiety, the changes over the specified time period were evaluated.

6WDWLVWLFDO $QDO\VLV

Data obtained in the study were analysed statistically using 6366 YQ VRIWZDUH ,%0 6WDWLVWLFV IRU :LQGRZV YHUVLRQ ,%0 &RUSRUDWLRQ $UPRQN 1< 86$ DQG 3$67 VRIWZDUH Ø+DPPHUSHU ' $ 7 5\DQ 3 ' 3DOHRQWRORJLFDO VWDWLVWLFV 7R DVVHVV WKH FRQIRUPLW\ RI GDWD QRUPDO GLVWULEXWLRQ WKH 6KDSLUR :LON WHVW ZDV DSSOLHG WR GDW ZLWK VLQJOH YDULDEOHV DQG WKH 0DUGLD WHVW 'RQLNDQG +DQVHQ RPQLEXV WR GDWD ZLWK PXOWLSOH YDULDEOHV 7KH /HYHQH WHVW ZDV used to evaluate variance homogeneity. Parametric methods were used in the analyses of variables with homogenous variance and normal distribution and non-parametric methods were used for variables not showing homogenous variance and normal distribution. In the comparisons of independent multiple groups with each other, the One-Way ANOVA 5REXVW WHVW %URZQ)RUV\WKH DQG .UXVNDO :DOOLV WHVWV ZHUH used, and for the post hoc analyses, the non-parametric post KRF WHVW 0LOOHU 7R H[DPLQH WKH LQWHUDFWLRQ RI UHSHDWHG measurements of dependent variables according to the groups,

uS 7À e2EP ÊÒEP Ã• BSe2EP Æ ª€Qe2EP ÁE2EP À Àí$U L $U LP WÒ UL z€Qe2EDT% Á=õ2EP ÊÒED€ 0 € @0measu

LQFUHDVHG LQ WKH ,0'6 DQG FRQWURO JURXSV ,0'6 DQG WKH 7US JURXS Z
VFRUHV PLQXWHV DIWHU WKH +6* SURFHGXUH ZHUH IRXQG WR EH VWDWLVWLFDOO\ S YH S UHVSHFWLYHO\ 7DEO
the values in the ACU group were found to be statistically VLJQLILFDQWO\ ORZHU WKDQ WKH ,0'6 DQG FRQWURO JURXS VLPLODU WR
the 5th minute before the procedure, but this difference was not GHWHUPLQHG EHWZHHQ WKH ,0'6 DQG FRQWURO JURXSV
7DEOH WKH FKDQJHV LQ WKH 67$, 6 VFRUHV EHWZHHQ WKH +6*
1 hour before-5 minutes ago, 1 hour before-30 minutes later DQG PLQXWHV EHIRUH PLQXWH DIWHU WKH $&8 JURXS ZHUH
DQDO\]HG WKH FKDQJHV LQ 67$, 6 VFRUHV ZHUH
found to be statistically significant for all three change values



)LJXUH 9$6 VFRUHV PLQXWH EHIRUH DQG PLQXWHV DIWHU +6*
9$6 9LVXDO $QDORJ VFDOH +6* +\VWHURVDOSLQJRJUDSK\

)LJXUH 67$, 6 VFRUHV PLQXWHV DIWHU +6*
+6* +\VWHURVDOSLQJRJUDSK\ 67$, 6 6WDWH DQG 7UDLW $Q[LHW\ ,QYHQWRU\
-state

7DEOH 67$, 6 YDOXHV DW KRXU DQG PLQXWHV EHIRUH DQG PLQXWHV DIWHU

Discussion

The results of the study showed that ACU reduced the pain WKH 16$,' GLFORIHQDF ,W ZDV DOVR YDOXDWHG WKDW ACU UHGXFHG DQ[LHW\ ZKHQ
DQDO\]HG WKH FKDQJHV LQ 67$, 6 VFRUHV DPRQJ WKH $&8 JURXS ZHUH
found to be statistically significant for all three change values. 7KHUH DUH PDQ\ VWXGLHV RQ WKH VX
that have investigated the types of pharmacological drugs used and the methods of use. A systematic Cochrane review in 2015 RQ WKH VXEMHFW RI SDLQ UHOLHI LQ
randomised studies. Although the level of evidence was low, it was concluded that topical anaesthetics and intravenous opioids could be effective in reducing pain during the procedure, but this effect was not seen after the procedure. It was reported that there was not sufficient evidence that other analgesic methods could be effective . In a review by Ahmad et al. RQ WKH VXE
of pain-relief in office-setting gynaecological interventions, WKHUH ZDV UHSRUWHG WR EH QR EHQ
first 30 mins and 30 mins after the procedure, but when local anaesthetics were used, it was shown that even if not in the first 30 mins, there could be beneficial effects after 30 mins.

7KH PDMRULW\ RI VWXGLHV LQ OLWHU
with non-pharmacological methods are studies where catheters have been used. It has been suggested that catheters used during +6* FRXOG KDYH GLIIHUHQW HIIHFWV R
al. and Varpula , it was determined that the use of flexible balloon catheters instead of a traditional metal cannula was not effective in reducing pain, while De Mello et al. reported in a study published in 2006 that the use of flexible balloon FDWKHWHUV UHVXOWHG in investigated the
efficacy of fast-release orodispersible tramadol, as a different analgesic method, in cases where traditional metal cannula and balloon catheter were used and reported that it was effective independently of the type of catheter used.

ACU is a complementary medicine application with increasingly widespread use. There have started to be wide areas of use especially in the elimination of pain symptoms. Previous studies have shown that the effect mechanisms of ACU are formed on D E L R O R J L F D O E D V L V & K R G J D Q G 3 R P H U D Q] analgesic efficacy of ACU occurred by increasing endogenous opioids and demonstrated that this effect could be removed with naloxane, which is an opioid antagonist. Using functional magnetic imaging technology, another study showed that the stimulation of ACU points affected the the limbic system and structures in both the cortical and subcortical areas in the brain . In a clinical study, Cho et al. determined activity signals in the cingulate gyrus and thalamic region with pain stimuli, and following ACU, reported a decrease both in the signals and in the pain felt by the patient.

Although there are no studies in literature examining the effect R I $&8 RQ DQ[LHW\ HQJHQGHUHG E\ WKH DSSOLFDWLRQ RI +6* there are studies related to the effect of lowering anxiety in general. The hypotheses of some of these studies are explained by biochemical mechanisms and some by physiological S D U D P H W H U V LQYHVWLJDWHG FKDQJHV LQ SODVPD DGUHQRFRUWLFRWURSLF KRUPRQH FRUWLFRVWHURLG DQG SODWHOHW + levels in response to anxiety treatment. Comparisons were made of ACU, pharmacological treatment and combined treatment groups, and similar results were found in the ACU group and the pharmacological treatment group. That the side-effects seen in the pharmacological treatment group were not seen in the ACU group was emphasised as a positive aspect. The effects of ACU on anxiety were investigated by observing changes in the parameters of oxygen saturation and heart rate by Karst et al. DQG LQ KHDUW UDWH DQG VNLQ FRQGXFWLYLW\ E\ 6KD\HVWHKIDU HW DO As ACU reduced heart rate in both groups, it was concluded to be effective on anxiety.

To the best of our knowledge, this is the first study in literature WR KDYH LQYHVWLJDWHG $&8 RQ WKLV VXEMHFW +RZHYHU WKHUH were some limitations to the study, the first of which is that WKH GLIIHUHQW VWDJHV RI +6* VSHFXOXP SODFHPHQW WHQDFXOXP SODFHPHQW RSDTXH PHGLXP DGPLQLVWUDWLRQ ZHUH QRW HYDOXDWHG ZLWK 9$6 ,Q DGGLWLRQ WKH VLGH HIIHFWV RI 16$,'V DQG $&8 were not examined, and when examining the pain scores, the +6* UHVXOWV ZHUH QRW WDNHQ LQWR FRQVLGHUDWLRQ

DQ[LHW\ DQG TXDOLW\ RI OLIH IRU ZRPHQ
FRQWUROOHG WULDO $FWD 2EVWHW *\QHFRO 6FDQG
<XTLQJ = 4LDQJOL &)XQGDPHQWDOV RI $FXSXQFWXUH DQG
0R[LEXVWLRQ 7LDQMLQ 6FLHQFH 7HFKQRORJ\ 7UDQVODWLRQ
Publishing Corporation, 1994.
.D\QDU 0 .R\XQFX) %XOGX þ 7HNLQDUVODQ (7HSHOHU $ .DUDWDý
T, et al. Comparison of the efficacy of diclofenac, acupuncture, and acetaminophen in the treatment of renal colic. Am J Emerg Med 2015;33:749-53.
$XVWLQ 5 6DFNV % 1RZHOO 0)HLWDO &
Radiology 1984;151:249.
9DUSXOD 0 +\VWHURVDOSLQJRJUDSK\ ZLWK D EDOORRQ FDWKHWHU YHUVXV D
cannula: evaluation of patient pain. Radiology 1989;172:745-7.
20. De Mello J, Abrao M, Cerri G, de Barros N. Evaluation of pain in three hysterosalpingography techniques: metal cannula with and without paracervical blockage and balloon catheter. Am J Roentgenol 2006;187:86-9.
6WRRS ' 'H %XFNHU 0 +DHQWMHQV 3 7DOHEL]DGHK $ GH 0H\ -
Devroey P. Fast-release orodispersible tramadol as analgesia in hysterosalpingography with a metal cannula or a balloon catheter.
+XP 5HSURG
&XHQQL 5 1RJH, 9 $ 0D 1 (GRPWHU
stereospecific opiate receptors and is reversed on antagonists of type
, UHFHSWRUV /LIH 6FL
+XL .. /LX - 0DNULV 1 *ROOXE 5/ &KH
Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in
QRUPDO VXEMHFWV +XP %UDLQ 0DSS
&KR =+ 6RQ <' +DQ -< I05, 1HXURSK\VL
acupuncture mechanisms. Med Acupuncture 2002;14:16-22.
<XDQ 4 /L -1 /LX % :X =) -LQ 5 (IIHFW R
on plasma corticosteroid, adrenocorticotrophic hormone and
SODWHOHW +7 OHYHOV LQ SDWLHQWV Z
Chin J Integr Med 2007;13:264-8.
.DUVW 0 :LQWHUKDOWHU 0 0•QWH 6)
A, Eckardt A, et al. Auricular acupuncture for dental anxiety: a
UDQGRPL]HG FRQWUROOHG WULDO $QHVWK
6KD\HVWHKIDU 0 6HLI %DUJKL 7 =DUHL
Anxiolytic Effects on Physiological and Psychological Assessments
IRU D &OLQLFDO 7ULDO 6FLHQWLILFD &D

Turk J Obstet Gynecol 2020;17:259-269

Antenatal pentoxifylline therapy to prevent endotoxin-induced fetal injury in the preterm goat model

3UHWHUP JHEH NHoL PRGHOLQGH HQ
KDVDU×Q |QOHQPHVLQGH DQWHQDWD

0HNLQ 6H]LNLQ[1], .|NHU 0HUOHP g]HQ[2], 0HKPHW +DOX]JX .DüN[3], $K×PHW $\GRÿD
2UKDQ g]DWLN[6]

[1]Süleyman Demirel University Faculty of Medicine, Department of Obstetrics and Gynecology, Isparta, Turkey
[2]Burdur Mehmet Akif Ersoy University Faculty of Veterinary Medicine, Department of Obstetrics and Gynecology, Burdur, Turkey
[3]Burdur Mehmet Akif Ersoy University Faculty of Veterinary Medicine, Department of Pathology, Burdur, Turkey
[4]Çukurova University Faculty of Ceyhan Veterinary Medicine, Department of Pathology, Adana, Turkey
[5]Isparta University of Applied Sciences Faculty of Agriculture, Department of Animal Science, Isparta, Turkey
[6]Kütahya Health Sciences University Faculty of Medicine, Department of Histology and Embryology, Kütahya, Turkey

$EVWUDFW

2EMHFWLYH 3HQWR[LI\OOLQH 37; KDV LPPXQRPRGXODWRU\ SURSHUWLHV DQG LV NQR
PDWHUQDO RUDO DQG LQWUD DPQLRWLF DGPLQLVWUDWLRQ RI 37; IRU WKH SUHYHQWLR
0DWHULDOV DQG 0HWKRGV ,QIODPPDWLRQ PHGLDWHG IHWDO LQMXU\ ZDV LQGXFHG ZLWK
DW RI JHVWDWLRQ LQ GDWH PDWHG SUHJQDQW JRDWV (LJKW JURXSV ZHUH IRUPHG
IRU GD\V IHWDO LQMXU\ LQWUD DPQLRWLF PJ NJ DQG PJ NJ HVWLPDWHG IHWD
by hysterotomy was performed at 0.80 of gestation to evaluate the fetal and placental effects. Immunochemistry for various markers including interleukin
caspases, cyclooxygenases, vimentin, myelin basic protein, and surfactant proteins were carried out in the fetal lungs, fetal brain, and placenta. Fetal pla
DQG DPQLRWLF IOXLG LQWHUOHXNLQV ZHUH DOVR HYDOXDWHG .UXVNDO :DOOLV + WHV
Results: +LJK GRVH PJ NJ GD\ PDWHUQDO SURSK\ODFWLF RUDO WUHDWPHQW DWWHQX
LQIODPPDWRU\ PDUNHU H[SUHVVLRQV FRPSDUDEOH WR WKH FRQWUROV S! H[FHSW F
DPQLRWLF IOXLG OHYHOV RI WKH VWXGLHG LQWHUOHXNLQV ZHUH DOVR ORZHU WKDQ WK
PTX was associated with inconsistent results and increased inflammatory markers in some fetuses.
&RQFOXVLRQ Oral PTX before preterm birth mitigates intrauterine inflammation with neuroprotective effects in the fetus. PTX can be cons
FDQGLGDWH GUXJ IRU IHWDO EUDLQ LQMXU\ SUHYHQWLRQ LQ WKH SUHWHUP SHULRG

.H\ZRUGV $QLPDO PRGHO HQGRWR[LQV IHWDO EUDLQ LQMXU\ QHXURSURWHFWLRQ SH

Öz

$PDo 3HQWRNVLILOLQ 37; LPP•Q G•]HQOH\LFL |]HOOLNOHUL VDKLSWLU YH VHSVLVH E
HQIODPDV\RQ YH KDVDU×Q |QOHQPHVLQGH PDWHUQDO RUDO YH LQWUD DPQL\RWLN 37; N
*HUHo YH <|QWHPOHU $\Q× J•QGH oLIWOHüWLULOHQ NHoLOHUGH PDWHUQDO JUDQ•ORV
IHWDO KDVDU JHVWDV\RQGD WHWLNOHQGL 6HNL] JUXS ROXüWXUXOGX KHU ELULQGH
37; IHWDO KDVDU IHWDO KDVDUO× YH\D KDVDUV×] WHN GR] LQWUD DPQL\RWLN PJ N
IHWDO YH SODVHQWDO HWNLOHQPHQLQ GHÿHUOHQGLULOPHVL DPDF× LOH SUHWHUP GRÿ
RNVLMHQD]ODU YLPHQWLQ PL\HOLQ ED]LN SURWHLQ YH VXUIDNWDQ SURWHLQOHUL JL
LQWHUO|NLQOHU GHÿHUOHQGLULOGL .DUü×ODüW×UPDODUGD .UXVNDO :DOOLV + WHVWL

PRECIS: 8VLQJ DQ LQIODPPDWLRQ PHGLDWHG IHWDO LQMXU\ FDSULQH PRGHO ZH GH
preterm delivery.

$GGUHVV IRU &RUUHVSRQGHQFH 0HNLQ 6H]LNLQ $GUHVL
6•OH\PDQ 'HPLUHO 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 2EVWHWULFV DQG *\QHFRORJ\ ,VSDUWD
Phone: +90 246 211 92 39 (PDLO PVH]LN#\DKRR FRP 25&,' ,' orcid.org/0000-0002-6989-081X
5HFHLYHG *HOLü 7DULKL 29.06.2020 $FFHSWHG .DEXO 7DULKL 01.09.2020

%XOJXODU <•NVHN GR] PJ NJ J•Q PDWHUQDO SURILODNWLN RUDO WHGDYL HQGR
HQIODPDWXYDU EHOLUWHoOHUGH NRQWURO VHYL\HOHULQH EHQ]HU S! G•]HOPHOHU
SUR HQIODPDWXYDU LQWHUO|NLQOHU GH VDGHFH HQGRWRNVLQH PDUX] NDODQODUGDN
37; ED]× IHW•VOHUGH HQIODPDWXYDU EHOLUWHoOHUGH DUW×üODU YH GHÿLüNHQ ELU H
6RQXo 3UHWHP GRÿXP |QFHVLQGH RUDO 37; LQWUDXWHULQ HQIODPDV\RQX D]DOWDUD
EH\LQ KDVDU×Q× |QOH\HELOHFHN ELU LODo DGD\× RODELOLU
$QDKWDU .HOLPHOHU +D\YDQ PRGHOL HQGRWRNVLQOHU IHWDO EH\LQ KDVDU× Q|URN

Introduction

Preterm birth is the most important cause of perinatal morbidity and mortality. There is growing evidence that subclinical intra-
DPQLRWLF ,$ PLFURELDO FRORQL]DWLRQ DQG LQIODPPDWLRQ LV
responsible for a significant number of preterm deliveries. Up to 40% of pregnancies that resulted in preterm deliveries were found to have positive inflammatory markers in the second-trimester amniotic fluid. Moreover, increased subclinical IA inflammation is suggested to affect the fetus, with the inflammation probably commencing from the lungs and then propagating to the vulnerable fetal brain. This condition has
EHHQ FDOOHG DV)HWDO ,QIODPPDWRU\ 5HVSRQVH 6\QGURPH)56
DQG LV DQ LQGLUHFW FRQVHTXHQFH RI $ PLFURELDO FRORQL]DWLRQ
most likely in an ascending manner through the cervix
8OWLPDWHO\ WKH RXWFRPH ZLOO EH IHWDO EUDLQ LQMXU\ ZKLFK PD\
PDQLIHVW LWVHOI DV FHUHEUDO SDOV\ &3 LQ WKH ORQJ WHUP Although
peripartum hypoxia has conventionally been accused for the development of neonatal encephalopathy, data controlling for confounders show that most cases are indeed associated with antenatal insults to the developing fetal brain
Given the medical and social negative consequences of fetal brain
LQMXU\ HIIHFWLYH DQWHQDWDO WUHDWPHQWV DUH QHHGHG 0DJQHVLXP
sulfate has been shown to have neuroprotective effects, and many clinicians now routinely administer magnesium sulfate
WUHDWPHQW EHIRUH LPPLQHQW HDUO\ SUHWHUP GHOLYHU\ +RZHYHU
some recent data have also indicated that magnesium sulfate may not be neuroprotective in the setting of chorioamnionitis.
+HQFH WDUJHWHG WKHUDSLHV WKDW KDYH D SRWHQWLDO WR VSHFLILFD
inhibit initial steps of the inflammatory cascades in the amniotic fluid and the chorioamniotic membranes may be required to
GHFUHDVH IHWDO EUDLQ LQMXU\ 0RUHRYHU XVH RI IHWDO QHXURSURWHFWLYH
agents in a combined form in relatively low cumulative doses may demonstrate a cocktail effect, decreasing the overall side effects to the fetus, and with various therapeutics acting on different steps of inflammation.
3HQWR[LI\OOLQH 37; LV D V\QWKHWLF PHWK\O[DQWKLQH GHULYDWLYH
that competitively inhibits phosphodiesterases with nonsteroidal immunomodulatory activities. Phosphodiesterase inhibition is believed to be associated with an anti-inflammatory effect, leading to decreased proinflammatory cytokine
DFWLYLW\ LQFOXGLQJ WXPRU QHFURVLV IDFWRU DOSKD 71)Į DQG
LQWHUIHURQ ,)1 On this basis, PTX is presently under clinical investigation against neonatal sepsis, and a Cochrane meta-analysis has shown decreased sepsis-associated neonatal
PRUWDOLW\ ZLWK XVH RI 37; $ UHFHQW PHWD DQDO\VLV VKRZHG

PHWD DQDO\VLV KDV DOVR FRQILUPHG
ULVN DQG FRQILGHQFH LQWHUY
following neonatal PTX treatment Therefore, maternal use of PTX for inflammation-driven pregnancy complications that might have effects on the fetus seems plausible, considering likely negligible toxicity to the preterm fetus.
In the sheep model, PTX was reported to decrease serum pro-inflammatory cytokines following experimentally induced endotoxemia. Another experimental study revealed that PTX was partly effective against pre-eclamptic-like symptoms in ewes. Considering these preliminary animal data, PTX can be considered to have fetal neuroprotective effects by
PLWLJDWLQJ ,$ LQIODPPDWLRQ 0RUHR
EH K\SRWKHVL]HG WR GHOLYHU WKH G
to act on the fetal alveolar capillary bed and the gastrointestinal system by fetal swallowing.
The experimental ovine and caprine pregnancy models have been in use for translational research due to the physiological similarities with the human pregnancy, avoidance of multiple pregnancies with proper mating strategies, feasibility of IA administrations and sampling, and availability of adequate
DPRXQW RI IHWDO EORRG DQG WLVVXH
may offer some advantages for experimental obstetric research.
The aim of the current study was to evaluate maternal oral and IA administration of PTX for the prevention of fetal
LQIODPPDWLRQ DQG LQMXU\ LQ D FDSU
that both oral and IA routes of PTX therapy were effective
DJDLQVW LQIODPPDWLRQ PHGLDWHG I
period, particularly in the developing lung and brain tissues. To test this hypothesis, we used the small ruminant experimental
PRGHO WKDW XWLOL]HG PDWHUQDO J
IDFWRU * &6) IROORZHG E\ KLJK G
aggravate intrauterine inflammation. We then evaluated various
LQIODPPDWRU\ DSRSWRWLF DQG LQM
fluid, fetal blood plasma, placenta, fetal lungs, and fetal brain of the preterm goat fetuses.

Materials and Methods

$QLPDO 0DWHULDO

6•OH\PDQ 'HPLUHO 8QLYHUVLW\ $QLPD
RI WKLV VWXG\ ZLWK WKH DSSURYDO
QXPEHU GDWH 3DU
regulations and principles of laboratory animal care were followed. A priori power analysis was conducted to test the difference between two independent group means for a 50%

decrease or increase in the mean, using a two-tailed test and an alpha of 0.05. Result showed that 4 animals in a group were required to achieve a power of 80%. Therefore, the experimental preterm goat model included 32 date-mated VLQJOHWRQ SUHJQDQW KDLU JRDWV Q HDFK IRUPHG DW GD\ RI JH… DSSUR[LPDWHO\ GD\V 7KH DQLPDOV… and/or standard food, given water and mineral salts ad libitum, and were sheltered in a semi-open pen. All experiments were carried out at the Faculty of Veterinary Medicine, Mehmet Akif Ersoy University. Maternal age and prepregnancy body weight was 4-5 years and 40±5 kg, respectively.

([SHULPHQWDO *URXSV

The experiments were carried out in 2 phases. The first phase included validation of inflammation-mediated preterm fetal LQMXU\ H[SHULPHQWDO PRGHO LQFOXGLQJ WKH YHKLFOH FRQWURO JURXS Q DQG WKH SRVLWLYH FRQWURO JURXS… Details and results of these first 2 groups with proper validation of the novel modified experimental model initially defined by Watanabe et al. have been described previously. 5HFRPELQDQW * &6) DW D GDLO\ GRVH RI… P/ QRUPDO VDOLQH 1HXSRJHQ 5RFKH… %DVHO 6ZLW]HUODQG WR LQGXFH… ZDV LQMHFWHG LQWR PDWHUQDO… JHVWDWLRQDO GD\V ZLWK FRQWURO… normal saline. At gestational day 115, amniocentesis with D JDXJH DPQLRFHQWHVLV QHHGOH… 8QLWHG 6WDWHV ZDV SHUIRUPHG… (FKR &DPHUD 66' $ORND 7RN\R… of inappropriate allantoic entry by the color and viscosity of the fluid . Amniotic fluid, watery in consistency and pale amber in color was aspirated from the inner amniotic sac close to the fetus. Using the amniocentesis needle in the amniotic VDF KLJK GRVH PJ ,$ HQGRWR[LQ… (VFKHULFKLD FROL 2 % / 6LJPD… was used to induce IA and fetal inflammation in group 1, while WKH SRVLWLYH FRQWURO JURXS… normal saline through amniocentesis. Validation of the model ZLWK UHVXOWDQW QHFURWL]LQJ… leukocyte infiltration leading to necrotic arc formation in the vascular wall of the umbilical vessel and secondary fetal brain LQMXU\ ZDV VKRZQ LQ DOO RI WKH… JURXS JURXS SRVLWLYH FRQWURO… Priming with maternal * &6) IROORZHG E\ KLJK GRVH… WKH),56 LQ ZKLFK ORZ JUDGH… IA inflammation is followed by a relatively abrupt insult that OHDGV WR IHWDO EUDLQ LQMXU\ WKDW… exposure .

The second phase of the experiments included treatment 37; JURXSV WR WHVW WKH RUDO… of antenatal PTX therapy. Group 3 and group 4 were designed to assess the prophylactic use of oral PTX at 2 different doses DJDLQVW VXEVHTXHQW LQIODPPDWLRQ… LQ ERWK RI WKHVH JURXSV Q HDFK… at day 100, and daily treatment continued for 15 days from gestation day 100 to 114 at a daily dose of 30 mg/kg maternal ZHLJKW ORZ GRVH DQG PJ NJ… PTX, respectively. A mortar and pestle were used to grind FRPPHUFLDOO\ DYDLODEOH… After weighing on precision scales to calculate the dose, the 37; SRZGHU ZDV GLVVROYHG LQ… administered to the does via an oral feeding catheter connected WR D P/ V\ULQJH 7KH GRHV ZHUH… postadministration, and the procedure was repeated if the solution was not properly swallowed or spitted out by the DQLPDO $QLPDOV LQ RWKHU… JLYHQ P/ RI VWHULOH ZDWHU… daily low- and high-doses of oral PTX, depending on previous pharmacokinetic data from large animals. Group 3 and 4 DQLPDOV DOVR UHFHLYHG * &6) GD\V… WR LQGXFH IHWDO LQMXU\ VLPLODU…

Group 5 and group 6 aimed to examine the therapeutic effectiveness of single-use IA PTX at 2 different doses against FRQFXUUHQW LQIODPPDWLRQ… GRHV LQ JURXS Q DQG JURXS… * &6) UHJLPHQ DQG KLJK GRVH… defined. Additionally at day 115, either single low-dose PJ NJ HVWLPDWHG IHWDO ZHLJKW… HVWLPDWHG IHWDO ZHLJKW 37; ZDV… following endotoxin administration, using an amniocentesis needle under ultrasound guidance. Estimated fetal weight was W\SLFDOO\ FRQVLGHUHG DV NJ… P/ DQG PJ P/ RI ,$ VLQJOH… 37; 7UHQWLOLQ DPSRXOH PJ P/… 7XUNH\ 'RVH FDOFXODWLRQ IRU ,$… the assumption that around 2.5% of IA administered inert substances would be swallowed by the fetus within 1 hour corresponding to 10 mg/kg fetal weight and 20 mg/kg fetal weight for the low- and high-dose regimens, respectively in line with the recommended oral pediatric doses for PTX.

7KH ODVW JURXSV JURXS DQG JURXS… PTX without intrauterine inflammation, i.e. non-administration RI * &6) DQG HQGRWR[LQ 7KHVH… fetoplacental effects of IA administration of standalone PTX in the absence of intrauterine inflammation. Does in group 7 and JURXS UHFHLYHG P/ RI QRUPDO… vein for 5 days followed by amniocentesis at gestational day ZLWK 37; LQMHFWLRQV RI PJ NJ… JURXS RU PJ NJ HVWLPDWHG…

,QGXFWLRQ RI 3UHWHUP 'HOLYHU\

$W JHVWDWLRQDO GD\ JHVWDW… cesarean section under epidural anesthesia with concurrent maternal sedation and incisional infiltration with local anesthetic…

sacrococcygeal epidural anesthesia into the sacrococcygeal VSDFH ZLWK D FP JDXJH VSLQDO 25 mg lidocaine hydrochloride and 0.016 mg epinephrine were performed. Then, the whole abdominal area was cleansed with 10% povidine iodine solution. A paralumbar skin incision of approximately 10 cm in length was used to reach the uterus, which was opened from its dorsal curvature with extension of the uterine incision using scissors as necessary. Before DPQLRWRP\ D P/ VWHULOH V\ULQJH ZDV XVHG amniotic fluid for sampling. Then, the fetus and the placenta were delivered, and an intact placentome was dissected and sampled. The uterus was comprehensively lavaged with sterile saline solution to clean of all blood clots and membranes. Then, the uterus and the abdominal wall were closed with polyglactin 9LFU\O LQWHUUXSWHG VXWXUHV was applied. Postpartum does were given systemic analgesic WUHDWPHQW ZLWK PHWDPL]ROH VRGLXP treatment with 200 mg i.m. procaine penicillin and 250 mg i.m. dihydrostreptomycine sulfate.

7KH QHRQDWH NLGV ZHUH GULHG euthanasia with 50 mg/kg of intraperitoneal sodium thiopental 3HQWDO 6RG\XP ,(8OXJD\ ,VWDQEXO transthoracic intracardiac blood sampling. Then, neonatal chest and skull were opened for en bloc dissection of the lung and brain. Parenchymal tissue from the lungs and white matter from the brains were sampled Tissue samples were fixed in 10% buffered formaldehyde and embedded into paraffin.

(YDOXDWLRQ RI WKH 6DPSOHV DQG ,PPXQRKLVWRFKHPLVWU\
'RXEOH DQWLERG\ VDQGZLFK HQ]\PH OLQNHG LPPXQRVRUEHQW DVVD\ ZDV XVHG WR HYDOXDWH LQWHUOHXNLQ and TNF-_ levels in the amniotic fluid and neonatal plasma VDPSOHV XVLQJ FRPPHUFLDO NLWV IRU JRDW VHUXP +DQJ]KRX &KLQD 5HVXOWV ZHUH HYDOXDWHG DW GHQVLW\ YDOXHV ZHUH FDOFXODWHG Immunochemical staining on fetal lung, fetal brain and placental tissues were carried out using a routine streptavidine-biotin peroxidase technique. After primary antibody incubation, streptoavidine peroxidase incubation of the slides for 20 minutes was carried out followed by washing with phosphate-buffered VDOLQH 3%6 ELRWLQLODWHG $EV IRU rinse the slides, and a peroxidase substrate solution containing 3,3v 'LDPLQREHQ]LGLQH '$% 6XEVWUDWH 8. ZDV XVHG IRU PLQXWHV RI LQFXEDWLRQ distilled water, counterstaining with hematoxylin, dehydration, and mounting of the slides were performed.

$OO WLVVXHV ZHUH LPPXQRVWDLQHG IRU FDVSDVH FDVSDVH FDVSDVH &2; ,)1 DOSKD ,)1 _ DQG ,)1 EHWD 8. $GGLWLRQDO LPPXQRVWDLQLQJ 63 $ % & DQG ' 6DQWD &UX] %LRWHFK SURVXUIDFWDQW SURWHLQ % SUR WLVVXHV DQG QHXURQ VSHFLILF HQRODVH ILEULOODU\ DFLGLF SURWHLQ *)$3

8. DQWL QHXURILODPHQW SURWHLQ P\HOLQ EDVLF SURWHLQ 0%3 $EFDP 8 Degree of immunostaining was assessed by the pathologists blindly, concerning experimental groups with an arbitrary visual scale that graded the immunoreaction as 0, no staining; 1, weak staining; 2, moderate staining; and 3, diffuse staining.)RU VHPLTXDQWLWDWLYH HYDOXDWLRQ /HLF 6FLHQFH ,PDJLQJ 6RIWZDUH 6\VWHP 7RN\R -DSDQ ZLWK DQ DXWRPDWHG WKUHVKROG ZDV XWLOL]HG

6WDWLVWLFDO $QDO\VLV

Data were expressed as mean and standard deviations. Kruskal-:DOOLV + WHVW DQG 0DQQ :KLWQH\ 8 WHVW DQG ELQDU\ FRPSDULVRQV UHVSHFWLYHO\ ZDV VHW DW S .UXVNDO :DOOLV + in the tables, whereas Mann-Whitney U test results for between-group comparisons were given in the text in more detail.

Results

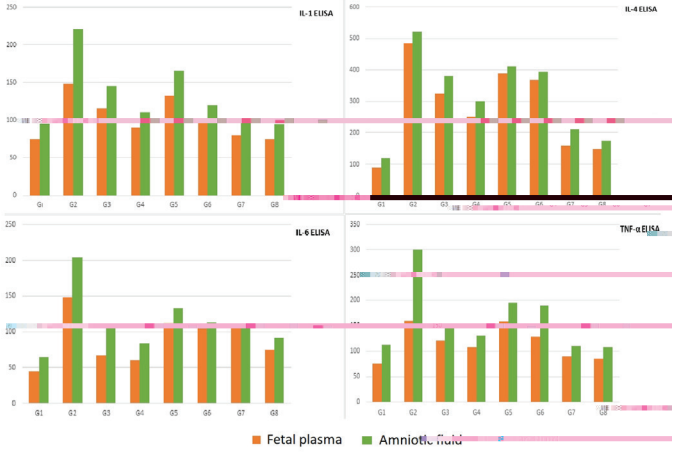
The mean neonatal weight was 1.453±260 g, and was similar DFURVV WKH JURXSV S 6LPLODU GLVWULEXWHG HTXDOO\ DFURVV WKH RI JURXS YHKLFOH FRQWURO DQG J E\ PDWHUQDO * &6) DQG KLJK GRVH ,$ specified in detail in our previous publication with validation of the current model of intrauterine inflammation. Briefly, PDWHUQDO * &6) DQG $ HQGRWR[LQ OH IFN-_, and IFN-`, COX-1, COX-2, caspase 3, 5, and 7, and UHOHDVH LQFUHDVH LQ ,/ DQG ,/ LQ D DORQJ ZLWK GHFUHDVHG SXOPRQDU\ 6 63 % DQG GHFUHDVHG EUDLQ YLPHQWLQ 16(QHXURILODPHQW SURWHLQ 1)3 SURWHLQ 0%3 H[SUHVVLRQV S $PQLRWLF)OXLG ,QIODPPDWRU\ 0DUNHU Data on amniotic fluid sampled at preterm cesarean delivery DUH JLYHQ LQ 7DEOH DQG VXPPDUL]HG KLJK GRVH RUDO 37; UHJLPHQV VLJQLI TNF-_ OHYHOV FRPSDUHG WR WKH PRGH FRPSDULVRQ 7KHQ +%6 ZHUH XVHG WR interleukins was more efficiently suppressed with high-dose oral 37; JURXS EHLQJ FRPSDUHG WR WKH ORZ G ,/ DQG ,/ 7KH UHVXOWV ZLWK IRU D dose oral administration was able to partially reverse IA LQIODPPDWLRQ ZLWK FRPSDUDEOH ,/ YDOXHV /DFN RI 37; _ YHKLFOH FRQ Both low-and high-dose PTX were also effective in reducing ,)1 _ DQG ,)1 EHWD ZLWK GHFUHDVHG ,$ LQGXFHG VXUIDFWDQW SURWHLQV H 7KH RQJRLQJ LQIODPPDWLRQ ,WV 63 % ,)1 EHWD 8.S IRU WKH ORZ FRPSDUL JURXSV 1'(3$% WKH 8.V ,)1 ,/ completely reverse the IA inflammation, since comparisons of

7DEOH &RPSDULVRQV RI DPQLRWLF IOXLG DQG QHRQDWDO SODVPD LQIODPPDWRU
caprine pregnancies

, Q I O D P P D W R U \ G U X J	Group 1	Group 2	Group 3	* U R X S	* U R X S	Group 6	* U R X S	* U R X S	p
$ P Q L R W L F I O X L G									
, Q W H U O H X N L Q	95.0±8.2	217.5±27.3	145.0±41.6	107.7±8.1	166.0±50.9	120.0±12.3	101.0±7.2	94.0±13.9	0.017
, Q W H U O H X N L Q	110.3±3.2	505.5±70.2	380.0±21.3	299.0±3.5	410.0±47.5	395.0±43.9	110.0±19.4	175.0±35.1	0.006
, Q W H U O H X N L Q	63.7±5.0	196.2±37.7	109.0±10.4	86.3±8.1	133.0±4.0	113.0±16.1	109.0±11.9	92.0±10.1	0.008
7 1) D O S K D S J	112.7±5.4	299.7±5.2	150.0±21.5	133.3±11.5	195.0±12.2	190.0±13.4	110.0±69.1	109.0±40.6	0.009
1 H R Q D W D O S O D V P D									
, Q W H U O H X N L Q	70.0±2.0	142.2±20.0	115.0±7.0	93.3±11.5	132.0±15.6	100.0±6.2	80.1±9.1	75.0±8.2	0.008
, Q W H U O H X N L Q	87.5±1.0	485.2±489	325.0±27.0	259.3±28.9	388.0±31.2	369.0±40.0	159.0±27.4	149.0±46.5	0.006
, Q W H U O H X N L Q	44.7±3.0	156.0±30.1	68.0±4.6	59.0±3.5	112.0±14.0	105.0±4.6	109.0±9.4	75.0±17.7	0.007
7 1) D O S K D S J	79.1±14.2	160.5±22.1	120.0±24.0	110.3±8.1	159.0±47.8	129.0±20.9	90.0±23.5	85.0±5.3	0.012

*URXS 1HJDWLYH FRQWURO *URXS 3RVLWLYH FRQWURO ZLWK LQIODPPDWLRQ PHGLDWHG IHWDO LQM
IHWDO LQMXU\ *URXS /RZ GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH IHWDO LQMXU\ *URXS +LJK GRVH
ZLWKRXW IHWDO LQMXU\ *URXS +LJK GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH ZLWKRXW IHWDO LQMXU\

all parameters between IA PTX treatment groups and vehicle FRQWURO VKRZHG VWDWLVWLFDOO\ IRU DOO 6WDQGDORQH ,$ 37; WUHDWPHQW ZDV was generally associated with similar IA inflammatory marker YDOXHV S! H[FHSW LQFUHDVHG 37; JURXS FRPSDUHG WR JURXS The current data underpinned the anti-inflammatory effects of both prophylactic oral and therapeutic IA PTX, although high-dose oral protocol showed a more robust activity to alleviate HQGRWR[LQ LQGXFHG ,$ LQIODPPDWRU\ 1HRQDWDO 3ODVPD ,QIODPPDWRU\ 0DUNHUV Comparisons of the studied inflammatory parameters in the neonatal blood plasma obtained following preterm delivery are VXPPDUL]HG LQ 7DEOH DQG)LJXUH



)LJXUH Fetal blood plasma and amniotic fluid interleukin-1, interleukin-4, interleukin-6, and tumor necrosis factor-alpha measurements obtained at preterm delivery in experimental study groups

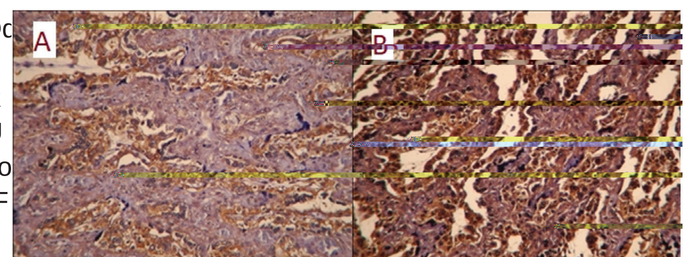
DVVRFLDWHG ZLWK GHFUHDVHG ,/ SODVPD LQIODPPDWRU\ PDUNHUV and TNF- VLJQLILFDQWO\ OHVV WKDQ W IRU DOO FRPSDULVRQV +RZHYHU RQ KLJK GRVH RUDO 37; ZHUH VLPLODU S indicating a partial reversal of inflammation following the high-dose oral regimen)RU ,$ WUHDWPHQW ZLWK 37; KLJK GRV WKH VWXGLHG QHRQDWDO SODVPD ,/V but not TNF- _ S FRPSDUHG WR HQGRWR[+RZHYHU RQO\ PHDQ ,/ OHYHO ZD of group 1 controls, indicating a partial reversal of inflammation ZLWK WKH KLJK GRVH DGPLQLVWUDWLR ZDV OHVV HIIHFWLYH ZLWK RQO\ ,/ O S LQ WKH QHRQDWDO SODVPD F controls. Despite these positive effects, standalone IA PTX was DVVRFLDWHG ZLWK LQFUHDVHG ,/ SOD ERWK ORZ GRVH DQG KLJK GRVH ,$ 37 UHVSHFWLYHO\ FRPSDUHG WR YHKLFO As a result, both high-dose oral and high-dose IA PTX effectively reduced the studied inflammatory markers in the neonatal plasma, but did not completely reverse the fetal inflammation back to control levels. A possible adverse effect of IA PTX may EH VWLPXODWLRQ RI DQ LPPXQH UHDF)LJXUH

3ODFHQWDO ,PPXQRKLVWRFKHPLFDO)L 7DEOH VXPPDUL]HV FRPSDULVRQV RI LQWHQVLWLHV EHWZHHQ WKH VWXG was associated with profound placental inflammation and apoptosis, as previously reported /RZ GRVH RUDO 37;

7DEOH &RPSDULVRQV RI SODFHQWDO LPPXQRVWDLQLQJ LQWHQVLWLHV EHWZHHQ

0DUNHU	Group 1	Group 2	Group 3	*URXS	*URXS	Group 6	*URXS	*URXS	p
Interleukin-1	0.25±0.5	3.0±0	1.3±0.6	0.3±0.6	1.0±0.0	1.3±1.5	1.0±0.8	1.3±1.1	0.012
Interleukin-4	0.5±0.6	2.75±0.5	1.0±1.0	0.7±0.6	1.3±1.1	1.7±1.5	1.2±0.9	1.3±1.1	0.035
Interleukin-6	0.25±0.5	2.75±0.5	1.0±1.0	0.3±0.6	0.7±1.1	1.3±1.5	1.5±1.0	1.0±1.0	0.026
Interferon-alpha	0.25±0.5	2.75±0.5	1.3±1.5	0.7±0.6	1.0±0.0	1.0±1.7	1.0±0.5	1.0±1.0	0.044
Interferon-beta	0.25±0.5	2.75±0.5	0.7±1.1	0.7±0.6	2.3±0.6	1.0±1.7	1.2±0.5	0.3±0.6	0.032
Tumor necrosis factor-alpha	0.25±0.5	2.5±1.0	1.0±1.7	0.3±0.6	1.3±1.5	1.7±1.5	1.0±0.8	1.0±1.0	0.081
Cyclooxygenase-1	0.75±0.5	2.5±0.6	1.3±1.1	0.7±1.1	2.0±1.7	1.0±1.0	1.0±0.8	1.7±0.6	0.071
Cyclooxygenase-2	0.0±0.0	2.75±0.5	0.7±1.1	1.0±0.0	0.7±1.1	1.7±0.6	1.0±1.1	0.7±1.1	0.014
Caspase 3	0.25±0.5	3.0±0.0	1.0±1.0	0.3±0.6	1.3±1.5	1.3±1.5	1.0±0.0	1.3±0.6	0.021
Caspase 5	0.25±0.5	2.5±0.6	0.7±1.1	0.3±0.6	0.7±1.1	1.7±1.6	1.0±1.1	1.0±1.0	0.036
Caspase 7	0.25±0.5	2.5±0.6	1.7±0.6	1.0±0.0	1.3±0.6	1.0±1.0	1.5±0.6	1.3±0.6	0.012

*URXS 1HJDWLYH FRQWURO *URXS 3RVLWLYH FRQWURO ZLWK LQIODPPDWLRQ PHGLDWHG IHWDO LQM IHWDO LQMXU\ *URXS /RZ GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH IHWDO LQMXU\ *URXS +LJK GRVH ZLWKRXW IHWDO LQMXU\ *URXS +LJK GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH ZLWKRXW IHWDO LQMXU\
1, weak staining; 2, moderate staining; and 3, diffuse staining



)LJXUH 3ODFHQWDO FDVSDVH LPP DQG %S JURXSV WKDW UHFHLYHG L with or without intra-amniotic endotoxin, respectively. Administration of pentoxifylline directly into the amniotic fluid could trigger apoptosis in the placenta

SDUWLDOO\ UHYHUVHG WKH ILQ ,/ S ,/ S FDVSDVH S H[SUHVVLRQV FRPSDUHG WR JURXSV +LJK GRVH RUDO 37; JU inflammation and apoptosis to a great extent with return to EDVHOLQH H[SUHVVLRQV S! H[F DQG JURXSV FRPSDULVRQ $OWKRXJK ORZ GRVH ,$ 37; JURXS OHG WR GHFUHDVHG expressions of some inflammatory parameters in the placenta ,/ ,/ ,)1 _ DQG &2; ZLWK S DQG S UHVSHFWLYHO\ FRPSDUHG WR SRVLWLYH FRQWURO KLJK GRVH ,$ 37; JURXSV VHHPHG LQHIIHFWLYH S! IRU DOO FRPSDULVRQV EHWZHHQ JURXSV DQG JURXSV 6WDQGDUGL]DWLRQ ORZ and high-dose IA PTX was associated with increased caspase 3 S DQG S UHVSHFWLYHO\ DQG FDVSDVH S UHVSHFWLYHO\ H[SUHVVLRQV a possible apoptotic process in the placenta following PTX LQMHFWLRQ LQWR WKH DPQLRWLF IOXLG)LJXUH

These results revealed that prophylactic oral PTX prevented placental inflammation and apoptosis, and high-dose oral regimen was probably more effective with return to baseline levels except COX2. On the other hand, IA PTX was less effective and may be associated with placental apoptosis.

)HWDO %UDLQ ,PPXQRKLVWRFKHPLFDO 6WDLQLQJ

7DEOH VXPPDUL]HV WKH LPPXQRVWDLQLQJ LQWHQVLWLHV)ROORZLQJ KLJK brain white matter. As previously shown, inflammatory and DSRSWRWLF PDUNHUV ZHUH LQFUHDVHG S EUDLQ LQMXU\ DSSDUHQW ZLWK GHFUHDVHG 16(1)3 *)$3 DQG 0%3 VWDLQLQJ LQ HQGRWR[LQ H[SRVHG GRVH RUDO 37; JURXSV ZDV DVVRFLDWHG ZLWK S ,)1 ` S FDVSDVH S S &2; DQG FDVSDVH S DQG GH

DQG LQFUHDVHG 16(S VWDLQLQJ LQ FRQWURO JURXSV DQG WKH RWKHU JURXSV LQ WKH KDOI D RUDO SURSK\OD[LV DQG DPHOLRUDWHG WKH IHWDO LPSURYHG H[SUHVVLRQV S RI DOO &2; S)LJXUH *)$3 S DQG 0%3 S ZHUH QR VLJQLILFDQW GLIIHUHQFHV EHWZHHQ JURXSV DQG YHKLFOH FRQW UHYHUVDO RI WKH EUDLQ LQMXU\ ZLWK /RZ GRVH ,$ 37; JURXSV OHG WR GHF IFN-_ S ,)1 ` S DQG 71) _ immunostaining in the fetal brain compared to endotoxin FRQWURO JURXSV LQWHQVLWLHV )ROORZLQJ KLJK RQO\ ,/ S DQG ,)1 ` S VWDL /RZ DQG KLJK GRVH ,$ 37; JURXSV DQG OHG WR IHWDO S IRU DOO)3 *)$3 DQG 0%3 FRQVLG dose IA PTX administration into the amniotic fluid without/fetal injury group decreased with R/LFDWHG DQG GHF

7DEOH &RPSDULVRQ RI IHWDO EUDLQ ZKLWH PDWWHU LPPXQRVWDLQLQJ LQWHQ

0DUNHU	Group 1	Group 2	Group 3	*URX$	*URX$	Group 6	*URX$	*URX$	p
Interleukin-1	0.25±0.5	3.0±0	1.7±0.6	0.3±0.6	1.3±0.6	1.3±0.6	1.2±0.9	1.0±1.0	0.010
Interleukin-4	0.25±0.5	2.25±0.5	0.7±0.6	0.7±0.6	1.0±1.0	1.0±1.7	1.2±0.9	1.0±1.0	0.023
Interleukin-6	0.25±0.5	2.5±1.0	0.7±1.1	0.3±0.6	0.7±1.1	1.0±1.0	1.0±0.8	0.7±1.1	0.053
Interferon-alpha	0.25±0.5	2.75±0.5	1.3±1.5	0.3±0.6	1.0±1.0	1.0±1.7	1.0±0.8	0.7±0.6	0.041
Interferon-beta	0.25±0.5	3.0±0	2.0±1.0	0.3±0.6	1.0±0.0	1.0±1.7	1.2±0.5	0.3±0.6	0.013
Tumor necrosis factor-alpha	0.25±0.5	2.75±0.5	0.7±0.6	0.3±0.6	0.7±1.1	1.0±1.0	1.5±1.3	1.0±1.0	0.024
Cyclooxygenase-1	0.5±0.6	2.5±0.6	1.0±0.0	0.3±0.6	1.3±1.1	1.3±1.1	1.0±0.8	1.7±0.6	0.018
Cyclooxygenase-2	0.25±0.5	2.25±0.9	1.3±1.5	0.7±0.6	1.3±1.5	1.3±1.5	0.5±0.6	1.0±1.0	0.088
Caspase 3	0.25±0.5	2.75±0.5	0.7±0.6	0.7±0.6	1.7±0.6	2.4±1.1	1.7±0.5	1.0±1.0	0.023
Caspase 5	0.25±0.5	2.25±0.5	1.3±0.6	0.7±0.6	1.0±1.0	1.7±0.6	1.2±0.5	1.0±1.0	0.018
Caspase 7	0.25±0.5	2.25±0.5	1.3±1.1	1.0±0.0	1.0±1.0	1.0±1.7	0.7±0.9	1.0±1.0	0.032
Vimentin	3.0±0	1.5±0.6	2.0±1.0	3.0±0	2.0±1.7	2.3±1.1	2.0±1.1	1.7±0.6	0.021
Neuron specific enolase	3.0±0	0.5±0.6	2.3±0.6	3.0±0	0.7±1.1	0.7±1.1	1.2±0.9	1.3±0.6	0.009
Neurofilament protein	3.0±0	1.0±0.8	2.0±1.0	3.0±0	2.0±1.0	1.0±0.0	1.7±1.5	2.3±0.6	0.017
Glial fibrillary acidic protein	3.0±0	1.5±1.0	2.7±0.6	3.0±0	1.0±1.0	2.0±1.0	2.2±0.9	2.3±0.6	0.062
Myelin basic protein	3.0±0	1.5±1.0	2.7±0.6	3.0±0	2.0±1.0	2.0±1.0	2.2±0.9	2.7±0.6	0.062

*URXS 1HJDWLYH FRQWURO *URXS 3RVLWLYH FRQWURO ZLWK LQIODPPDWLRQ PHGLDWHG IHWDO LQM IHWDO LQMXU\ *URXS /RZ GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH IHWDO LQMXU\ *URXS +LJK GRVH ZLWKRXW IHWDO LQMXU\ *URXS +LJK GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH ZLWKRXW IHWDO LQMXU\ weak staining; 2, moderate staining; and 3, diffuse staining

ZKHUHDV KLJK GRVH JURXS OHG 16(S IRU ERWK FRPSDUHG WR Therefore, high-dose oral PTX seemed more effective than ORZ GRVH RUDO 37; DJDLQVW IHWDO indicated some anti-inflammatory effect of IA PTX on the preterm fetal brain, although PTX might lead to increased white PDWWHU DSRSWRVLV DQG QHXURQDO amniotic fluid.

)HWDO 3XOPRQDU\ ,PPXQRKLVWRFKHPLFDO)LQGLQJV

Table 4 shows the immunostaining intensities of the fetal pulmonary parenchyma. As expected, inflammatory and apoptotic parameters were increased, whereas surfactants ZHUH GHFUHDVHG LQ WKH PRGHO RUDO 37; JURXS DOOHYLDWHG ,/ IFN-_ S ,)1 ` S FDVSDVH S FDVSDVH S DQG &2; S H[SUHVVLRQV FRPSDUHG WR SRVLWLYH FRQWURO JURXS +LJK GRVH RUDO 37; JURXS ZDV more effective, as shown by amelioration of all lung parameters WR EDVHOLQH JURXS FRQWURO OHYHOV S! IRU DOO and significantly decreased inflammation and apoptosis S IRU DOO H[FHSW &2; VWDLQLQJ VXUIDFWDQW SURWHLQ OHYHOV S IA PTX was generally associated with improved fetal pulmonary inflammation; however, lacked any positive effects on apoptosis and surfactant synthesis. Both low- and high-dose IA PTX

JURXS HFUHDVHG SX YRKLFOH FRQWURO JURXS IFN-_ VWDLQLQJ S DQG S UHVS WR EDVHOLQH OHYHOV H[FHSW FRQWURO DOV also associated with decreased pulmonary COX1 expressions S 1R VLJQLILFDQW GLIIHUHQFHV parameters, when group 5 or 6 were compared with group 2 LQMXU\ ZKHQ LQMHFWHG LQWR WKH 6WDQGDORQH L H ZLWKRXW HQGRWR[KLJK JURXS GRVHV GLG QRW JHQHU WKH VWXGLHG SDUDPHWHUV S! IRU FRQWURO GHPRQVWUDWLQJ WKDW effects on fetal lungs after IA administration.

Overall, high-dose oral PTX was the most effective treatment modality against inflammation-driven preterm fetal pulmonary LQMXU\ ZLWK UHWXUQ WR EDVHOLQH H

Discussion

In the current study, we tested the therapeutic efficacy of oral and IA PTX administrations against inflammation-mediated SODFHQWDO DQG IHWDO LQMXU\ LQ 37; ZDV JLYHQ SURSK\ODFWLFDOO\ L LQMHFWLRQ ZKHUHDV ,$ 37; ZDV DG with endotoxin. Two different doses labeled as low- and high-dose treatments were evaluated for both the oral and IA ways RI DGPLQLVWUDWLRQ 2YHUDOO GDWD NJ PDWHUQDO ZHLJKW GDLO\ XVH RI

7DEOH &RPSDULVRQV RI IHWDO SXOPRQDU\ SDUHQFK\PDO LPPXQRVWDLQLQJ LQW kids

0DUNHU	Group 1	Group 2	Group 3	*URXS	*URXS	Group 6	*URXS	*URXS	S YD
Interleukin-1	0.25±0.5	3.0±0	0.7±0.6	0.7±0.6	1.3±0.6	0.7±1.1	0.7±0.5	0.7±1.1	0.022
Interleukin-4	0.25±0.5	2.75±0.5	0.7±1.1	0.3±0.6	1.0±1.0	1.0±1.0	1.5±1.0	1.3±1.1	0.030
Interleukin-6	0.5±0.6	2.5±0.6	1.0±1.0	0.7±0.6	0.7±0.6	0.7±1.1	1.0±1.1	0.3±0.6	0.040
Interferon-alpha	0.25±0.5	3.0±0	1.3±0.6	0.7±0.6	1.0±0.0	1.3±1.1	1.7±1.3	0.7±0.6	0.013
Interferon-beta	0.25±0.5	2.75±0.5	2.0±1.0	0.3±0.6	2.0±1.0	2.0±1.7	1.0±0.8	0.3±0.6	0.017
Tumor necrosis factor-alpha	0.25±0.5	2.75±0.5	0.7±0.6	0.7±0.6	1.3±0.6	2.0±1.0	1.5±1.3	2.0±0.0	0.023
Cyclooxygenase-1	0.25±0.5	2.75±0.5	1.0±0.0	0.3±0.6	2.0±1.0	1.0±0.0	1.2±1.2	0.7±0.6	0.014
Cyclooxygenase-2	0.75±0.5	2.5±1.0	0.7±1.1	1.0±0.0	1.3±1.5	0.7±1.1	1.2±1.5	1.0±1.0	0.095
Caspase 3	0.25±0.5	2.5±0.6	0.7±0.6	0.3±0.6	1.0±1.0	1.7±1.5	0.5±0.6	1.0±1.0	0.024
Caspase 5	0.25±0.5	2.25±0.5	0.3±0.6	0.7±0.6	1.0±1.0	1.3±1.1	0.7±0.9	1.0±1.0	0.024
Caspase 7	0.25±0.5	2.5±1.0	1.0±0.0	0.3±0.6	1.3±0.6	2.0±0.0	1.2±0.9	1.7±0.6	0.040
6XUIDFWDQW SURWHLQ $	2.5±0.6	0.25±0.5	1.3±0.6	2.3±0.6	1.7±1.1	0.7±0.6	1.2±1.2	2.3±0.6	0.016
6XUIDFWDQW SURWHLQ %	2.5±0.6	0.5±0.6	1.0±1.0	2.7±0.6	0.7±1.1	1.0±1.7	1.5±1.3	2.0±1.0	0.023
6XUIDFWDQW SURWHLQ &	2.75±0.5	0.25±0.5	1.0±1.0	3.0±0	0.3±0.6	0.7±1.1	1.2±1.2	2.3±0.6	0.012
6XUIDFWDQW SURWHLQ '	3.0±0	0.75±0.9	1.0±1.7	3.0±0	1.3±1.1	1.0±1.0	2.0±1.4	2.3±1.2	0.026
Pro-surfactant protein B	3.0±0	0.5±0.6	1.0±1.0	3.0±0	1.0±1.7	0.7±0.6	2.0±0.8	2.7±0.6	0.009

*URXS 1HJDWLYH FRQWURO *URXS 3RVLWLYH FRQWURO ZLWK LQIODPPDWLRQ PHGLDWHG IHWDO LQM IHWDO LQMXU\ *URXS /RZ GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH IHWDO LQMXU\ *URXS +LJK GRVH ZLWKRXW IHWDO LQMXU\ *URXS +LJK GRVH LQWUD DPQLRWLF SHQWR[LI\OOLQH ZLWKRXW IHWDO LQMXU\ weak staining; 2, moderate staining; and 3, diffuse staining

endotoxin insult as the most effective protective therapeutic RSWLRQ DJDLQVW LQIODPPDWLRQ PTX when given into the amniotic fluid had some potential to decrease the IA inflammation, some adverse effects such as increased apoptosis in the placenta and fetal brain secondary to stimulation of an immune or toxic reaction is a concern that may restrict use of IA PTX for preterm fetal neuroprotection. There are some potential explanations why oral PTX was more HIIHFWLYH LQ RXU GHVLJQ 6LQFH in nature with repeated daily doses, the neuroprotective effects of PTX might have become more apparent before the inflammatory insult. This may imply that PTX is generally active as a preventive therapy, when given relatively early in the inflammation-driven preterm birth model with limited action following delayed administration. Repeated doses of PTX instead of a single-dose may be required for relevant action, DV ZHOO +RZHYHU PDWHUQDO DQG PTX may also play a role. Oral PTX administered maternally is PHWDEROL]HG LQWR DW OHDVW liver, and the main active metabolite called lisofylline has been shown to have anti-inflammatory and antifibrotic activity. Moreover, the anti-inflammatory actions of both PTX and lisofylline were attributed to 8-oxo derivatives rather than the parent forms 6LQFH DGPLQLVWUDWLRQ DPQLRWLF IOXLG ZLOO QRW HQDEOH

into active forms, IA drug delivery may have inadequate anti-inflammatory and fetal neuroprotective actions. Furthermore, it can be speculated that the maternal liver and possibly the placenta "detoxify" the parent compound into more active and less fetotoxic compounds. Evidence in favor of such an effect can be adverse fetal reactions we encountered in our design, including increased apoptosis in fetal brain following IA PTX administrations in pregnancies without intrauterine inflammation. In summary, oral PTX administered to high-risk groups for preterm delivery should be the preferred way of administration for fetal neuroprotection.

Experimental data on use of PTX for inflammation-induced adverse effects in the placenta are scarce. In a tissue culture model that used second trimester human placentas treated with endotoxin and PTX, placental expression and production RI LQIODPPDWRU\ PDUNHUV VXFK DV , shown to decrease with administration of PTX. These in vivo results are in agreement with in vivo data from our experiments, anti-inflammatory actions of PTX on the placenta. 6RPH SUHYLRXV DQLPDO VWXGLHV K placental and fetal effects of maternal PTX in the endotoxin-induced intrauterine inflammation models. PTX was reported to mitigate endotoxin-induced up-regulation of placental heme oxygenase-1 in pregnant mice. PTX was also shown to decrease embryo resorption, fetal mortality, and fetal

JURZWK UHVWULFWLRQ IROORZLQJ L pregnant mice +RZHYHU WKHVH SRVLW partially replicated in a rabbit model. In pregnant rabbits given intrauterine endotoxin, animals that received PTX 20 mg/kg/day in 3 divided doses had similar preterm delivery rates, despite prolonged time until fetal death compared to controls. On the other hand, in experimentally induced equine placentitis using intracervical inoculation of Streptococcus equi, 17 mg/kg daily maternal dose of PTX given orally from the onset of clinical signs to delivery was associated with improved viability of foals and negative fetal bacterial cultures. Depending on these results in association with our current data, oral maternal PTX treatment given for a longer period, particularly before SODFHQWDO DQG IHWDO LQMXU\ FRPPHQFHV alleviate subsequent intrauterine inflammation.

In the English literature, we were able to identify only one experimental study that specifically evaluated the fetal neuroprotective effects of antenatally administered PTX. This study by Dilek et al. used intraperitoneal endotoxin WR LQGXFH IHWDO LQMXU\ LQ SUHJQDQW UDWV DQG GRVHV NJ RI PDWHUQDOO\ LQMHFWHG 37; associated with decreased apoptosis and MBP immunostaining in periventricular white matter of the pups. The results imply that PTX is a potential neuroprotective agent against fetal term EUDLQ LQMXU\. Our data from a phylogenetically diverse animal model in the early preterm period with numerous inflammatory DQG QHXURQDO LQMXU\ PDUNHUV HODERUDWH WKHVH SUHYLRXV ILQGLQJV.

In summary, previous experimental data show that prophylactic maternal PTX treatment may decrease placental and fetal EUDLQ LQMXU\ IROORZLQJ DQ LQWUDXWHULQH but probably do not prevent preterm delivery. Although we did not specifically address the timing of preterm delivery in our experiments, our results generally elaborate these findings and support use of maternal PTX as a fetal neuroprotective agent, particularly for pregnancies at risk for preterm delivery. Moreover, we showed the efficacy of oral daily doses at 60 mg/NJ ZKLFK LV FOLQLFDOO\ PRUH IHDVLEOH.

We could identify only one clinical study on the use of antenatal 37; LQ KXPDQ SUHJQDQFLHV 7KH UDQGRPL]HG SLORW by /DXWHUEDFK HW DO included 96 women between 23-34 ZHHNV RI JHVWDWLRQ ZLWK LPPLQHQW SUHWHUP GHOLYHU\ WR PJ GD\ 37; Q DQG FRQWURO Q or until delivery, with all the women receiving standard beta-mimetic tocolysis, corticosteroids for fetal lung maturation, and magnesium sulfate for neuroprotection. The cerebroplacental ratio at week 3 of treatment was found to be significantly higher in the treatment arm. Moreover, composite neonatal outcome LQWUDYHQWULFXODU EOHHGLQJ QHRQDWDO PRUWDOLW\ ZDV ORZHU delivery was similar. Our results are principally in line with the findings from this pilot clinical study. We did not specifically HYDOXDWH IHWDO 'RSSOHU VWXGLHV our results similarly imply that PTX given for at least 2 weeks has

... administered half of the daily 800 mg dose as an intravenous infusion, and the rest 400 mg as oral tablet. Considering the dose scheme in our study that corresponds to higher oral doses than that of /DXWHUEDFK HW DO, the necessity and feasibility of additional daily intravenous administrations are questionable. Therefore, future clinical studies evaluating fetal neuroprotective effects of prophylactic antenatal PTX therapy can focus on relatively low PJ GDLO\ RUDO GRVHV RI 37; administrations, which necessities admission to the hospital.

6WXG\ /LPLWDWLRQV

There were certain limitations of the current experimental study. Although various tissue parameters for inflammation, apoptosis, DQG WLVVXH LQMXU\ ZHUH VWXGLHG additional methods such as genetic expressions and Western EORW ZHUH QRW HYDOXDWHG. 6LQFH and clinical evidence in favor of safety of oral PTX use during the third-trimester of pregnancy, our design did not include standalone oral PTX experimental groups. There was also no RUDO SODFHER JURXS. +RZHYHU, DGG groups into the present design would be unethical. C-reactive protein and white blood cell count and differential in fetal blood samples were not measured, as interleukins and TNF-_ were considered more specific for fetal inflammatory response. The current design was also unable to reveal data on temporal changes of the studied parameters. In our validated model, preterm birth was induced 5 days after IA endotoxin, a time period supposed to be most suitable for evaluation of fetal LQIODPPDWRU\ UHVSRQVH. +RZHYHU, time points, including postpartum alterations, since newborn NLGV ZHUH HXWKDQL]HG DIWHU in utero tissue responses. The present experimental model cannot also distinguish whether the experimental IA inflammation created in the intervention groups in the study essentially caused spontaneous preterm birth, since preterm delivery was induced iatrogenically to retrieve fetal and placental samples. Finally, CP is multifactorial condition that can occur during the intrapartum period, during, or after delivery. The current data do not explicitly reveal information on preterm birth related to CP and/or related complications, and are restricted WR H[SHULPHQWDO IHWDO LQMXU\ analysis of mid- and long-term results of CP.

Conclusion

Maternal PTX given orally before inflammation-mediated preterm delivery in a prophylactic fashion alleviates fetal inflammatory response and may exhibit fetal neuroprotective effects in the caprine model. Considering the favorable fetal safety profile of PTX during the third trimester of pregnancy, clinical studies evaluating its antenatal use in imminent preterm delivery against subsequent development of possible brain LQMXU\ DUH ZDUUDQWHG.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO 7KH VWXG\ SURWRFRO ZDV VXEMHFWHG WR DQLPDO HWKLFV FRPPLWWHH DSSURYDO E\ 6•OH\PDQ 'HPLUHO 8QLYHUVLW\ $QLPDO ([SHULPHQWDWLRQ /RFDO (WKLFV &RPPLWWHH DSSURYDO GDWH DQG QR

,QIRUPHG &RQVHQW Experimental study.

$XWKRUVKLS &RQWULEXWLRQV

&RQFHSW 0 6 $. gg 0+ '. $ 'HVLJQ 0 6 $. '. 'DWD &ROOHFWLRQ RU 3URFHVVLQJ 0 6 gg 0+ '. $ $ 2 g $QDO\VLV RU ,QWHUSUHWDWLRQ 0 6 gg 0+ 2 g /LWHUDWXUH 6HDUFK 0 6 $) 2 g :ULWLQJ 0 6 gg

&RQIOLFW RI ,QWHUHVW No conflict of interest was declared by the authors.

)LQDQFLDO 'LVFORVXUH The present study was supported by IXQGV IURP WKH 6FLHQWLILF DQG 7HFKQRORJLFDO 5HVHDUFK &RXQFLO RI 7XUNH\ UHVHDUFK SURMHFW QR

Preliminary data were presented as abstracts at the 23th World Congress on Ultrasound in Obstetrics and Gynecology, 6-9 2FWREHU 6\GQH\ $XVWUDOLD DQG DW WKH th World Congress RQ 8OWUDVRXQG LQ 2EVWHWULFV *\QHFRORJ\ 6HSWHPEHU %DUFHORQD 6SDLQ

References

1. Romero R, EspLQR]D - .XVDQRYLF -3 *RWVFK) +DVVDQ 6 (UH] 2 HW al. The preterm parturition syndrome. BJOG 2006;113:17-42.
2. *RWVFK) 5RPHUR 5 .XVDQRYLF -3 0D]DNL 7RYL 6 3LQHOHV %/ (UH] O, et al. The fetal inflammatory response syndrome. Clin Obstet Gynecol 2007;50:652-83.
3. 5LQDOGL 6) +XWFKLQVRQ -/ 5RVVL $* 1RUPDQ -($Q\WL LQIODPPDWRU\ mediators as physiological and pharmacological regulators of parturition. Expert Rev Clin Immunol 2011;7:675-96.
4. %DVKLUL $ %XUVWHLQ (0D]RU 0 &HUHEUDO SDOV\ DQG IHWDO LQIODPPDWRU\ response syndrome: a review. J Perinat Med 2006;34:5-12.
5. *XUEX] $ .DUDWHNH $ <LOPD] 8 .DEDFD & 7KH UROH RI SHULQDWDO and intrapartum risk factors in the etiology of cerebral palsy in term deliveries in a Turkish population. J Matern Fetal Neonatal Med 2006;19:147-55.
6. 'R\OH /: &URZWKHU &$ 0LGGOHWRQ 3 0DUUHW 6 5RXVH ' 0DJQHVLXP sulphate for women at risk of preterm birth for neuroprotection of WKH IHWXV &RFKUDQH 'DWDEDVH 6\VW 5HY &
7. (GZDUGV -0 (GZDUGV /(6ZDP\ *. *URWHJXW &$ 0DJQHVLXP sulfate for neuroprotection in the setting of chorioamnionitis. J Matern Fetal Neonatal Med 2018;31:1156-60.
8. +DUULV (6FKXO]NH 60 3DWROH 6. 3HQWR[LI\OOLQH LQ SUHWHUP neonates: a systematic review. Paediatr Drugs 2010;12:301-11.
9. 3DPPL 0 +DTXH .1 3HQWR[LI\OOLQH IRU WUHDWPHQW RI VHSVLV DQG QHFURWL]LQJ HQWHURFROLWLV LQ QHRQDWHV &RFKUDQH 'DWDEDVH 6\VW 5HY 2015;3:CD004205.
10. 7LDQ - 6KHQ 3 3DQ . =KRX 4 (IILFDF\ RI SHQWR[LI\OOLQH WUHDWPHQW IRU QHRQDWDO VHSVLV D PHWD DQDO\VLV RI UDQGRPL]HG FRQWUROOHG studies. Ital J Pediatr 2019;45:108.
11. &KDOPHK $ 5DKPDQL 6KDKUDNL $ +HLGDUL 0 6DIDUL 0 3RXUMDIDU 0 1D]LIL 6 HW DO 7KH FRPSDUDWLYH HIIHFWV RI GH[DPHWKDVRQH versus pentoxifylline against induced acute phase response in an ovine experimental endotoxemia model. Inflammopharmacology 2016;24:59-64.
12. 7jQRVL * 1pPHWK , 3LQWpU 6 QKLELWRU\ HIIHFWV RI SHQWR[LI\OOLQH on the pre-eclamptic-like symptoms in ewes. Eur J Obstet Gynecol Reprod Biol 2001;99:25-32.
13. :DWDQDEH 7 0DWVXGD 7 +DQLWD 7 2NX\ . HW DO ,QGXFWLRQ RI QHFURWL]LQJ IX of intravenous granulocyte-colony stimulating factor and intra-amniotic endotoxin in premature fetal sheep. Pediatr Res 2007;62:670-3.
14. 6H]LN 0 6XUJHRQ 'HVLJQ 3UHFHVVLRQ $ 0 6LPVHN g +DO×J•U 0 .D HW DO 3UHSDUDWLRQ RI DQ DQLPDO PRGHO PHGLDWHG IHWDO colony stimulating factor and high-dose intraamniotic endotoxin in the caprine model. Turk J Obstet Gynecol 2019;16:41-9.
15. $QWDO\DO× 0 2]PHQ 2 +DO×J•U 0 6H]LN 0 following single high-dose intra-amniotic betamethasone treatment in preterm goat kids. J Turk Ger Gynecol Assoc 2012;13:242-6.
16. /LVND $ $MNXFHZLFK /+ 0DUVHOOD 5 0D] Pharmacokinetics of pentoxifylline and its 5-hydroxyhexyl metabolite after oral and intravenous administration of pentoxifylline to healthy adult horses. Am J Vet Res 2006;67:1621-7.
17. 0DUVHOOD 5 1LFNOLQ &) 0XQVRQ -: 5REHUWV of pentoxifylline in dogs after oral and intravenous administration. Am J Vet Res 2000;61:631-7.
18. ,OOLD 5 6RODQD & 2OLYHULH 3 7REROO - of fetal pulmonary aspiration of intra-amniotic administered surfactant in animal experiment. J Perinat Med 2004;32:354-8.
19. %HVW %0 %XUQV -& 'H9LQFHQ]R - 3KHOSV JT, et al. Pediatric Pharmacology Research Unit Network. Pharmacokinetic and tolerability assessment of a pediatric oral formulation of pentoxifylline in kawasaki disease. Curr Ther Res Clin Exp 2003;64:96-115.
20. 1LFNODVVRQ 0 %M|UNPDQ 6 5RWK % 6WHUHRVHOHFWLYH PHWDEROLVP RI SHQWR[LI\OOLQH LQ humans. Chirality 2002;14:643-52.
21. :yMFLN 3D]FKRÑ . :QXN 'LQGD ' .RF]XUNLHZLF] 3 6DQDN 0 HW DO 3HQWR[LI\OOLQH LQIODPPDWRU\ DQG attenuate transforming growth factor 1-induced asthmatic bronchial fibroblast-to-myofibroblast transition. Acta Biochim Pol 2016;63:437-42.
22. Bhat VB, Madyastha KM. Antioxidant and radical scavenging properties of 8-oxo derivatives of xanthine drugs pentoxifylline and lisofylline. Biochem Biophys Res Commun 2001;288:1212-7.
23. 6SHHU (0 /LQ ; 0XUWK\ $ +RX : ,VODP 6 inhibits lipopolysaccharide-induced inflammatory mediators in human second trimester placenta explants. Placenta 2017;58:60-6.
24. =KDQJ & /L ,< =KDR / :DQJ + ;X '; /36 XS UHJXODWHV WKH H[SUHVVLRQ RI placenta. Placenta 2007;28:951-7.
25. =KRQJ ;+ 6KL :< 0D $7 *RQJ ;& =KDL ;+ (IIHFWV RI 5DGL[VFXWHOODULDH DQG 5 LQGXFHG DERUWLRQ DQG WKH XWHULQH ,$ Med 2008;36:141-8.
26. ;X '; &KHQ <+ :DQJ + =KDR / :DQJ -3 :HL factor alpha partially contributes to lipopolysaccharide-induced intra-uterine fetal growth restriction and skeletal development UHWDUGDWLRQ LQ PLFH 7R[LFRO /HWW
27. /DGGDG 0 :HLGH 0 :LHOO 0DUWLQH] 2)RMDFR Pentoxifylline does not delay bacterially induced preterm delivery in rabbits. J Perinatol 1996;16:281-4.

%DLOH\ &6 0DFSKHUVRQ 0/ 3R]RU 0$ %HQVRQ 6 *LJXHUH 6 HW DO 7UHDWPHQW HIILFDF\ RI WULPHWKRSULP VXOIDPHWKR[D]ROH SHQWR[LI\OOLQH DQG DOWUHQRJHVW LQ H[SHULPHQWDOO\ induced equine placentitis. Theriogenology 2010;74:402-12.
'LOHN 0 .XPUDO $ 2N\D\ (2]EDO 6 7XJ\DQ . 7X]XQ) HW DO Protective effects of pentoxifylline on lipopolysaccharide-induced ZKLWH PDWWHU LQMXU\ LQ D UDW PRGHO Matern Fetal Neonatal Med 2013;26:1865-71.
/DXWHUEDFK 5 5\WOHZVNL . 3DZOLN ' +XUNDOD - :RMWRZLF] $ %REURZLF] * HW DO (IIHFW RI SHQWR[preterm labour, on the foetal-placental circulation and neonatal RXWFRPH D UDQGRPL]HG SURVSHFWLY Pharmacol Toxicol 2012;110:342-6.

Turk J Obstet Gynecol 2020;17:270-277

The relationship between isolated pes equinovarus and aneuploidies and perinatal outcomes: Results of a tertiary center

þ]ROH SHV HNLQRYDUXV LOH DQ|SORL VRQXoODU 7HUVL\HU WHN PHUNH] VR

0HWH 6×F× 0H\PDQ &DQVXQ 'HPLU

Çukurova University Faculty of Medicine, Department of Obstetrics and Gynecology, Adana, Turkey

$EVWUDFW

2EMHFWLYH &RQJHQLWDO SHV HTXLQRYDUXV 3(9 LV WKH PRVW FRPPRQ FRQJHQLWDO 0.2-0.3%. It can be diagnosed from the 12th week of pregnancy. Non-isolated cases tend to be syndromic and complex. We aimed to evaluate the results of perinatally diagnosed isolated PEV.

0DWHULDOV DQG 0HWKRGV This was a retrospective cohort study conducted between March 2015-March 2020. Women who pres VFUHHQLQJ RU ZHUH UHIHUUHG GXH WR DQ\ VXVSHFWHG IHWDO DQRPDO\ ZHUH VXEMH Karyotype analysis was discussed for patients with PEV. Pregnancy termination was recommended for those with chromosomal/life-threatening anomal The diagnosis was confirmed by postnatal examination/autopsy. Postnatal diagnosis was accepted as false-positive in those with no PEV.

Results: 2QH KXQGUHG WKLUW\ HLJKW SDWLHQWV ZHUH IRXQG WR KDYH 3(9 RI ZK WKH ILUVW WULPHVWHU ZDV VLJQLILFDQWO\ KLJKHU FRPSDUHG ZLWK WKH VHFRQG WULI LQ SDWLHQWV LQ WKH LVRODWHG JURXS 7HUPLQDWLRQ ZDV SHUIRUPHG WR DQRPDOLHV ZHUH GHWHFWHG LQ SDWLHQWV DQG WHUPLQDWLRQ ZDV UHFRPPH DQRPDOLHV LQFRPSDWLEOH ZLWK OLIH ,Q WKH SRVWQDWDO HYDOXDWLRQ WKH VXUJLF

&RQFOXVLRQ When PEV is diagnosed, detailed fetal anomaly screening must be performed, patients should be informed about the chromoso ULVN +LJK IDOVH SRVLWLYH UDWHV LQ WKH ILUVW WULPHVWHU VKRXOG EH NHSW LQ PL It should be remembered that some neuromuscular/skeletal system anomalies may occur for the first time in the postnatal period in isolated cases.

.H\ZRUGV Clubfoot, Down syndrome, diagnostic imaging, karyotyping

Öz

$PDo .RQMHQLWDO SHV HNLQRYDUXV 3(9 D\Dÿ×Q HQ V×N J|U•OHQ NRQMHQLWDO GHIR V×NO×NOD J|U•O•U *HEHOLÿLQ KDIWDV×QGDQ LWLEDUHQ WHüKLV HWPHN P•PN•QG• dDO×üPDP×]GD SHULQDWDO G|QHPGH WHüKLV HGLOHQ L]ROH 3(9 ROJXODU×Q×Q VRQXoO *HUHo YH <|QWHPOHU dDO×üPDP×] 0DUW 0DUW WDULKOHUL DUDV×QGD \•U•W•OH EDüYXUDQ YH\D KHUKDQJL ü•SKHOL IHWDO DQRPDOL QHGHQL\OH VHYN HGLOHQ NDG×QOD DQRPDOLOHU Do×V×QGDQ NRQWURO HGLOGL 3(9 VDSWDQDQ KDVWDODUOD NDU\RWLS D JHEHOLN WHUPLQDV\RQX |QHULOGL 7DQ× SRVWQDWDO PXD\HQH YH\D RWRSVL LOH GRÿU %XOJXODU <•] RWX] VHNL] KDVWDGD 3(9 VDSWDQG× .×UN ELUL L]ROH LGL þ]RO N×\DVODQG×ÿ×QGD DQODPO× GHUHFHGH \•NVHNWL V×UDV×\OD YH S þ]ROH KDVWD\D WUL]RPL QHGHQL\OH WHUPLQDV\RQ X\JXODQG× 1RQ L]ROH JUXSWD KDVWD\D \DüDPOD EDÿGDüPD\DQ DQRPDOLOHU QHGHQL\OH JHEHOLN WHUPLDQV\ WHGDYL RUDQ× V×UDV× LOH YH LGL YH DUDGDNL IDUN LVWDWLNVHO RODUDN DQO

PRECIS: We aimed to evaluate the perinatal and neonatal results of pregnant women who were found to have isolated PEV during the first a second trimester ultrasonographic screening in our clinic.

$GGUHVV IRU &RUUHVSRQGHQFH 0HWH 6×F× 0PD $GUHVL
dXNXURYD 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 2EVWHWULFV DQG *\QHFRORJ\ $GDQD 7XUNH\
Phone: +90 505 617 65 38 (PDLO metesucu@yahoo.com 25&,' ,' orcid.org/0000-0002-6889-7147
5HFHLYHG *HOLü 7DULKL 29.11.2020 $FFHSWHG .DEXO 7DULKL 30.11.2020

6RQXo 3(9 WHüKLVL NRQGXÿXQGD HüOLN HGHQ DQRPDOLOHU LoLQ D\U×QW×O× ELU IH
KDNN×QGD ELOJLOHQGLULOPHOLGLU 7DQ× LoLQ LON WULPHVWHUGHNL \•NVHN \DQO×ü S
%D]× Q|URP•VN•OHU YH LVNHOHW VLVWHPL DQRPDOLOHULQLQ L]ROH ROJXODUGD LON N
$QDKWDU .HOLPHOHU dDUS×N D\DN 'RZQ VHQGURPX WDQ×VDO J|U•QW•OHPH NDU\RWL

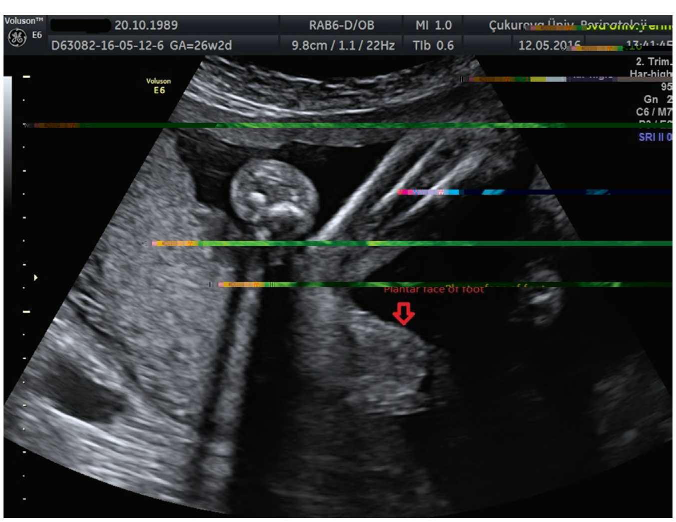
Introduction

Congenital pes equinovDUXV 3(9 RU FOXEIRRW LV D FRQJHQLWDO PDOIRUPDWLRQ FKDUDFWHUL]HG E\ H[FHVVLYH SODQWDU IOH[LRQ RI RQH foot or both feet, inward tilting of the heel, and adduction of the forefoot . It is seen with a frequency of 2-3 per 1000 live births and is the most common congenital deformity of the foot. It can be unilateral or bilateral, and its incidence in male fetuses is 2 times higher.

Although the diagnosis of congenital PEV is usually made from WKH VHFRQG WULPHVWHU ZLWK XOWUDVRQRJUDSK\ )LJXUH LW LV possible to diagnose it from 12th week in the late first trimester. Congenital PEV can be diagnosed more frequently through the development of ultrasound technology and the increase in the skills of physicians over time.

6\QGURPLF FDVHV WHQG WR EH PRUH FRPSOH[DQG WKHLU DVVRFLDWLRQ with other congenital malformations and/or chromosomal and genetic anomalies is common. It has been associated with some aneuploidies, deletion syndromes, sex chromosome abnormalities, neuromuscular disorders, microdeletion and duplications. Despite advances in molecular gene studies, D PDMRU FDXVDWLYH JHQH KDV QRW EHHQ LGHQWLILHG DQG FOLQLFDO features of even familial cases show heterogeneity.

Positional PEV is mostly associated with intrauterine factors limiting fetal movements, such as oligohydramnios, twin pregnancy and uterine anomalies. Early amniocentesis is one of the iatrogenic reasons that may lead to this. There may be accompanying anomalies or it can be seen as isolated. Idiopathic PEV is usually isolated and generally have a good prognosis,



)LJXUH PEV ultrasonography image

PEV: Pes equinovarus

their relationship with chromosomal anomalies is limited, and familial cases have been reported. The fact that it has a higher prevalence in some populations and that it is more common among the male sex suggests that it is the result of a polygenetic predisposition .

Environmental and genetic factors are thought to play a role in the etiology. It has been shown that maternal smoking, LQFUHDVHG ERG\ PDVV LQGH[%0, D... reuptake inhibitor use in the first trimester increases the risk of congenital PEV . ,W ZDV UHSRUWHG WKDW /D... during the prenatal period increased the risk of congenital PEV .

Conservative treatment is the primary method recommended LQ 3(9 WUHDWPHQW 6XUJHU\ LV UHFR... do not respond to conservative treatment or who are late for treatment. Untreated patients may experience limitation of motion, deformity, and pain in the long term. Conservative PHWKRGV LQFOXGH FRUUHFWLYH VSOL... physiotherapy, and serial manipulations. The surgical method may vary depending on the severity of the clinical course and accompanying anomalies.

In this study, we aimed to evaluate the perinatal, neonatal and orthopedic results of pregnant women who were found to have isolated PEV during the first and second-trimester ultrasonographic screening in our clinic.

Materials and Methods

This study was a retrospective cohort study conducted in the 3HULQDWRORJ\ 8QLW RI dXNXURYD 8QL... Department of Obstetrics and Gynecology, between March 2015 and March 2020. Patients who presented to our clinic for routine first-trimester and second-trimester fetal anomaly screening and patients referred to our clinic due to any suspected fetal anomaly or positive screening test were included in this study. Among the patients admitted in the first trimester, those between 12 and 14 weeks were included in the study. All SDWLHQWV ZHUH VXEMHFWHG WR D GH... FKHFNHG IRU WKH SUHVHQFH RI 3(9 ... of all patients were performed by four researchers experienced LQ IHWDO DQRPDO\ VFUHHQLQJ XVLQJ... SUREH ZLWK D 9ROXVRQ (*(0HGLFD... device, and information of all patients was recorded on the 0LFURVRIW 9LHZSRLQW *(0HGLFDO 6... system. Information of the patients and accompanying anomalies were obtained retrospectively from patient files and 0LFURVRIW 9LHZSRLQW *(0HGLFDO 6\V... comprised a heterogeneous patient group including high and

low-risk patients. Approval for the study was obtained from WKH (WKLFV &RPPLWWHH RI dXNXURYD 8QLYHUVLW\ 0HGLFDO)DFXOW\

were confirmed by karyotype analysis in peripheral blood. 7ULVRP\ ZDV GHWHFWHG LQ RQH patient.

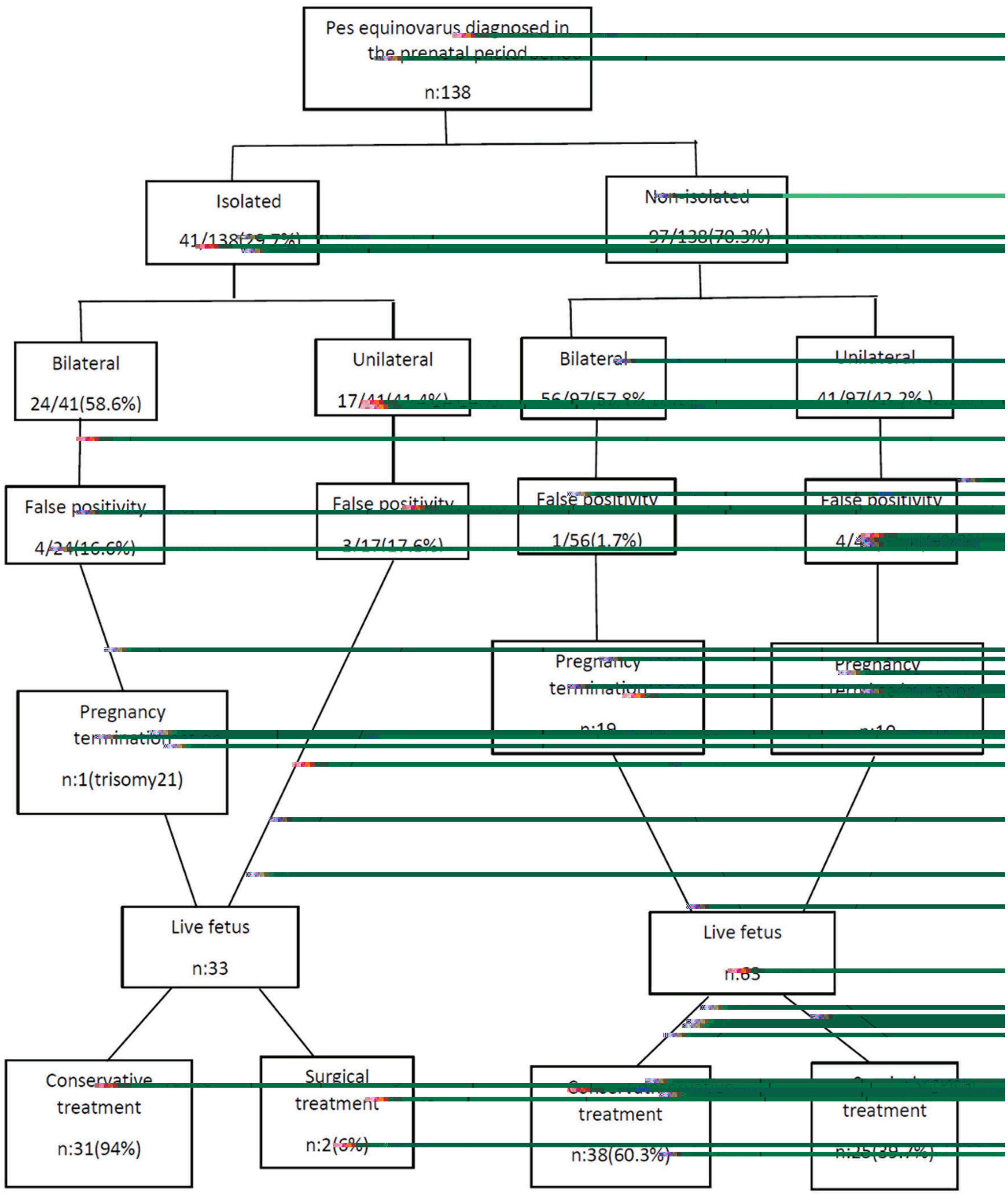
When the frequency of chromosomal anomalies was evaluated according to unilaterality or bilaterality, it was found as 5.88%

LQ WKH XQLODWHUDO JURXS DQG ... GLIIHUHQFH ZDV VWDWLVW...

Trisomy 21 was detected in 51 patients in the entire study group

@ ,Q ILYH RI IHWXVHV Z...

KDG 3(9 $IWHU WKH HOLPLQDWL...



)LJXUH Clinical course of PEV cases diagnosed in the prenatal period

PEV: Pes equinovarus

7DEOH Distribution of postnatal false positivity rate of PEV due to laterality in antenatally diagnosed isolated and non-isolated groups

	8QLODWHUDO	%LODWHUDO	7RWDO
,VRODWHG Q			
Non-isolated Q			
P-value*			

*chi-square test was used, PEV: Pes equinovarus

7DEOH Postnatal false positivity distribution according to the gestational week at the time of antenatal diagnosis in the isolated and non-isolated groups

	)LUVW 7ULPHVWHU	Second 7ULPHVWHU	S YDO
,VRODWHG Q			
1RQ LVRODWHG Q			
7RWDO Q			

*chi-square test was used

21 in the entire group, the PEV rate was calculated as 1.58

7KH UDWH RI WULVRP\ L

+RZHYHU WKH UDWH RI

ZLWKRXW 3(9 ZDV IRXQG DV

6.6-fold increase in the risk for trisomy 21 in patients with PEV.

7KLUW\ RQH SDWLHQWV LQ WKH

conservative treatment. Conservative treatment was performe

RQ SDWLHQWV LQ WKH QRQ

ZDV VWDWLVWLFDOO\ VLJQLILFDQW

rate was statistically significantly higher in the isolated group

S 6XUJLFDO WUHDWPHQW ZDV

did not respond to conservative treatment or who were late fo

WUHDWPHQW &RUUHFWLYH FDVWLQ

used in conservative treatment. In terms of surgery, the mos

preferred methods were achillotomy and posteromedial releas

surgery.

Discussion

First-trimester and second-trimester fetal anomaly screenin

are recommended to all pregnant women during antenata

follow-up. Although PEV incidence is stated as 0.2-0.3% in the

literature, the results in our study were far from these values,

as some of the patients were referred. Although the diagnosis

of PEV is usually made in the second trimester, Keret et al.

showed that it was possible to make a diagnosis from the 12

ZHHN LQ WKH ILUVW WULPHVWHU

the first trimester has some drawbacks. Bogers et al. showed

that there was a temporary PEV position during the norma

development of the lower extremity in the first trimester and

this development continued until the 13th week. Diagnoses

made without waiting for this physiologic positional change

will cause an increase in false positivity. In our study, the rate

R L IDOVH SRVLWLYLW\ LQ WKH HQWLU

The false-positive rate was statistically significantly higher in

SDWLHQWV LQ WKH ILUVW WULPHVWHU

YV S ,Q WKH LVRODWHG JURX

ZDV IRXQG DV UHDFKLQJ L

In the literature, this rate varies between 0% and 40% for isolated cases . Our findings were similar to the literature.

+RZHYHU LQ WKH LVRODWHG JURXS

diagnosed in the first trimester draws attention, which can be explained by the fact that the patients in the isolated group were milder and by the physiologic position change of the foot in the first trimester. Due to high false-positive rates, isolated cases,

7DEOH Clinical features of PEV patients diagnosed in the prenata

period

	Isolated Q	1RQ LVRODWHG Q	S YDO
Age	25.32±4.25	26.12±4.72	0.193
BMI			0.396
Conception method			
Natural			0.406
,9) ,&6, (7			0.305
Other ART			0.105
Gestational week at the time of GLDJQRVLV ZHHN	7KLV LQGLFDWHV D		
/DWHUDOLW\			
Unilateral			0.354
Bilateral	7KH FRQVHUYDWLYH WUHDWPHQ		0.413
Fetal Karyotyping			
Normal			
Trisomy 21			0.82
Trisomy 18			0.79
Trisomy 13	-		0.73
6H[FKURPRVRPDO anomalies	-		ZHUH
Pregnancy result			
Pregnancy termination			
Delivery			
Vaginal birth			0.31
Caesarean			0.42
Birth week			
Birth weight	3230		
6H[	+RZHYHU WKH GLDJQRVLV PDGH LQ		
Girl			0.23
Boy			0.24
Neonatal intensive care need			

*chi-square test was used, PEV: Pes equinovarus, BMI: Body mass index

especially those diagnosed in the first trimester, should be followed up with serial examinations to confirm the diagnosis. In this study, the median gestational week at the time of diagnosis of PEV was determined as 21.5 and 19.1 for the isolated and non-isolated groups, respectively. This can be explained by the fact that the disease is more complex and severe in the presence of accompanying anomalies and therefore can be diagnosed earlier + D U W J H reported the median gestational week at the time of diagnosis as 23 weeks.

Postnatal examinations allow the detection of accompanying ILQGLQJV WKDW FRXOG QRW EH IRXQG LQ WKH SUHQDWDOO SHULRG in the non-isolated group, chromosomal anomalies were found in two patients who did not undergo amniocentesis during the DQWHQDWDO SHULRG WULVRP\ LQ SDWLHQW , Q WKH LVRODWHG JURXS chromosomal anomalies were found in the postnatal period. / DXVRQ HWDO stated that neurologic, developmental, and additional structural anomalies could be detected in postnatal follow-up in isolated cases. In their studies, it was observed that 10% of isolated cases turned into complex cases after a minimum of 1-year follow-up. Di Mascio et al.reported that anomalies related to the skeletal system and neuromuscular system were detected at a rate of 7% in the postnatal follow-up of patients diagnosed as having isolated PEV in the prenatal period. Offerdal et al. made a minimum of 2-years follow-up and found that 15% of the cases turned into complex cases. 6KLSS DQG %HUQDHIHU UDWHV in their study. Our study has limitations in this regard because we have not yet followed-up all patients for at least one year.

2XU VH[GLVWULEXWLRQ ER\ JLUO which was consistent with the literature. In our study, the percentage of non-isolated PEV was 73%. Although this rate varies between 48% and 51% in some community studies, rates up to 80% have been reported in tertiary centers such as our clinic where high-risk patients are treated .

In our study, although chromosome anomalies were detected with a rate of 5.8% in the isolated group, the rate was 16.3% in the non-isolated group. Many authors believe that karyotype is necessary in the presence of anomalies accompanying PEV, however, there are ongoing discussions for isolated cases. The most common chromosomal anomalies associated with PEV DUH WULVRPLHV DQG , W LV SRVVLEOH WR GHWHFW ZLWK trisomy 13 and 18 using ultrasonography due to accompanying DQRPDOLHV +RZHYHU VH[FKURPRVRPH DQHXSORLGLHV VXFK as trisomy 21 sometimes display very limited or no findings. For this reason, especially in isolated PEV cases, karyotyping comes to the fore due to the risk of trisomy 21. In the study of Viaris et al. , the rate of chromosomal anomalies in the isolated JURXS ZDV / D Xreported the incidence of chromosomal anomalies as 2.3% in the isolated group. Recommending karyotype to isolated cases in the presence of advanced maternal age or positive screening test should not be avoided . PEV was detected in five of 51 patients with trisomy LQ RXU VWXG\ SRSXODWLRQ 7K risk of trisomy 21 in patients with PEV 6.6 times. Offerdal et al. detected aneuploidy at the rate of 13% in patients with PEV and showed that there was a strong relationship between PEV and chromosomal anomalies, and they recommended karyotyping for all patients including isolated cases. Tegnander and Eik-Nes reached similar results.

According to the findings of Bakalis et al.the prognosis was worse and the frequency of chromosomal anomalies was higher LQ WKH SUHQDWDO SHULRG + HQFH in the bilateral group, similar to our study. In the study of Viaris et al. , no difference was found between the two groups.

Despite the high incidence of PEV, only a few causative genes are known *PITX1 (MIM 601542), IGF1R (MIM 147370), TBX4 (MIM 601719), FOXP1 (MIM 605515), and RBM10 genes have been found to be associated with isolated PEV . Recommending chromosomal microarray studies in addition to conventional karyotyping to patients with PEV will help to better understand the factors causing the disease because multigenetic factors play a role in the etiology

Conservative treatment is the primary method recommended in WKH WUHDWPHQW RI 3(9 6XUJHU\ LV U to not respond to conservative treatment. There is no treatment in the prenatal period. The accepted method in conservative WUHDWPHQW LV 3RQVHWL FDVWLQJ ZDV SHUIRUPHG RQ WZR SDWLHQWV SDWLHQWV LQ WKH QRQ LVRO ZDV VWDWLVWLFDOO\ VLJQLILFDQW S screening performed to detect accompanying anomalies will help us understand whether the cases are isolated and predict the postnatal prognosis.

6WXG\ /LPLWDWLRQV

The limitations of this study are that it had a retrospective design, only patients diagnosed during the intrauterine period could be reached, and the rate of PEV detection could not be specified due to the exclusion of patients diagnosed for the first time in the postnatal period.

Another limitation is that only conventional karyotyping could be performed in patients, chromosomal microarray was QRW SHUIRUPHG 6WXGLHV LQYROYLQ evaluations are needed to better understand the etiology of the disease.

Conclusion

The diagnosis of PEV can be made in the late first and second trimesters. In the first trimester, the rate of false positivity is higher, and the diagnosis should be confirmed with serial examinations. When PEV is diagnosed, detailed fetal anomaly screening should be performed for anomalies that may accompany, and patients should be informed about the

increased incidence of chromosomal anomalies, and karyotype and chromosomal microarray analysis should be recommended. Chromosomal microarray can identify clinically significant FKURPRVRPH DEQRUPDOLWLHV JDLQV DQG ORVVHV RI 1$ WKDW DUH below the resolution of conventional chromosome analysis. The risk of this chromosomal and structural anomaly further increases in the presence of accompanying additional findings. It should be kept in mind that some neuromuscular and skeletal system anomalies may occur for the first time in the postnatal period in isolated cases.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO Approval for the study was REWDLQHG IURP WKH (WKLFV &RPPLWWHH RI dXNXURYD 8QLYHUVLW\ 0HGLFDO)DFXOW\ 5HJLVWUDWLRQ QXPEHU

,QIRUPHG &RQVHQW Written informed consent was obtained from all patients.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV 6 & 7' %&RQFHSW 0 6 'HVLJQ 0 6 'DWD &ROOHFWLRQ RU 3URFHVVLQJ 0 6 $QDO\VLV RU ,QWHUSUHWDWLRQ 6 & ' /LWHUDWXUH 6HDUFK 6 & ' :ULWLQJ 6 & '

&RQIOLFW RI ,QWHUHVW No conflict of interest was declared by the authors.

)LQDQFLDO 'LVFORVXUH Authors have no financial interests about the research.

References

1. /RFKPLOOHU & -RKQVWRQ ' 6FRWW $ 5LVPDQ 0 +HFKW - 7 *HQHWLF epidemiology study of idiopathic talipes equinovarus. Am J Med Genet 1998;79:90-6.

6KDURQ :HLQHU 0 6XNHQLN +DOHY\ 5 7HSSHU 5)LVKPDQ $ %LURQ 6KHQWDO 7 0DUNRYLWFK 2 'LDJQRVWLF DFFXUDF\ ZRUN XS and outcomes of pregnancies with clubfoot detected by prenatal sonography. Prenat Diagn 2017;37:754-63.

$OGHUPDQ %: 7DNDKDVKL (5 /H0LUH 0 5LVN LQGLFDWRUV IRU WDOLSHV HTXLQRYDUXV LQ :DVKLQJWRQ 6WDWH (SLGHPLRORJ\ 1991;2:289-92.

.HUHW ' (]UD (/RNLHF) +D\HN 6 6HJHY (:LHQWURXE 6 (IILFDF\ of prenatal ultrasonography in confirmed club foot. J Bone Joint 6XUJ %U

%DVLW 6 .KRVKKDO ., *HQHWLFV RI FOXEIRRW UHFHQW SURJUHVV DQG future perspectives. Eur J Med Genet 2018;61:107-13.

6DQ]DUHOOR , 1DQQL 0)DOGLQL & 7KH FOXEIRRW RYHU WKH FHQWXULHV Pediatr Orthop B 2017;26:143-51.

3DYRQH 9 &KLVDUL (9HVFLR $ /XFHQWL / 0HVVD * 7HVWD 8 7KH etiology of idiopathic congenital talipes equinovarus: a systematic UHYLHZ - 2UWKRS 6XUJ 5HV

:HPDNRU $ &DVVRQ . *DUQH (%DNNHU 0 $GGRU 0 $UULROD / HW DO 6HOHFWLYH VHURWRQLQ UHXSWDNH LQKLELWRU 9LH LQ ULVN ... first trimester pregnancy and risk of specific congenital anomalies: a European register-based study. Eur J Epidemiol 2015;30:1187-98.

<D]G\ 00 0LWFKHOO $$ /RXLN & :HUOHU 00 8VH RI VHOHFWLYH serotonin-reuptake inhibitors during pregnancy and the risk of clubfoot. Epidemiology 2014;25:859-65.

'RON + -HQWLQN - /RDQH 0 0RUULV - GH lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? Neurology 2008;71:714-22.

*DQHVDQ % /X[LPRQ $ $O XPDLO\ $ %D Ponseti method in the management of clubfoot under 2 years of DJH $ V\VWHPDWLF UHYLHZ 3/R6 2QH

6KDEWDL / 6SHFKW 6& +HU]HQEHUJ -(Ponseti method for clubfoot. World J Orthop 2014;5:585-90.

)HUUHLUD *) 6WpIDQL .& +DMH '3 1RJXHL LQ FKLOGUHQ ZLWK FOXEIRRW DIWHU ZDO PHWDDQDO\VLV RI REVHUYDWLRQDO VWXGL

%RJHUV + 5LIRXQD 06 &RKHQ 2YHUEHH :LOOHPVHQ 63 YDQ GHU 6SHN 3- HW DO development of the fetal foot position using three-dimensional ultrasound in virtual reality. J Obstet Gynaecol Res 2019;45:280-8.

2IIHUGDO . -HEHQV 1 %ODDV +* (LN 1HV detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway. Ultrasound Obstet Gynecol 2007;30:838-44.

6KLS6 6&7' %HQDFHUUDI %5 67KH VLJQLILFD isolated clubfoot: is amniocentesis indicated? Am J Obstet Gynecol 1998;178:600-2.

%DNDOLV 6 6DLUDP 6 +RPIUD\ 7 +DUU Thilaganathan B. Outcome of antenatally diagnosed talipes equinovarus in an unselected obstetric population. Ultrasound Obstet Gynecol 2002;20:226-9.

&RKHQ 2YHUEHHN 7(*ULMVHHOV (: /DPI Wladimiroff JW, Diepstraten AF. Congenital talipes equinovarus: comparison of outcome between a prenatal diagnosis and a diagnosis after delivery. Prenat Diagn 2006;26:1248-53.

0DKDQ 67 <D]G\ 00 .DVVHU -5 :HUOHU 0 for clubfoot: what factors predict prenatal detection? Prenat Diagn 2014;34:389-93.

'L 0DVFLR ' %XFFD .KDOLO $ 5L]]R * 0D al. Outcome of isolated fetal talipes: A systematic review and meta-DQDO\VLV $FWD 2EVWHW *\QHFRO 6FDQG

+DUWJH '5 *DHUWQHU 6 :HLFKHUW - 3UH outcome of congenital talipes equinovarus in 106 fetuses. Arch Gynecol Obstet 2012;286:831-42.

/DXVRQ 6 $OYDUH] & 3DWHO 06 /DQJORL diagnosed isolated clubfoot. Ultrasound Obstet Gynecol 2010;35:708-14.

0DPPHQ / %HQVRQ &% 2XWFRPH RI IHWXV by prenatal sonography. J Ultrasound Med 2004;23:497-500.

24. Malone FD, Marino T, Bianchi DW, Johnston K, D'Alton ME. Isolated clubfoot diagnosed prenatally: is karyotyping indicated? Obstet Gynecol 2000;95:437-40.

:RRGURZ 1 7UDQ 7 8PVWDG 0 *UDKDP &UHVSLJQ\ / 0LG WULPHVWHU XOWUDVRX equinovarus: accuracy and outcome for infants. Aust N Z J Obstet Gynaecol 1998;38:301-5.

9LDUULV LGH 0RU 6HQQR % *UXEVKQ %URQ N, Creveuil C, et al. Prenatal diagnosis of clubfoot: Chromosomal abnormalities associated with fetal defects and outcome in a tertiary center. J Clin Ultrasound 2016;44:100-5.

7HJQDQGHU ((LN 1HV 6+ 7KH H[DPLQHU has a significant impact on the detection rate of congenital heart

defects at the second-trimester fetal examination. Ultrasound Obstet Gynecol 2006;28:8-14.
(VWHU $5 :H\PRXWK .6 %XUW $:LVH &$
HW DO $OWHUHG WUDQVPLVVLRQ RI +2;
a potential common pathway for clubfoot. Am J Med Genet A 2009;149a:2745-52.

29. Menke DB, Guenther C, Kingsley DM. Dual hindlimb control HOHPHQWV LQ WKH 7E[JHQH DQG UHJLRQ
in vertebrate limbs. Development 2008;135:2543-53.
<DQJ + =KHQJ = &DL + /L + <H ; =KDQJ
missense mutations in the filamin B gene are associated with isolated FRQJHQLWDO WDOLSHV HTXLQRYDUXV +X

Turk J Obstet Gynecol 2020;17:278-284

$EVWUDFW

2EMHFWLYH 7R FUHDWH D QHZ DQG VLPSOH PRGHO IRU SUHGLFWLQJ WKH OLNHOLKRRG
time of admission.
0DWHULDOV DQG 0HWKRGV $ SURVSHFWLYH REVHUYDWLRQDO VWXG\ ZDV SHUIRUPHG D
'HFHPEHU LQ SUHJQDQW ZRPHQ DWWHQGLQJ WKH ODERXU URRP ZLWK RQH SUHYLRX
FHVDUHDQ 72/$& 7KH VDPSOH VL]H ZDV $ 9%$& VFRUH ZDV FDOFXODWHG IRU HDFK
at the time of admission such as maternal age, gestational age, Bishop’s score, body mass index, indication for primary cesarean section, and clini
HVWLPDWHG IHWDO ZHLJKW 7KH UHVXOWV RI WKH 9%$& VFRUHV ZHUH FRUUHODWHG ZLW
t-test was used for comparison among the groups. Descriptive and regression analysis was performed for the study variables.
Results: 2XW RI 72/$& FDVHV KDG VXFFHVVIXO 9%$& DQG WKH UHPDLQGHU KDG I

Öz

$PDo %X oDO×üPD EDüYXUXGD RODQ GHÿLüNHQOHUL NXOODQDUDN VH]DU\HQ VRQUDV×
ROXüWXUPDN LoLQ \DS×OP×üW×U
*HUHo YH <|QWHPOHU +DU\DQD·GDNL •o•QF• EDVDPDN VDÿO×N PHUNH]LQGH D\O×N EL
GDKD |QFH ELU NH] VH]DU\HQ LOH GRÿXP \DSDQ YH ´*HEHOHUGH 6H]DU\HQ 6RQUDV× 'Rÿ
J|]OHPVHO oDO×üPD \DS×OG× YH |UQHNOHP E•\•NO•ÿ• LGL +HU KDVWD LoLQ 669' VNRU
VH]DU\HQ HQGLNDV\RQX YH NOLQLN RODUDN WDKPLQ HGLOHQ IHWDO Dÿ×UO×N JLEL KD
KHVDSODQG× 669' VNRUXQXQ VRQXoODU× EüDU×O× YH\D EüDU×V×] 669' üHNOLQGH
6WXGHQW·V W WHVWL NXOODQ×OG× dDO×üPD GHÿLüNHQOHUL LoLQ WDQ×POD\×F× DQDOL
%XOJXODU <•] HOOL 72/$& NULWHUOHULQH X\DQ JHEHQLQ ·LQGH EüDU×O× 669' YH
VDKLS ROPD RODV×O×ÿ× LoLQ LoLQ YH ! LoLQ LGL 7DKPLQ PRGHOL D
LOD HÿUL DOW×QGDNL DODQ LOH L\L SHUIRUPDQV J|VWHUPLüWLU
6RQXo %X oDO×üPD |QHULOHQ 669' WDKPLQ PRGHOLQLQ 72/$& VRQXFXQX WDKPLQ HWPH
GRÿXP üHNOL NRQXVXQGD GDQ×üPDQO×N \DSPDN LoLQ NXOODQ×ODELOHFHÿLQL J|VWHUP
VDKLS GLÿHU EX W•U PRGHOOHUOH LOJLOL GDKD ID]OD oDO×üPD \DS×OPDV× JHUHNPHNW
$QDKWDU .HOLPHOHU 6H]DU\HQ VRQUDV× YDMLQDO GRÿXP WDKPLQ PRGHO

PRECIS: A new prediction model of vaginal birth after cesarean containing factors available at the time of admission was tested and it was fou
to be a good tool.

$GGUHVV IRU &RUUHVSRQGHQFH 3LQNH\ /DO×üPD $VGRH V1URI
%KDJDW 3KRRO 6LQJK *RYHUQPHQW 0HGLFDO &ROOHJH IRU :RPHQ .KDQSXU .DODQ 6RQHSDW +DU\DQD ,QGLD
Phone: +91 839 883 61 81 (PDLO drpinki_18@yahoo.com 25&,' ,' orcid.org/0000-0002-9252-6864
5HFHLYHG *HOLü 7DULKL 03.06.2020 $FFHSWHG .DEXO 7DULKL 18.10.2020

Introduction

The effective and safe use of cesarean delivery has been a focus and concern for last the three decades. It was the result of WKH 1DWLRQDO ,QVWLWXWHV RI +HDOWK &RQVHQVXV &RQIHUHQFH on Cesarean Childbirth held in response to the three-fold LQFUHDVH LQ WKH UDWH RI FHVDUHDQ GHOLYHULHV WURP LQ WR LQ WKDW YDJLQDO ELUWK DIWHU FHVDUHDQ 9%$& came into being. As a result, the VBAC rate rose from 19.9% in 1990 to 28.3% in about a decade and the cesarean delivery rate decreased from 22.7% to 20.7%/ DWHU ZLWK LQFUHDVLQJ incidence of uterine rupture, VBAC had a setback and went into disrepute, once again leading to an increase in the cesarean rates. This has led to significant research in determining the best permutations and combinations of the factors to achieve the optimum outcome of a previous cesarean delivery. There are numerous factors such as maternal age, body mass index %0, JHVWDWLRQDO DJH VSRQWDQHRXV RU LQGXFHG ODERU LQWHUYDO conception period, estimated fetal weight, Bishop's score, type of previous cesarean scar, and indication for primary cesarean delivery, which can influence the decision to undergo a trial RI ODERXU DIWHU FHVDUHDQ 72/$& 9%$& HPHUJHQF\ UHSHDW FHVDUHDQ YDJLQDO GHOLYHU\ Rates of maternal complications are highest among women who attempt vaginal birth and fail, intermediate among women who have planned cesarean delivery, and lowest among women who attempt vaginal birth and succeed.VBAC success rates also vary between institutions and service providers. Thus, it is worth remarking that as of now, there is no reliable and demonstrable algorithm or nomogram that correctly identifies or accurately predicts the success of VBAC +HQFH PDQDJHPHQW RI SUHYLRXV of previous lower segment cesarean section continues to be an obstetric dilemma.

Therefore, an accurate and reliable prediction model must be designed and validated to predict a successful outcome, but literature is scarce from India that could assess the ante-partum and intrapartum determinants for predicting successful VBAC +HQFH WKLV VWXG\ The aim of the study was to create a new model for predicting the likelihood of VBAC using variables available at the time of admission.

7KH REMHFWLYH RI WKH VWXG\ ZDV prediction model for success of VBAC delivery.

Materials and Methods

This prospective observational study was conducted at a WHUWLDU\ FDUH FHQWUH RYHU D SHULRG WR 'HFHPEHU pregnant women attending the labour room with one previous cesarean section. This hospital a UHIHUUDO FHQWHU IRU WKUHH PDMRU India with annual live birth rates ranging from 4,500 to 5,000, average overall cesarean rate of 20-25% of total deliveries, and a repeat cesarean rate of 30-35% of total cesareans. At 5% alpha HUURU SRZHU DQG FRQILGHQFH % LQWHUYDO &, WKH VDPSOH F VL]H FDOFXODWHG XVLQJ 0DVWHU (WKLFDO FRPPLWWHH DSSURYDO RI WKH QXPEHU %36*0&: 5& ,(& DQG LQIR consent was given by each patient who fulfilled the following LQFOXVLRQ DQG H[FOXVLRQ FULWHULD QFOXVLRQ FULWHULD • SUHJQDQF\ YH • ZHHNV FRQILUPHG LQ ILUVW WULP KLVWRU\ PDWHUQDO DJH \HDUV (FOXVLRQ FULWHULD • LQWHUYDO FHVDUHDQ \HDUV RU ! \HDUV fetal death, lethal fetal anomalies, non-reassuring fetal heart rate on admission, cephalopelvic disproportion, malpresentation, history of antepartum haemorrhage or adherent placenta in the current pregnancy, history of uterine surgery other than cesarean section.

The following system was designed using the relative weights of significant factors used in previous models given by Troyer and Parisi et al., Flamm and Geiger, Grobman et al. , Wen et al. DQG 0HW. In the proposed model, we included six variables, four of which, namely maternal age in years, gestational age in weeks, indication for primary cesarean, and BMI were also included in Grobman's model in place of cervical dilation, we used Bishop's score, which was the main IDFWRU LQ WKH VWXG\ Estimated fetal weight was DO the sixth variable, which was also used in the study by Wen et al. There are only a few Indian studies on prediction models and most studied individual factors instead of prediction models, which is why statistically significant factors previously studied in Indian studies as well as supported by the American College of Obstetrics and Gynecology and the Royal College of Obstetrics and Gynaecology guidelines were included. Each variable used in the prediction model was assigned a score of 0, RU 6FRUHV ZHUH GHFLGHG EDVHG Flamm and Geigerand Troyer and Parisi et al.who gave a score of 0 to those with a primary indication of cesarean section as failure to progress . A score of 2 was chosen for breech and fetal distress because, according to the literature, this group had a statistically significant favourable VBAC outcomes LQ 72/$& 9%$& RWKHU IDFWRUV accordingly. A pilot study of this model was performed on 50 SDWLHQWV WR WHVW WKH SHUIRUPDQFH RI WKH made, and later it was performed on 150 more patients.

VBAC scoring system used in the proposed prediction model:

0DWHUQDO DJH LQ \HDUV

*HVWDWLRQDO DJH LQ ZHHNV D

3. Indication for primary caesarean-section:

E ,QWUDXWHULQH JURZWK UHVWULFW

$QWHSDUWXP KDHPRUUKDJH

a EUHHFK SUHVHQWDWLRQ RU IHWDO

5. BMI in kg/m² on admission:

D E F

6. Clinically estimated fetal weight in grams according to Johnson's formula:

D ! E F

VBAC scores were calculated for each patient fulfilling the FULWHULD WR XQGHUJR 72/$& DW WKH WLPH RI DGPLVVLRQ DQG WKH result obtained was correlated with the outcome i.e. failed VBAC or successful VBAC.

6WDWLVWLFDO $QDO\VLV

6WDWLVWLFDO SDFNDJH IRU WKH V ... ZDV XVHG for statistical analysis. Descriptive statistics were used for the demographic features such as age, parity, gestational age, BMI, Bishop's score, and the indication for primary cesarean VHFWLRQ 7KH FKL VTXDUH WHVW ZDV ... comparisons among the groups. Multivariate logistic regression analysis using the enter method was performed to calculate the DGMXVWHG RGGV UDWLR IRU HDFK I... model to determine their association with successful VBAC. A S YDOXH RI ” ZDV FRQVLGHUHG V... WKH UHFHLYHU RSHUDWLQJ FKDUDFW... E\ FDOFXODWLQJ WKH FRUUHVSRQG... and 95% CI.

Results

2XW RI 72/$& FDVHV KDG VXFFH UHPDLQGHU KDG IDLOHG 9%$& HP VHFWLRQ 7DEOH GHSLFWV WKH LQG prediction model, their frequency distribution, and their means with standard deviation. Table 2 shows the indications of cesarean section in the failed VBAC group. The most common indication was fetal distress followed by scar tenderness and IDLOHG LQGXFWLRQ LQ respectively. Out of eight cases of scar tenderness, three had thinned out scar of previous cesarean section. ZDV XVHG

We developed a total score of 0-12. The final cumulative VBAC score ranged from 2 to 11 in the present study. It was 10 or more in 5.30%, 7 to 9 in 47.3%, 4 to 6 in 40.10%, and 3 or less in 7.30% of the cases. As can be seen in graph 1, the observed probability of having a successful VBAC for VBAC score 0-3 ZDV ZDV ZDV DQG • DEFWRU... predicted VBAC percentages also mentioned in graph 1 were calculated using binary logistic regression analysis and were closely related to the observed ones. The multivariate regression analysis of all six variables as depicted in the Table 3 shows that two variables i.e. gestational age and Bishops score had the odds of 2.047 and 3.082,

7DEOH 'HPRJUDSKLF FKDUDFWHULVWLFV RI ZRPHQ XQGHUJRLQJ WULDO RI ODERX

'HPRJUDSKLFV FKDUDFWHULVWLFV	)DLOHG 9%$&	6XFFHVVIXO 9%$&	p	Q 1
1XPEHU RI ZRPHQ XQGHUZHQW 9%$&				
0DWHUQDO DJH \UV 25-30 !	25.93±3.51	25.82±3.70	0.92	
%0, NJ P 25-30 !	25.08±3.62	23.19±2.63	0.04	
*HVWDWLRQDO DJH ZHHNV 39-40 !	38.12±1.36	38.96±1.24	0.16	
Indication of primary cesarean 132/ RWKHUV ,8*5 ROLJRK\GUDPQLRV $3+ breech, fetal distress				
&OLQLFDOO\ HVWLPDWHG IHWDO ZHLJ 2500-3500 !	3389.54±471.45	3402±470.5	0.61	
Bishop's score 0-3 4-5 6-10	3.60±0.82	6.34±2.35		

'DWD DUH H[SUHVVHG DV SHUFHQWDJHV ZLWK IUHTXHQFLHV LQ WKH SDUHQWKHVHV DQG PHDQ “ VWDQGDUG ODERXU ,8*5 ,QWUDXWHULQH JURZWK UHVWULFWLRQ $3+ $QWHSDUWXP KDHPRUUKDJH

respectively, for having a successful VBAC with significant p-values in both, and with each 1 unit increase in BMI the odds RI KDYLQJ D VXFFHVVIXO 9%$& UHGXFH other three factors i.e. age, indication for previous cesarean, and HVWLPDWHG IHWDO ZHLJKW -RKQVRQ·V associated with successful VBAC.

As shown in Table 4, we studied five additional variables out of the model variables, namely spontaneous onset of labour, parity, interdelivery interval in months, previous history of successful VBAC, and previous history of normal vaginal delivery. These variables were chosen because they were also included in the previous models by Grobman and Flamm, Geiger and Wen et al. . Out of these five, two i.e. spontaneous onset of labour and parity were significantly associated with successful VBAC with odds of 2.58 and 5.138, respectively; the remaining three had no significant effect.

6HYHQWHHQ SDWLHQWV RXW R
72/$& KDG FRPSOLFDWLRQV VXFK DV Q
DGPLVVLRQV Q IDLOHG DQG VXFFHV

* U D S K Predicted compared with observed vaginal birth after
F HV DU HD Q VHFWLRQ 9%$& 6XFFHVVIXO

) L J X U H ROC curve for the scoring system showing area und
WKH FXUYH $8&

ROC: Receiver operating characteristic curve

Zs H ¡ À § Ö X ?Ã¢5p š œ ¬ À

ERWK DQG EODGGHU LQMXU\ Q
D WRWDO RI FDVHV RI 33+ DOO DWRQLF
VBAC group and six in the failed VBAC group. There were no cases of uterine rupture and ICU admissions in the present study.
)LJXUH VKRZV WKH 52& FXUYH ZLWK DQ $8& HTXDO WR
&, WR

Discussion

The ACOG 2010 quoted the success rate of VBAC as 60-80%. VBAC success rates also vary between institutions and service providers. The success rate of VBAC in the present study was 78%, similar to the quoted percentage. The mean age of the women in the present study was 25.84±4.20 years and there was no significant difference in the ages of the women in the two groups i.e. successful VBAC and failed VBAC groups, similar to
VWXG\ E\ 0HW]JHU HW DO “ S
mean age in the current study was lower as compared with the study by Xing et al. because 76.6% of the women were from rural areas where young marriage and childbirth is common; the mean age in the successful VBAC and failed VBAC group was higher and there was a significant difference between the
WZR JURXSV “ DQG “ S
Troyer and Parisi in 1992 studied 264 women with one previous cesarean section and developed a model with four factors, namely previous dysfunctional labour, non-reassuring fetal heart tracing at admission, no previous vaginal delivery, and labour induction. Each variable was given one point and the total score ranged from 0-4. The patients with the lowest
VFRUH L H KDG WKH KLJKHVW 9%$& VXFFHVV UDWH
compared with those with higher scores. This model has not been studied extensively and needs further research and validation. The indication of primary cesarean section i.e. previous dysfunctional labour was also included in the present
VWXG\ PHQWLRQHG KHUH DV 132/
]HUR VFRUH
There is a popular model known as the Flamm scoring system, which was developed in 1997 in California. The research was performed on 5022 pregnant women including four variables known at the time of admission i.e. age of the patient, vaginal delivery before and after the cesarean section, a non-recurring indication of primary caesarean, cervical dilatation and cervical effacement. The result was given as a score of 0-10 and each score had a different percentage of success i.e. 0-2 corresponded to 49.1%, 3-7 corresponded to 59.9%, 66.7%, 77%, 88.65%, and 92.65%, and the success of 8-10 was 94.9%. In the present study, we used two of the above factors in the VBAC prediction model i.e. patient age, but instead of cervical dilation, we used Bishop's score.
Patel et al. IURP *XMDUDW ,QGLD LQ
prospective observational study on 150 women with one previous cesarean section using the Flamm scoring system. They
IRXQG D PHDQ)ODPP VFRUH IRU VXFFHVVIXO 9%$& RI

&Q WKH WRWDO RI 9%$& JURXS FRPSDUHG ZLWK WKH IDLOHG
WRQLF 33+ DQG RWKHU FDXVHV LQ WKH FRQWURO JURXS
LQFUHDVLQJ)ODPP VFRUHV 6LPLODUO\
VBAC score of the failed VBAC group was 5.03±1.82 and that
RI WKH VXFFHVVIXO 9%$& JURXS ZDV
7KH DXWKRUV FRQFOXGHG WKDW
D IDLU MXGJPHQW RI VXFFHVVIXO YDJL
Flamm scores and monitoring though partogram would reduce the rate of cesarean sections in patients with one previous lower
VHJPHQW FHVDUHDQ VHFWLRQ +RZHYHU
supprting data and needs further validation.
The most studied prediction model of VBAC was developed by Grobman of the northwestern University of Chicago in 2007.
LQFOXGHG VL[YDULDEOHV PDWHUQDO
$PHULFDQ +LVSDQLF DQ\ SUHYLRXV Y
delivery since the last cesarean, and indication for primary cesarean of the arrest of dilation or descent. All variables were those that could be determined at the first antenatal visit with
WKH LGHD RI VWDUWLQJ WKH FRXQVHO
this model was improved in 2009 by adding certain other factors like most recent BMI within 2 weeks of delivery, gestational age at delivery, gestational diabetes mellitus, preeclampsia, cervical examination findings at admission, and the undertaking of labour induction. The result was expressed as the percentage of
VXFFHVV RI 72/$& ,QFOXVLRQ RI WKHV
LPSURYHG WKH SHUIRUPDQFH RI WKH F
to include those variables in the present prediction model, which were available at the time of admission because our hospital is a referral hospital and most of the time our patients
DUH XQERRNHG LQ WKH SUHVH
The AUC of the ROC curve of Grobman's 2007 model was 0.751, and that of the new model was 0.779, and these values
ZHUH VLJQLILFDQWO\ GLIIHUHQW S
known as the MFMU calculator and is freely available on the internet. The AUC of the ROC curve of our model was 0.77,
VLPLODU WR WKDW RI *UREPDQ·V
DQG ZKLFK VXJJHVWV WKDW WKH
performed well.
In 2018, Wen et al. conducted a retrospective cohort study on 444 women with one cesarean delivery and at least one
VXEVHTXHQW DWWHPSW IRU D WULDO
They used Grobman's model and also a modified version of this model and compared the two. The considered potential VBAC predictors included Grobman's background variables and two new variables, maternal height and estimated fetal weight. Their overall VBAC success rate was 83.3%. The AUC
RI *UREPDQ·V PRGHO ZDV &,
the AUC of their own modified model with two new variables
DGGHG ZDV VHQVLWLYLW\
+RZHYHU WKH GLIIHUHQFH EHWZHHQ W
ZDV QRW VLJQLILFDQW = S
Grobman's model was well accepted in the Chinese population, also that the modified model supplemented with maternal

height and estimated fetal weight needed to be further studied in the Chinese population.

There was no case of uterine rupture in the present study, whereas the incidence was 0.90% in the study by Patel et al. and 0.28% in the study by Xing et al.A recent meta-analysis VXJJHVWHG WKDW PHDVXUHPHQW RI ORZHU XWHULQH VHJPHQW /86 thickness antenatally in women with a previous caesarean delivery could be used to predict the occurrence of a uterine GHIHFW VFDU GHKLVFHQFH RU VFDU UXSWXUH LQ ZRPHQ XQGHUJRLQJ VBAC . Furtherprospective observational studies are needed XVLQJ D VWDQGDUG PHWKRG RI LQWUDSDUWXP /86 WKLFNQHVV PHDVXUHPHQW WR SUHGLFW WKH RXWFRPH RI 72/$& DQG ULVN RI uterine rupture.

The present study included a very important variable i.e. Bishop's score that has not been incorporated in any of the popular models by Flamm and Geiger and Grobman et al., who included only the individual components of Bishop's score VXFK DV FHUYLFDO GLODWLRQ HIIDFHPHQW DQG VWDWLRQ 0HW] HW DO and Xing et al. included Bishop's score in their model, despite LW EHLQJ D VXEMHFWLYH YDULDEOH their study also 0HW] HW DO used its value as the main factor in developing a score to which a value of 2 to 4 was DGGHG IRU DQRWKHU IRXU YDULDEOHV BMI, primary cesarean delivery because of nonrecurring LQGLFDWLRQ PDWHUQDO DJH \HDUV WR JHW WKH ILQDO 9%$& VFRUH ,Q WKH SUHVHQW VWXG\ LW KDV DQ DGMXVWHG RGGV UDWLR RI DQG KDV D YHU\ VWURQJ DVVRFLDWLRQ ZLWK VXFFHVVIXO 9%$& S 6SRQWDQHRXV RQVHW RI ODERXU DQG variables that may be incorporated in the present model and a further study can be planned. There are insufficient studies about VBAC prediction models and most studied only individual variables. Other variables studied in other prediction models are weight gain in pregnancy, preeclampsia, gestational diabetes, insurance. and race . There is a need for the development of a standard prediction model and further studies of this model and many more such models with different permutations and combinations of various variables are required to help predict WKH VXFFHVV RI 72/$& ZLWK KLJK DFFXUDF\

6WXG\ /LPLWDWLRQV

7KH VPDOO VDPSOH VL]H LV WKH OLPLWDWLRQ RI WKH SUHVHQW VWXG\ The study was approved by the institutional ethics committee and was performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration RI +HOVLQNL DV UHYLVHG LQ 7KHUH LV QR FRQIOLFW RI LQWHUHVW among the authors and this study was not funded by any RUJDQL]DWLRQ

Conclusion

The present study tests a new VBAC prediction model and shows that it is a good tool for predicting VBAC and hence can be used to counsel women regarding the mode of delivery in current and subsequent pregnancies. Parity, spontaneous onset of labour, admission Bishop's score, gestational age, and BMI were the factors with a statistically significant association with successful VBAC. Further studies could be proposed such as the comparison of two different types of scoring systems, each system with different variables in a given population.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO Ethical con WKH VWXG\ ZDV REWDLQHG DSSURYDO ,(&

,QIRUPHG &RQVHQW Informed and written consent by each patient

3HHU UHYLHZ Externally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV 9 6 5 0 &RQFHSW 3 / % 3 6 6 0 'HVLJQ 3 / % 3 6 6 0 8 6 6K 9 6 RU 3URFHVVLQJ 3 / % 3 6 6 0 8 6 $QDO\VLV RU ,QWHUSUHWDWLRQ 3 / % 3 6 6 /LWHUDWXUH 6HDUFK 3 / % 3 6 6 :ULWLQJ 3 / % 3 6 6 0 8 6 6K 9

&RQIOLFW RI ,QWHUHVW The authors report no c

)LQDQFLDO 'LVFORVXUH Authors have no financia the research.

References

1. &HVDUHDQ &KLOGELUWK 1 + &RQVHQVXV 6 0DUWLQ -$ +DPLOWRQ %(6XWWRQ 3 .LUPH\HU 6 HW DO %LUWKV ILQDO GDW 2006;55:1-31.
3. American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 115: Vaginal birth after previous cesarean delivery. Obstet Gynecol 2010;116:450-63.
&XQQLQJKDP)* /HYHQR .- %ORRP 6/ 'D Casey BM, et al. Prior Caesarean Delivery. Williams Obstetrics. 25th HG 1HZ 'HOKL 0F*UDZ +,// S
7UR\HU /5 3DULVL 90 2EVWHWULF SDUD trial of labour: designating of a scoring system. Am J Obstet Gynecol 1992;167:1099-104.
)ODPP %/ *HLJHU $0 9DJLQDO ELUWK DI admission scoring system. Obstet Gynecol 1997;90:907-10.
*UREPDQ :$ /DL < /DQGRQ 0% 6SRQJ &< et al. Development of a nomogram for prediction of vaginal birth after cesarean delivery. Obstet Gynecol 2007;109:806-12.
*UREPDQ :$ /DL < /DQGRQ 0% 6SRQJ &< DJ, et al. Does information available at admission for delivery improve prediction of vaginal birth after cesarean? Am J Perinatol 2009;26:693-701.
:HQ - 6RQJ ; 'LQJ + 6KHQ ; 6KHQ 5 +X / YDJLQDO ELUWK DIWHU FHVDUHDQ GHOLY 2018;8.
0HW] 7' 6WRGGDUG *- +HQU\ (-DFNV (VSOLQ 6 6LPSOH YDOLGDWHG YDJLQDO prediction model for use at the time of admission. Obstet Gynecol 2013;122:571-8.

11. Royal College of Obstetricians and Gynaecologists. Birth After 3UHYLRXV &DHVDUHDQ %LUWK *UHHQ WRS RCOG; 2015.

3DWHO 50 .DQVDUD 90 3DWHO 6. $QDQG scoring on cesarean section rate in previous one lower segment cesarean section patient. Int J Reprod Contracept Obstet Gynecol 2016;5:3820-3.

'RVKL +8 -DLQ 5. 9D]LUDQL $ 3URJQRVWLF IRU VXFFHVVIXO vaginal birth after cesarean section- Analysis of 162 cases. J Obstet Gynecol India 2010;60:498-502.

%LOO < :LQGULP 5 9DJLQDO ELUWK DIWHU FHVDUHDQ VHFWLRQ UHYLHZ RI antenatal predictors of success. J Obstet Gynaecol Can 2003;25:275-86.

;LQJ <3 4L ;< :DQJ ;= <DQJ)= 'HYHORS score system as prediction model for successful vaginal birth after FHVDUHDQ GHOLYHU\ &OLQ 7UDQVO 6FL

.RN 1 :LHUVPD ,& 2SPHHU %& GH *UDDI (6RQRJUDSKLF PHDVXUHPHQW RI ORZHU to predict uterine rupture during a trial of labor in women with previous cesarean section: a meta-analysis. Ultrasound Obstet Gynecol 2013;42:132-9.

Turk J Obstet Gynecol 2020;17:285-291

Impact of the expanded examination of fetal heart to the prenatal diagnosis of congenital heart diseases

*HQLüOHWLOPLü IHWDO NDUGL\DN GH
KDVWDO×NODU×Q×Q SUHQDWDO WDQ×

3HOLQ[1] .RüJHU, 0HOLK 9HOLSDüDRJOX[2], 7XQD\ (VNLQ[3], .×]LOFÕN[1],]WDQ %DU×üK[1], 8oDU

[1](VNLüHKLU 2VPDQJD]L 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 3HGLDW
[2](VNLüHKLU 2VPDQJD]L 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 2EVWHW
[3](VNLüHKLU 6WDWH +RVSLWDO &OLQLF RI 3HGLDWULF &DUGLRORJ\ (VNLüHKLU 7XU

$EVWUDFW

2EMHFWLYH In the present study, for which reasons fetal cardiac evaluation was requested from our pediatric cardiology clinic, the effects of
FDUGLDF HYDOXDWLRQ LQ REVWHWULF XOWUDVRQRJUDSK\ 86* RQ WKH GHWHFWLRQ RI
&+' DFFRUGLQJ WR SUHJQDQF\ ULVN SURILOHV ZHUH UHWURVSHFWLYHO\ DQDO\]HG

0DWHULDOV DQG 0HWKRGV Fetal echocardiography reports which containing the nineteen-month period were retrospectively exar
IHWDO HFKRFDUGLRJUDSK\ IRU DOO SUHJQDQW ZRPHQ ZKR ZHUH UHIHUUHG WR SHGLDW
FDWHJRUL]HG LQWR WZR JURXSV EDVHG RQ WKH ULVN RI &+' /RZ ULVN DQG KLJK ULVN J
as complex, moderate, and mild according to perinatal mortality risk.

Results: 2I WKH SUHJQDQFLHV ZHUH WZLQ DQG IHWDO FDUGLDF HYDOXDWLRQ ZDV SH
ULVN JURXS DQG SUHJQDQFLHV LQ WKH ORZ ULVN JURXS 7KH PRVW FRPPRQ U
YLVXDOL]H WKH IHWDO KHDUW ZKLOH VXVSHFWHG IHWDO FDUGLDF DEQRUPDOLW\
FDUGLDF DEQRUPDOLWLHV ZDV DPRQJ KLJK ULVN SUHJQDQFLHV DQG DPR
ZDV VLPSOH FDUGLDF DEQRUPDOLWLHV IROORZHG E\ FRPSOH[OHVLRQV 7KH PR
RI FDVHV ZKLOH WKH PRVW FRPPRQ FRPSOH[FDUGLDF DEQRUPDOLW\ ZDV SXOP
obstetricians and pediatric cardiologist in terms of the diagnosis of the congenital cardiac malformations.

&RQFOXVLRQ 5RXWLQH HYDOXDWLRQ RI WKH IHWDO KHDUW E\ PHDQV RI REVWHWULF 86
for diagnosing congenital cardiac malformations to a large extent during the intrauterine period.

.H\ZRUGV Congenital heart disease, fetal echocardiography, high risk pregnancy, low risk pregnancy, prenatal diagnosis

Öz

$PDo %X oDO×üPDGD SHGLDWULN NDUGL\RORML NOLQLÿLPL]GHQ IHWDO NDUGL\DN GHÿH
UXWLQ IHWDO NDUGL\DN GHÿHUOHQGLUPHQLQ NRQMHQLWDO NDOS KDVWDO×NODU×Q×Q
JHEHOLN ULVN SURILOLQH J|UH GDÿ×O×P× UHWURVSHNWLI RODUDN LQFHOHQPLüWLU
*HUHo YH <|QWHPOHU 2Q GRNX] D\O×N G|QHPH DLW IHWDO HNRNDUGL\RJUDIL UDSRUO
D\U×QW×O× REVWHWULN 86* WDUDPDV× VRQUDV×QGD SHGLDWULN NDUGL\RORML NOLQLÿ
J|UH G•ü•N YH \•NVHN ULVNOL RODUDN LNL JUXED D\U×OG× 7HVSLW HGLOHQ NRQMHQLW
KDILI GHUHFH ROPDN •]HUH V×Q×IODQG×U×OG×
%XOJXODU 7RSODP JHEHQLQ WDQHVL LNL] JHEHOLN ROXS EHEHÿH IHWDO NDU
ULVN JUXEXQGD LVH JHEHOLN PHYFXWWX)HWDO HNRNDUGL\RJUDILN GHÿHUOH
ROXS IHWDO NDUGL\DN DQRPDOOLN ü•SKHVL LNLQFL HQ V×N QHGHQGL .D
G•ü•N ULVNOL JHEHOHUGH LGL (Q \•NVHN RUDQGD VDSWDQDQ PDOIRUPDV\RQ WLS
LNLQFL V×UDGD\G× (Q V×N VDSWDQDQ NDUGL\DN DQRPDOL YHQWULN•OHU VHSWD

PRECIS: 7KH H[SDQGHG H[DPLQDWLRQ RI WKH IHWDO KHDUW E\ PHDQV RI REVWHWULF

$GGUHVV IRU &RUUHVSRQGHQFH 3HOLQ .|üJHU $VVW 3URI
(VNLüHKLU 2VPDQJD]L 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 3HGLDWULF &DUGLRORJ\ (VNLüHKLU
Phone: +90 222 239 29 79 (PDLO pelinkosger@gmail.com 25&,' ,' orcid.org/0000-0002-3926-9002
5HFHLYHG *HOLü 7DULKL 24.03.2020 $FFHSWHG .DEXO 7DULKL 27.06.2020

SXOPRQHU DWUH]L\GL ..+·QLQ WDQ×QPDV× Do×V×QGDQ REVWHWULV\HQ YH SHGLDW
6RQXo)HWDO NDOELQ G|UW ERüOXN YHQWULN•OOHULQ o×N×P \ROODU× YH •o GDPDU
NRQMHQLWDO NDUGL\DN PDOIRUPDV\RQODU×Q LQWUDXWHULQ G|QHPGH E•\•N RUDQGD W
$QDKWDU .HOLPHOHU .RQMHQLWDO NDOS KDVWDO×NODU× IHWDO HNRNDUGL\RJUDIL \•

Introduction

&RQJHQLWDO KHDUW GLVHDVH &+' LV WKH PRVW FRPPRQ congenital abnormality, and it is six times more common than chromosomal abnormalities and four times more common than neural tube defect 7KH LQFLGHQFH RI &+' LV FDVHV SHU OLYH ELUWKV IRU IXOO WHUP ELUWKV DQG WKLV UDWH LV DSSUR[LPDWHO\ WLPHV PRUH IRU SUHWHUP births $SSUR[LPDWHO\ RI &+'V LQFOXGH FULWLFDO malformations, which must be intervened directly after ELUWK DQG RU MXVW EHIRUH ELUWK 8QIRUWXQDWHO\ RI WKHVH malformations are diagnosed after the infant is discharged from the hospital, and the mortality risk increases because of the delay. The identification of severe cardiac abnormalities during the intrauterine period enables the use of approaches that lead to significant decreases in perinatal morbidity and mortality, such as performing the delivery at a center where cardiac surgery can be performed, providing the required medical support in the newborn intensive care unit until transfer to the relevant center, and/or if needed, promptly performing transcatheter palliative interventions. Therefore, fetal cardiac evaluation has become an LPSRUWDQW SDUW RI REVWHWULF XOWUDVRQRJUDSK\ 86* DQG IHWDO echocardiography evaluation requests have increased due to LQFUHDVHG LQFLGHQFHV RI VXVSHFWHG &+' $OWKRXJK WKH ULVN\V RI &+' DUH GHILQHG DQG IHWDO FDUGLDF HYDOXDWLRQ LV UHFRPPHQGHG IRU DOO KLJK ULVN SUHJQDQFLHV risk pregnancies .

The current approach in many clinics in Turkey involves performing fetal cardiac evaluations within defined indications owing to long examination times and inadequate number of pediatric cardiologists and cardiovascular surgery experts. Our hospital is a tertiary center and includes the only perinatology and pediatric cardiology clinic that provides services to a large region, which consists of our city and neighboring cities. In the present study, for which reasons fetal cardiac evaluation was requested from our pediatric cardiology clinic, WKH HIIHFWV RI URXWLQH IHWDO FDUGLDF HYDOXDWLRQ 8 RQ WKH GHWHFWLRQ RI &+'V DQG WKH GLVWULEXWLRQ RI SUHQDWDO GLDJQRVLV RI &+'V DFFRUGLQJ WR WKH LQGLFDWLRQV ZHUH UHWURVSHFWLYHO\ DQDO\]HG

Materials and Methods

In this retrospective study, the total number of anomaly VFDQV LQ WKH SHULQDWRORJ\ XQLW GXULQJ WKH VWXG\ SHULRG -DQXDU\ ZHUH DQG WKH QXPEHU RI UHIHUUHG pregnancies for fetal echocardiography evaluations were 736. All patients in the study underwent routine fetal anatomic VFDQQLQJ DFFRUGLQJ WR WKH ,QWHUQDWLRQDO 6RFLHW\ RI 8OWUDVRXQG in Obstetrics and Gynecology guidelines between the 18th and 22nd weeks of pregnancy in the Department of Perinatology at our university. In this scan, four chambers of the heart, three vessel and trachea, left and right ventricular outflows, and the KHDUW ZHUH H[DPLQHG XVLQJ [illegible] the patients were referred to the Department of Pediatric Cardiology unit form perinatology division of our university hospital either suspected cardiac abnormalities, accompanying diseases that increase risk of fetal cardiac malformations, parental congenital heart malformation or suboptimal evaluation during routine anomaly scan. To identify all reasons for fetal echocardiography requests, detailed obstetric 86* UHSRUWV RI HDFK FDVH ZHUH UHW[illegible] examined, and the reasons for fetal echocardiography requests were determined as accurately as possible by comparing these with our records. Pre-gestational and gestational medical data of pregnant women were retrieved. Comorbid medical SUREOHPV WKDW PD\ EH FRQVLGHUHG [illegible] use, and characteristics of previous pregnancies were recorded. 7KH SUHJQDQFLHV ZHUH FDWHJRUL]HG WKH ULVN RI &+' ORZ ULVN DQG KLJK HYDOXDWLRQ ZDV SHUIRUPHG E\ WKH in the Department of Pediatric Cardiology using a C5-1 convex SUREH ZLWK DQ $JLOQW\ 3KLOLSV IHWDO HFKRFDUGLRJUDSK\ H[DPLQDWL position, systemic and pulmonary venous connections, atrial and ventricular chambers, atrioventricular and semilunar valves, ventriculoatrial shunts, great vessels outflow tracts, ductal and aortic arches, and rhythm were evaluated. If all views could not be clearly evaluated or if a suspicious finding is detected in the first evaluation, repeated evaluations may be required. Echocardiography images and reports of each patient were recorded. Fetal echocardiographic evaluation was scheduled according to the gestational week of the pregnancy, the referral diagnosis of the fetus, and the availability of our out-patient clinic. Each case was informed about applying for postnatal cardiac evaluation even if no pathology was detected in the fetal evaluation. For the purpose of performing as many evaluations as early as possible, postnatal echocardiography evaluations are performed without appointment in our clinic. The postnatal data of 261 infants were retrieved of 714 single and 22 sets of twins, and 758 infants in total from 736 pregnancies were examined. Prenatal and postnatal echocardiography data of 261 cases, for which postnatal data could be retrieved, were compared.

Detected congenital cardiac structural malformations were classified as complex, moderate, and mild according to perinatal PRUWDOLW\ ULVN. Malformations that are not included in this classification, and malformations with low mortality risk

7DEOH Classification of prenatally diagnosed congenital heart defects

Complex; atresia or severe hypoplasia of a valve or chamber	+HWHURWD[\ RU DWULDO LVRPHULVP VLQJOH ventricle, hypoplastic left heart, pulmonary atresia, tricuspid atresia, aortic atresia, mitral atresia, and Ebstein's anomaly, complet atrioventricular septal defect, truncus arteriosus, congenitally corrected transposition of the great arteries, double outlet left or right ventricle
Modere; congenital heart disease requiring operation or intervention, but not included in the complex group	Transposition of the great vessels, tetralogy of Fallot, coarctation of the aorta, aortopulmonary window, critical aortic or pulmonary stenosis, partial atrioventricular septal defect, total anomalous pulmonary venous connection, large ventricular septal defect
Minor; no intervention	6PDOO YHQWULFXODU VHSWDO GHIHFW DWULDO septal defect and less severe aortic or pulmonary stenosis
Others	Dysrhthmias, cardiomyopathies, secondary dextrocardia/levocardia and restrictive ductus

were evaluated in the others category. This study was approved E\ WKH (VNLüHKLU 2VPDQJD]L 8QLYHUVLW\ ,QVWLWXWLRQDO (WKLFV Committee.

6WDWLVWLFDO $QDO\VLV

6WDWLVWLFDO DQDO\VLV ZDV SHUIRUPHG XVLQJ 6WDWLVWLFDO 3DFNDJH IRU 6RFLDO 6FLHQFHV YHUVLRQ SUHJQDQFLHV ZHUH FDWHJRUL]HG LQWR WZR JURXSV RI &+' 7KH IHWDO HFKRFDUGLRJUDSK\ congenital cardiac malformation rates were classified according WR SUHJQDQF\ ULVN SURILOH 7KH high- risk pregnancies was compared using the chi-square test. 6WDWLVWLFDO VLJQLILFDQFH ZDV LQIHUUHG DW S

Results

7KH PHDQ DJH RI WKH PRWKHUV ZDV \HDUV DQG WKH PHDQ JHVWDWLRQDO echocardiography examination was performed was 26.4±4.4 weeks. Of the 736 pregnancies, 22 were twin pregnancies, and fetal cardiac evaluation was performed in 758 fetuses. Twelve patients underwent examination for a second time. In total, 37.9% of the examinations were performed before the 24th week of pregnancy, while 62.1% were performed after the 24th week of pregnancy. Number of fetuses with congenital structural FDUGLDF PDOIRUPDWLRQ ZDV IHWXVHV ZLWK DUUK\WKPLD ZDV The reasons for fetal echocardiography requests were classified DFFRUGLQJ WR &+' ULVN SURILOHV $VVRFLDWLRQ UHFRPPHQGDWLRQV The prevalence of &+' DFFRUGLQJ WR ULVN IDFWRUV ZDV

SUHJQDQFLHV LQ WKH KLJK ULVN pregnancies in the low-risk group. The most common cause for fetal cardiac evaluation request was inability to adequately YLVXDOL]H WKH IHWDO KHDUW DEQRUPDOLW\ ZDV WKH VHFRQG PRVW cardiac malformation was detected as the most frequent among pregnant women referred to the pediatric cardiology due to VXERSWLPDO HYDOXDWLRQ GXULQJ UR 7KH GLVWULEXWLRQ RI &+'V ZKLFK Z echocardiography and classified according to mortality risk according to pregnancy risk groups was presented in Table 3. Number of fetuses detected with cardiac abnormalities was DPRQJ KLJK ULVN SXHJQDQFLH low-risk pregnancies. The prevalence of cardiac abnormalities LQ HDFK FDWHJRU\ ZDV KLJKHU LQ KLJ The most common type of malformation was simple cardiac DEQRUPDOLWLHV IROORZHG E\ FRP most common cardiac abnormality was ventricular septal GHIHFW 96' FRPSULVHG RI FDVHV common complex cardiac abnormality was pulmonary atresia 3$ 7KH PRGHUDWH FDUGLDF D LQFOXGLQJ QLQH FDVHV 2XW RI with suspected fetal cardiac arrhythmia, two had complete atrioventricular block, two fetuses had blocked premature atrial contractions, and two fetuses had supraventricular tachycardia. The other nine fetuses had premature atrial and ventricular contractions, which recovered during the late weeks of pregnancies.

The number of fetuses for which postnatal cardiac evaluation records could be retrieved via echocardiography examinations performed after birth, autopsy reports of terminated fetuses, and late period presentations to our clinic for follow-up purposes ZDV 2I WKH LQIDQWV the prenatal and postnatal results were compared, there were 24 GLVFRUGDQW GLDJQRVHV 2QH PD fetus for which fetal echocardiography was requested because of the presence of a sibling with heart disease and which did not have fetal cardiac abnormalities, total anomalous pulmonary venous return was detected in the first postnatal week. Twenty-WKUHH DIWHU ELUWK ZKLFK WKH IHWDO 96' ELFXVSLG DRUWLF YDOYH to the class of simple heart diseases.

Discussion

'LDJQRVLV RI &+' GXULQJ WKH LQWUD significant benefits as performing of the birth under appropriate conditions, mentally prepared family, defining potential genetic abnormalities, and termination of pregnancy in the presence of complex malformations. Moreover, it was reported that GLDJQRVLV RI VRPH VSHFLILF &+'V increases the survival rate as well. However, due to the duration of fetal echocardiography and requirement of an experienced pediatric cardiologist, it is not routinely performed

7DEOH The distribution of the fetal echocardiography request reasons and the congenital cardiac malformation rates according to pregnancy risk profile*

,QGLFDWLRQV ZLWK KLJKHU ULVN SURILOH	7RWDO Q	&+' Q
Gestational diabetes		
Pregestational diabetes		
Collagen tissue disease maternal DXWRDQWLERGLHV		
&+' LQ WKH ILUVW GHJUHH UHODWLYHV RI WKH IHWXV PRWKHU IDWKHU VLEOLQJV		
Fetal cardiac abnormality suspected on obstetrical ultrasound		
Fetal extracardiac abnormality suspected on obstetrical ultrasound		
Fetal tachycardia or bradycardia, or frequent or persistent irregular heart rhythm		
)HWDO LQFUHDVHG 17 ! • PP		
Monochorionic twinning		
Fetal hydrops or effusions		
Polyhidramnios		
7RWDO		
,QGLFDWLRQV ZLWK ORZHU ULVN SURILOH		
0DWHUQDO PHGLFDWLRQV DQWLFRQYXOVDQWV 16$,'6 LQ ILUVW VHFRQG WULPHVWHUV		
Fetal abnormality of the umblical cord or placenta		
Abnormal first or second trimester screening tests		
Oligohydramnios		
/DWH PDWHUQDO DJH		
6XERSWLPDO HYDOXDWLRQ		
7RWDO		

&+' &RQJHQLWDO KHDUW GLVHDVH 16$,'6 1RQ VWHURLGDO DQWL LQIODPPDWRU\ GUXJ 17 1XFKDO WUDQV

in all pregnant women. Thus, basic fetal cardiac evaluation has EHFRPH D SDUW RI WKH 86* LQ URXWLQH can be detected during the intrauterine period at a rate of 4.5%-8.1% with the evaluation of the fetal heart in four chamber view and at 43.8%-85.5% with the additional examination of the right and left ventricular outflow tracts Therefore, the prevalence of LQWUDXWHULQH GLDJQRVLV RI &+' Y performed by the centers for fetal cardiac evaluation. In the present study consisting of an eighteen-month period, fetal congenital cardiac malformation prevalence was 13.7%. Fetal congenital cardiac malformation prevalence was reported to be 5.6% from another tertiary center in Turkey At our center, evaluation of the fetal heart in four chamber view is a routine part RI WKH REVWHWULF 86* 0RUHRYHU including right and left ventricular outflow tracts and three vessels and trachea view is routinely performed in each pregnant woman by skilled perinatologists between the 18th and 22nd weeks of pregnancy. Furthermore, since the fetal echocardiography was performed in selected pregnancies who were identified as risky in antenatal screening in our tertiary reference center, the reported prevalence may be higher than expected.

In the present study, while suspected fetal cardiac abnormality ZDV WKH VHFRQG PRVW FRPPRQ

echocardiography request, inadequate evaluation of the fetal KHDUW ZDV WKH PRVW FRPPRQ &+' UHDVRQ IDPLO\ KLVWRU\ RI &+' DQG PDWHUQDO which were reported to be the top two most common reasons for fetal echocardiography requests in the previous studies, were 3.4% and 7.8%, respectively in the present study. In the present study, similar to Ozat et al. detection of an abnormal cardiac finding during obstetric follow-up was more FRPPRQ WKDQ IDPLO\ KLVWRU\ RI &+' D the reasons for fetal echocardiography requests. Compatibility between the findings of the pediatric cardiologist and the obstetrician in the cases referred to fetal echocardiography ZLWK VXVSHFWHG &+' E\ WKH REVWHW the experience of the centers. In the current study, the rate of consistency was 40.1% between obstetricians and pediatric cardiologist in terms of the diagnosis of the congenital cardiac PDOIRUPDWLRQ reported that cardiac malformation was detected during fetal echocardiography in 45 of 275 SUHJQDQW ZRPHQ UHIHUUHG ZLWK Meyer-Wittkopf et al. demonstrated that cardiac abnormality ZDV GHWHFWHG LQ RXW RI referred to fetal echocardiography with suspected fetal cardiac abnormality, and the diagnosis was fully compatible in 62% of

7DEOH Intrauterine detected congenital heart diseases and their distribution according to pregnancy risk groups*

Results of fetal HFKRFDUGLRJUDSK\	+LJK ULVN JURXS	/RZ ULVN JURXS	7RWDO Q
&RPSOH[			
3$ ZLWK ,96 96' $96'	5	0	
6LQJOH YHQWULFXOH	2	0	
+/+6	6	0	
DORV	3	1	
Ebstein's anomaly	2	0	
Idiopatic diffuse calsification	1	0	
6KRQH FRPSOH[	2	0	
/HIW DWULDO LVRPHULVP	2	0	
$96'	2	0	
7RWDO	29	1	
0RGHUH			
TOF	7	2	
CoA	5	1	
d-TGA	4	0	
7RWDO	16	3	
6LPSOH			
96'	14	4	
Possible CoA	4	3	
36	0	3	
$6	8	2	
$6'	2	3	
7RWDO	28	15	
Other			
Tricuspid regurgitation	1	0	
/39&6	3	0	
Intracardiac Mass	2	0	
Double aortic arch	1	0	
Dextrocardia	1	0	
Dysrhythmias	14	1	
7RWDO	22	1	

&R$ &RDUFWDWLRQ RI DRUWD $6 $RUWLF VWHQRVLV $6' $WULDO VHSWDO GHIHFW $96' $WULR YHQWULFXODU VHSWDO GHIHFW '259 'RXEOH RXWOHW ULJKW YHQWULFOH +/+6 +\SRSODVWLF OHIW KHDUW V\QGURPH ,96 ,QWDFW YHQWULFXODU VHSWXP /39&6 /HIW SHUVLVWDQW YHQD FDYD VXSHULRU 3$ 3XOPRQDU\ DWUHVLD 36 3XOPRQDU\ VWHQRVLV 7*$ 7UDQVSRVLWLRQ RI JUHDW DUWHULHV YHVVHOV 72) 7HWUDORJ\ RI)DOORW 96' 9HQWULFXODU VHSWDO GHIHFW
*The prevalence of cardiac abnormalities in each category was higher in high-risk SUHJQDQFLHV $FFRUGLQJ WR WKH FKL VTXDUH WHVW S

these patients. Obstetricians' increasing experience in evaluating IHWDO KHDUW HQDEOHV XV WR GLDJQRVH D KLJKHU UDWH RI &+' GXULQJ the intrauterine period.

When pregnant women that underwent fetal echocardiography were classified according to risk levels in terms of fetal cardiac

7DEOH Comparison of pregnancy risk groups in terms of fetal echocardiography results

)HWDO FDUGLDF DQRPDO\	+LJK ULVN Q	/RZ ULVN Q	JURXS
&RPSOH[			
0RGHUH			
6LPSOH			
Other			

*chi-square test

malformation; 46.3% were in the high-risk group, and 53.6% ZKHUH LQ WKH ORZ ULVN JURXS ,Q IHW was detected most commonly in the high-risk group with a rate of 23.5%. In the low-risk group, determination of congenital heart abnormality rate was 5%, and it was significantly higher among high-risk pregnancies. This was associated with the detection of cardiac malformation in 40.1% of pregnancies referred to fetal echocardiography due to suspected fetal cardiac PDOIRUPDWLRQ LQ WKH REVWHWULF 8 al. , in which fetal echocardiography was performed in all pregnant women over a period of 4 years, they highlighted the importance of fetal echocardiography. They concluded that the fetal echocardiography should be included as a part of routine antenatal screening irrespective of risk factors for &+' $FFRUGLQJ WR WKH WKHLU UHVXO &+' ZDV VLPLODU EHWZHHQ KLJK DQ EXW WKH PDMRULW\ RI SUHJQDQFLHV was in the low-risk group, which is contrary to our finding. Operator misevaluation, failure to notice cardiac malformation, and inadequacy of and failure to interpret fetal cardiac image views were given as the reasons for failure to detect complex- VWUXFWXUHG IHWDO FDUGLDF PDOIRU missing diagnoses in these pregnancies, which were referred with low-risk, were made with fetal echocardiography (YDOXDWLRQ RI IHWDO KHDUW LQ REV and knowledge, and obstetric fetal cardiac evaluation which is not optimally performed owing to various reasons can cause complex cardiac malformations to be missed. Therefore, we find it appropriate to refer these pregnant women in whom IHWDO KHDUW FRXOG QRW EH DGHTXD with reasons similar to those stated by Nayak et al. to fetal echocardiography in our center as well. According to our results, LQDGHTXDWH HYDOXDWLRQ RI IHWDO K FRPPRQ UHDVRQ IRU [illegible] WLQJ +RZHYHU IHWDO FDUGLDF PDOIRUPDWL This was associated to a large extent with high-risk pregnancies in which obstetric fetal cardiac evaluation was conducted by an experienced perinatologist.

,W LV NQRZQ WKDW WKH SUHYDOHQF LQWUDXWHULQH DQG SRVWQDWDO SHU FRPPRQ &+' GXULQJ WKH SRVWQDWDO UHSRUWHG WR EH WKH PRVW FRPPRQ

intrauterine period as well . In the present study, consistent with the literature, the most common cardiac malformation in IHWDO HFKRFDUGLRJUDSK\ LV 96' ,Q WKH SUHYLRXV VWXGLHV FRPSOH[cardiac malformations were reported to be the most common JURXS RI &+'+RZHYHU ZH IRXQG FRPSOH[FDUGLDF malformations as the second most common following minor lesions. It was considered that this variation may be related to some differences in the classification of cardiac lesions between the studies. Moreover, in the present study, consideration of the higher but insignificant increases in flow velocities at semilunar valves may have played a role in the increased number of minor lesions. In previous studies, atrioventricular septal defect $96' DQG K\SRSODVWLF OHIW KHDUW ... reported to be complex cardiac lesions that are detected at a similar or higher prevalence . In the present study, the PRVW FRPPRQ FRPSOH[&+' ZDV 3$ IROORZHG E\ +/+6 6LQFH WKH SUHJQDQFLHV GLDJQRVHG ZLWK FRPSOH[W\SH FRQJHQLWDO cardiac malformations were referred to the surgical center during the prenatal or postnatal period, and the others diagnosed as moderate type lesions gave birth in our hospital, postnatal results of all of these pregnancies were retrieved. 0RUHRYHU PRVW RI WKH ... FDVHV ZKRVH SRVWQDWDO echocardiography results could be retrieved, were diagnosed with fetal cardiac abnormality by an obstetrician or pediatric cardiologist. The incompatibility between prenatal and postnatal echocardiography in these 261 cases were mostly due to simple lesions. It was found that the diagnoses did not change in complex lesions which were detected by a pediatric cardiologist, but one case with a normal fetal echocardiography was diagnosed with total anomalous pulmonary venous return abnormality during the postnatal period. Pulmonary venous UHWXUQ DEQRUPDOLWLHV VPDOO RU PRGHUDWH VL]HG ... $6' DQG PLQRU YDOYH OHVLRQV FDQQRW ... fetal echocardiography, and are frequently diagnosed after birth . Meyer-Wittkopf et al. also reported that a total anomalous pulmonary venous return abnormality diagnosed in the postnatal period could not be detected in the fetal echocardiography.

6WXG\ /LPLWDWLRQV

Although each evaluated pregnant woman was informed about the importance of postnatal echocardiography, a significant amount of postnatal echocardiographic evaluation, in which a statistical analysis for sensitivity and specificity could not be performed in order to make a confirmation or comparison.

Conclusion

,Q PDQ\ FHQWHUV UHJDUGOHVV RI &+' ULVN LW LV VWLOO QRW SRVVLEOH ... perform fetal echocardiography by a pediatric cardiologist to all pregnant women. Therefore, routine evaluation of the fetal heart E\ PHDQV RI REVWHWULF 86* LQFOXGLQJ IRXU FKDPEHUV RXWIORZ tracts' and three vessel views, would allow for diagnosing congenital cardiac malformations to a large extent during the intrauterine period.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO This study w... (VNLúHKLU 2VPDQJD]L 8QLYHUVLW\ ,QV... DSSURYDO QR

,QIRUPHG &RQVHQW The study is retrospective.

3HHU UHYLHZ Externally and internally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV ... Concept: P.K., M.V., B.U. Design: P.K., M.V., B.U., Data &ROOHFWLRQ RU 3URFHVVLQJ 3. 7. ... ,QWHUSUHWDWLRQ 3. 7. +. 09 ... P.K., M.V., Writing: P.K., M.V. +/+6 ZHUH

&RQIOLFW RI ,QWHUHVW The authors report no conflict of interest.

)LQDQFLDO 'LVFORVXUH Authors have no financial interests about the research.

References

1. Midan MF, Alsheem \ 5, (LG 60 $EGHO 6DODP 0(... echocardiography in prenatal diagnosis of congenital heart diseases. Int J Reprod Contracept Obstet Gynecol 2016;5:1553-7.
%UDYR 9DOHQ]XHOD 1- 3HxDWR $% $UDX... of congenital heart disease: A review of current knowledge. Indian +HDUW - ...
/HYL 6 8OWUDVRXQG LQ SUHQDWDO GLDJ... ultrasound screening for second trimester foetal mal-formations. Prenat Diagn 2002;22:285-95.
6DLQ] -$ =XULWD 0- *XLOOHQ , %RUUHU... C, et al. Prenatal screening of congenital heart defects in population DW ORZ ULVN RI FRQJHQLWDO GHIHFWV ... 2015;82:27-34.
,QWHUQDWLRQDO 6RFLHW\ RI 8OWUDVRXQ... &DUYDOKR -6 $OOHQ /' &KDRXL 5 &RSHO ... 3UDFWLFH *XLGHOLQHV XSGDWHG VRQR... of the fetal heart. Ultrasound Obstet Gynecol 2013;41:348-59.
'RON + /RDQH 0 *DUQH ((XURSHDQ 6XU... $QRPDOLHV (852&$7 :RUNLQJ *URXS &R... in Europe: prevalence and perinatal mortality, 2000 to 2005. Circulation 2011;123:841-9.
6ORGNL 0 5HVSRQGHN /LEHUVND 0 1HZ F... diagnosed congenital heart defects and their influence on neonatal survivability. Prenat Cardio 2015;5:6-8.
'RQRIULR 07 0RRQ *UDG\ $- +RUQEHUJHU... 06 $EXKDPDG $ HW DO 'LDJQRVLV DQG ... GLVHDVH D VFLHQWLILF VWDWHPHQW IUR... Circulation 2014;129:2183-242.
1D\DN . &KDQGUD *6 6KHWW\ 5 1DUD\DQ... echocardiography as a routine antenatal screening tool for detection of congenital heart disase. Cardiovasc Diagn Ther 2016;6:44-9.
=KDQJ <) =HQJ ;/ =KDR () /X +: 'LDJQR... (FKRFDUGLRJUDSK\ IRU &RQJHQLWDO +H... 5HYLHZ DQG 0HWD $QDO\VLV 0HGLFLQH ...
5HQ << /L ;7 *XL <+ <DQ </ &KDQJ & =KD... of the prenatal screening mode for fetal congenital heart diseases by ultrasound. Zhonghua Fu Chan Ke Za Zhi 2008;43:589-92.
2]EDUODV 1 (UGHP 6 .•o•NRVPDQRJOX 2 ... & (YU•NH & HW DO 3UHYDOHQFH DQG G...

diseases in high and low risk pregnancies. Anadolu Kardiol Derg 2011;11:125-30.

)ULHGEHUJ 0. 6LOYHUPDQ 1+ &KDQJLQJ LQGLFDWLRQV IRU IHWDO echocardiography in a University Center population. Prenat Diagn 2004;24:781-6.

&KD 6 .LP *% .ZRQ %6 %DH (- 1RK &,, /LP +* HW DO 5HFHQW trends in indications of fetal echocardiography and postnatal outcomes in fetuses diagnosed as congenital heart disease. Korean Circ J 2012;42:839-44.

6LPSVRQ // ,QGLFDWLRQV IRU IHWDO HFKRFDUGLRJUDSK\ IURP D WHUWLDU\ care obstetric sonography practice. J Clin Ultrasound 2004;32:123-8.

0H\HU :LWWNRSI 0 &RRSHU 6 6KROOHU */ &RUUHODWLRQ EHWZHHQ fetal cardiac diagnosis by obstetric and pediatric cardiologist sonographers and comparison with postnatal findings. Ultrasound Obstet Gynecol 2001;17:392-7.

6KDUPD 6 .DXU 1 .DXU : 3DZDU 1& 5ROH prenatal screening of congenital heart diseases and its correlation with postnatal outcome. J Clin Diagn Res 2017;11:12-4.

5RFKD /$ -XQLRU $UDXMR (5ROR /& %DU AT, et al. Prenatal detection of congenital heart diseases: One-year survey performing a screening protocol in a single reference center LQ %UD]LO &DUGLRO 5HV 3UDFW

&KDUDIHGGLQH) +DFKHP $ .LEEL 1 $EX Z, et al. The first fetal echocardiography exper,ence for prenatal GLDJQRVLV RI FRQJHQLWDO KHDUW GLVH FKDOOHQJHV - 6DXGL +HDUW $VVRF

<DVLQ 'XUPXü, .DU$SXOKHU, 6LQHP $\üH 'XUX, 1XUHWWLQ 0HKPHW hQVDO
*|NKDQ %R\UD]

8QLYHUVLW\ RI +HDOWK 6FLHQFHV 7XUNH\ (WOLN =•EH\GH +DQ×P :RPHQ·V +HDOWK
Turkey

PRECIS: Transdiaphragmatic thoracotomy, colon resection, ileostomy and development of any extra-pulmonary complication were identified a
independent predictors of pulmonary morbidity.

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL <DVLQ 'XUPXü 0'
8QLYHUVLW\ RI +HDOWK 6FLHQFHV 7XUNH\ (WOLN =•EH\GH +DQ×P :RPHQ·V +HDOWK 7UDLQLQJ DQG 5HVHDUFK +
Phone: +90 312 567 40 00 (PDLO dr_yasindurmus@hotmail.com 25&,' ,' orcid.org/0000-0002-5404-0118
5HFHLYHG *HOLü 7DULKL 05.05.2020 $FFHSWHG .DEXO 7DULKL 18.07.2020

6RQXo 7UDQVGL\DIUDP WRUDNRWRPL GL\DIUDP FHUUDKLVL JHoLUHQ KDVWDODUGD SXO
WUDVGL\DIUDP WRUDNRWRPLOHUGHQ NDo×QPDN YH WDP NDW GL\DIUDP UH]HNVL\RQODU
SXOPRQHU PRUELGLWH RUDQ×Q×Q D]DOW×OPDV×QD YH SRVWRSHUDWLI EDN×P PDVUDIO
$QDKWDU .HOLPHOHU 'L\DIUDJP FHUUDKL VLWRUHG•NWLI RYHU NDQVHUL PRUELGLWH

Introduction

6WXGLHV KDYH VKRZQ WKDW RSWLPDO F\WRUHGXFWLRQ LV WKH FRUQHUVWR of initial treatment for advanced epithelial ovarian cancers It is estimated that nearly 40% of patients with advanced ovarian cancer have gross disease located on the diaphragm. Patients with advanced ovarian cancer and diaphragm involvement who had undergone diaphragm surgery had better survival rates than those who had not. Thus, a significant proportion of patients with advanced ovarian cancers require diaphragm surgery to achieve optimal cytoreduction and therefore better survival rates. Complete cytoreduction is also associated with improved overall survival in advanced uterine corpus cancers, and patients with metastatic diaphragm disease require diaphragm surgery .

Previous studies reported that diaphragm surgery was associated with pulmonary morbidity, and they reported higher rates of pleural effusion , higher rates of pneumothorax and longer hospital stay after diaphragm surgery. Furthermore, several studies showed higher rates of pulmonary morbidity after diaphragm full-thickness resections compared with diaphragm peritoneal stripping ,but others did not show a significant difference . Previous studies were not able to assess other types of pulmonary morbidity such as pneumonitis and atelectasis due to the small number of cases. Thus, pulmonary morbidity related to diaphragm surgery needs further evaluation with a larger number of cases. We performed the present study to improve knowledge about pulmonary morbidity related to diaphragm surgery, and we also assessed other potential surgical factors that may contribute to pulmonary morbidity.

Materials and Methods

All patients who had undergone diaphragm surgery as a part of cytoreductive surgery procedures performed for advanced or recurrent ovarian and uterine corpus cancers between January 1, 2001, and June 1, 2018, were reviewed retrospectively. Data were obtained from hospital medical records. Patients who had an ablative intervention to the diaphragm were excluded from the study. We included only cases involving surgical resections of the diaphragm peritoneum with or without diaphragm muscle and overlying parietal pleura. Patients with preoperative pleural effusions and intraoperative chest tube replacements would lead to unreliable evaluation of the postoperative pulmonary complications so they were excluded.

Diaphragm debulking surgery to excise all visible metastatic tumoral deposits on the diaphragm surface was performed SULPDULO\ E\ H[FLVLRQ RI WKH GLD VWULSSLQJ 7KH H[WHQW RI WKH was classified as “total hemi-diaphragm peritoneal stripping”, “partial hemi-diaphragm peritoneal stripping”, or “focal implant resection.” Excision of the whole hemi-diaphragm peritoneum starting from the anterior costal margin was identified as “total KHPL GLDSKUDJP SHULWRQHDO VWULS LPSODQWV ” FP LQ GLDPHWHU ZDV LG resection”. All the other peritoneal excisions that were not compatible with the above definitions were classified as “partial hemi-diaphragm peritoneal stripping”.

)XOO PRELOL]DWLRQ RI WKH OLYHU ZD starting a right hemi-diaphragm total peritoneal stripping SURFHGXUH /LYHU PRELOL]DWLRQ ZDV partial hemi-diaphragm stripping or a focal implant resection procedure depending on the location of the tumor. Tumor involvement on the left hemi-diaphragm is more easily resected ZLWKRXW PRELOL]LQJ WKH OLYHU

Diaphragm surgery may be complicated by transdiaphragmatic thoracotomy. In our study, we classified the cause of transdiaphragmatic thoracotomy as either “willful partial hemi-diaphragm full-thickness resection” or “accidental transdiaphragmatic thoracotomy”. If the surgical report indicated a histologically confirmed tumor implant invading the diaphragm muscle with or without parietal pleura, we identified the cause of the transdiaphragmatic thoracotomy as “willful partial hemi-diaphragm full-thickness resection”. If not, we identified the cause as “accidental transdiaphragmatic thoracotomy”.

Diaphragm repair was done by continuous suturing of the GHIHFW ZLWK SUROHQH VXWXUHV anesthetist was performing a forced inspiration with the help of the ventilator and the surgical team was applying a negative pressure to the thorax cavity with the help of a thin aspiration tube positioned through the remaining diaphragm defect. The second surgeon pulled out the aspiration tube as the first VXUJHRQ WLHG WKH NQRW /DUJH GLDS with prolene mesh.

All patients received preoperative antibiotics and anticoagulant prophylaxis. No prophylactic antibiotics were used SRVWRSHUDWLYHO\ (QR[DSDULQH was administered 2 hours before the surgery and then repeated daily for 30 days after the surgery if the body mass index of the SDWLHQW Z², Devoxaparine NJ 6000 IU was administered LI WKH ERG\ PDVV LQ². All patients were NJ assessed with a chest radiography on the first postoperative day DQG ZLWK SK\VLFDO H[DPLQDWLRQ GD Chest radiography was repeated on the following days if any pathologic signs were detected on the physical examination. Chest computed tomography was performed when needed. Admission to the postoperative general care room or the

intensive care unit was carried out according to the decision of the anesthetist. Replacement of the chest tube in the postoperative period was decided and performed by the thorax surgeon when needed. Referral to the intensive care unit during postoperative general care was decided by the senior surgeon and anesthetist when needed.

We reviewed intraoperative complications and postoperative complications that occurred within 30 days. Pulmonary morbidity was identified as the development of at least one of the following pulmonary complications: Pleural effusion, pneumothorax, pneumonitis, atelectasis, pulmonary embolism. Extra-pulmonary complications in the study group included wound infection, wound dehiscence, evisceration, intestina anastomosis leak, ureterovaginal fistulas, vesicovaginal fistulas, gastrointestinal fistulas, ileus, acute cerebrovascular diseas chylous ascites, intraabdominal abscess, subphrenic absce intestinal perforation, gastric perforation, bladder perforation, pancreatic leak/fistula, appendectomy site leak, intestina ischemia, ureter ischemia, deep venous thrombosis, arterial embolism, and myocardial infarction.

7KLV VWXG\ ZDV DSSURYHG E\ LQVW JRYDO GDWH DQG QXPEHU

informed consent for anonymous publication of disease related information was obtained from each patient.

6WDWLVWLFDO $QDO\VLV

'DWD ZHUH DQDO\]HG XVLQJ WKH FK test for categorical variables, and the independent sample t-test was used for continuous variables. A binary logistic regressio model was used for the multivariate analysis. Differences wer FRQVLGHUHG VLJQLILFDQW DW S 6FLHQFH 6366 YHUVLRQ 6366 used for the statistical analyses.

Results

We included 232 patients who had undergone diaphragm VXUJHU\ 7KH PHDQ DJH ZDV “ \HDUV 7ZR KXQGUHG QLQH SDWLHQWV SHULWRQHDO FDQFHUV KD KDG V\QFKURQL]HG FDQFHUV 7KH RYDULDQ WXEDO VXEJURXSV DUH VXPPDUL]HG LQ 7DEOH 2OH KXQGUHG WZR SDWLHQWV KDG XQGHU within the context of primary cytoreduction surgery. Forty SDWLHQWV KDG XQGHUJRQH G recurrent cancers. Cytoreductive surgery resulted in excision of DOO YLVLEOH WXPRUV LQ SDWLHQWV 2QH KXQGUHG HLJKW\ WKUHH SDWL ULJKW KHPL GLDSKUDJP VXUJHU\ undergone left hemi-diaphragm surgery, and 47 patients KDG XQGHUJRQH ELODWHUDO 2QH KXQGUHG VL[W\ WZR SDWLHQWV hemi-diaphragm peritoneal stripping procedure, 9 patients KDG XQGHUJRQH D SDUWLDO

VWULSSLQJ SURFHGXUH SDWLHQWV implant resection. The surgical notes reported presence of DVFLWHV LQ SDWLHQWV 0HDQ ZDV “ P/ 0HDQ RSHUDWLRQ WL PLQXWHV 7KLUW\ HLJKW SDWLHQWV intensive care. The median hospital stay was 9 days, and the

7DEOH +LVWRSDWKRORJLF FKDUDFWHULV

+LVWRSDWKRORJ\	1XPEHU
2YDULDQ WXEDO SHULWRQHDO FDQFHUV	
Ovarian serous adenocarcinoma	
Ovarian endometrioid adenocarcinoma	
Ovarian clear cell adenocarcinoma	
Ovarian transitional cell adenocarcinoma	
Ovarian borderline mucinous tumor	
Ovarian mixed epithelial cancers	
Tubal serous adenocarcinoma	
Peritoneal serous adenocarcinoma	
(6LJQHG	
Immature teratoma	
Granulosa cell tumor	
Tubal carcinosarcoma	
Ovarian carcinosarcoma	
8WHULQH FRUSXV FDQFHUV	
Endometrium endometrioid adenocarcinoma	
Endometrium serous adenocarcinoma	
Endometrium undifferentiated adenocarcinoma with neuroendocrine differentiation	
Uterine carcinosarcoma	
Uterine tumor resembling ovarian sex-cord tumor	
Uterine leiomyosarcoma	
6\QFKURQL]HG FDQFHUV	
6\QFKURQL]HG ULJKW RYDULDQ VHURX adenocarcinoma-left ovarian granulosa cell tumor	
6\QFKURQL]HG RYDULDQ VHURXV DGHQ endometrium endometrioid adenocarcinoma	
6\QFKURQL]HG RYDULDQ HQGRPHWULR adenocarcinoma + endometrium endometrioid adenocarcinoma	
6\QFKURQL]HG RYDULDQ PXFLQRXV adenocarcinoma + cervical large cell neuroendocrine carcinoma	

median time from surgery to the first chemotherapy cycle was GD\V 1R FRPSOLFDWLRQV RFFXUUHG LQ 7ZHQW\ QLQH SDWLHQWV KDG RQO\ SDWLHQWV KDG H[WU RQO\ DQG SDWLHQWV KDG pulmonary complications. Three patients died within the 30-day period after surgery, and the mortality rate was 1.3%. One patient died because of aspiration pneumonitis and 2 died as a result septic complications.

In our study, accidental transdiaphragmatic thoracotomy RFFXUUHG LQ SDWLHQWV excision of the hemi-diaphragm was performed in 33 patients. 2QH ZLOOIXO SDUWLDO KHP resection procedure was performed with a gastrointestinal stapler device avoiding an entry into the pleural cavity so she was not included in the transdiaphragmatic thoracotomy group, thus UHPDLQLQJ SDWLHQWV IRU thoracotomy group. In the study period, one large diaphragm defect required repair with prolene mesh.

:H DQDO\]HG DOO FOLQLFRSDWKRO regard to pulmonary morbidity. There was a higher rate of pulmonary complications when the surgical notes reported the presence of transdiaphragmatic thoracotomy. Twenty-one SDWLHQWV ZKR KDG D WUDQV developed a pulmonary complication. Thirty-seven patients ZKR GLG QRW KDYH D WUDQV developed a pulmonary complication postoperatively. The GLIIHUHQFH ZDV VWDWLVWLFDOO\

According to our data, patients who developed pulmonary complications and patients who did not develop pulmonary complications showed insignificant difference with regard to age. The mean age of patients who developed pulmonary complications was 57.4±7.9. The mean age of patients who did not develop pulmonary complications was 60.9±9.7. The GLIIHUHQFH EHWZHHQ WZR JURXSV ZDV LQVLJQLILFDQW S

Patients who underwent small-bowel resection, colon resection, pelvic peritonectomy, appendectomy, tumor resection from liver Glisson's capsule, tumor resection from the omentum minus, tumor resection from Morrison's pouch, tumor resection from colon serosa, ileostomy, colostomy concurrently had significantly higher rates of pulmonary complication. The mean intraoperative blood loss of the patients who developed pulmonary complications was significantly higher than that of patients who did not develop any pulmonary complications S 3DWLHQWV ZKR GHYHORSHG complication had significantly higher rate of pulmonary FRPSOLFDWLRQV FRPSDUHG ZLWK Patients who developed an intestinal anastomosis leak had VLJQLILFDQWO\ KLJKHU UDWH RI SXOPRQDU\ 7DEOH

The factors associated with pulmonary morbidity are VXPPDUL]HG LQ 7DEOH DQG ZH D logistic regression model. We found that transdiaphragmatic WKRUDFRWRP\ >RGGV UDWLR 25 &, SDWLHQW@V FRORQ UHVHFWL CI, 2.34-11.63; p< FRPSOLFDWLRQV 25 1.64-25.00; p= RQDU\ HDFK DQG H[WU FRQ... RFFXUUHQFH 25 DQG H[W &, LQGHSHQGHQW SUHGLFWRUV RI SXOPR ,Q RXU VWXG\ SDWLHQWV GHY SRVWRSHUDWLYHO\ SDWLHQWV WKDW QHFHVVLWDWHG GUDLQDJH SQHXPRWKRUD[SDWLHQWV :LOO SXOPRQDU\ IXGHYHORSHG developed pulmonary embolism. We divided the study population into 2 groups according to the absence or presence of transdiaphragmatic thoracotomy and compared the pulmonary complication subtypes separately. Patients in the transdiaphragmatic thoracotomy group developed pleural effusion, pleural effusion necessitating drainage, pneumothorax, pneumonitis, and atelectasis more frequently than patients in WKH QR WUDQVGLDSKUDJPDWLF WKRUD

Mean hospital stay, mean time interval from surgery to chemotherapy, and rate of postoperative admission to intensive care for patients with or without pulmonary complications and transdiaphragmatic thoracotomy are shown in Table 5. Patients who developed pulmonary complications had significantly longer hospital stay, longer time interval to chemotherapy, and needed postoperative intensive care more frequently. The differences in mean hospital stay and mean time interval to chemotherapy between the groups with and without transdiaphragmatic thoracotomy were insignificant. But the rate of admission to postoperative intensive care of patients with transdiaphragmatic thoracotomy was significantly higher than that of patients without transdiaphragmatic thoracotomy 7DEOH

Discussion

Diaphragmatic surgery is performed frequently within the context of cytoreductive surgery for advanced ovarian cancers, and cytoreduction to microscopic disease improves survival. Complete cytoreduction is also associated with improved overall survival in advanced uterine corpus cancers, and patients with metastatic diaphragm disease require diaphragm surgery. When diaphragm surgery is performed, it may cause pulmonary complications and additional morbidity. In this study, 25% of patients developed a pulmonary complication. Pleural effusion was the most common complication and 20.7% developed pleural effusions postoperatively; 2.6% developed pneumothorax. Other studies reported pleural effusion rates after diaphragm surgery of between 2% and 59%, and pneumothorax rates between 0% and 5% S Eisenhauer et al. DQDO\]HG SOHXUDO HIIXV patients who had undergone diaphragm peritonectomy or resection. They reported that ipsilateral postoperative pleural HIIXVLRQV RFFXUUHG LQ SDWLHQWV

7 D E O H Factors associated with pulmonary morbidity

Factors		'HYHORSPHQW RI SXOPRQDU\ FRP		p
		Yes	No	
Transdiaphragmatic thoracotomy	< H V No			0.004
Unilateral versus bilateral diaphragm stripping	Unilateral Bilateral			0.109
Total versus partial or focal diaphragm stripping	Total Partial/focal			0.069
Transdiaphragmatic thoracotomy	Accidental Partial full-thickness resection			0.089
+ L V W R S D W K R O R J \	Ovarian-tubal-peritoneal invasive epithelial cancer Others			0.518
Primary site	Ovary-tuba-peritoneum Uterine corpus			0.786
Cytoreduction	Primary •			0.422
3 U H R S H U D W L Y H & D , 8 P / P H D Q “ 6 '		1328.70±1465.32	1151.96±1353.90	0.484
Intraoperative ascites	< H V No			0.356
$ V F L W H V Y R O X P H P / P H D Q “ 6 '		2447.62±2127.35	2760.26±2599.02	0.613
6 X S U D K H S D W L F G U D L Q	< H V No			0.422
' X U D W L R Q R I W K H V X S U D K H S D W L F G U D L Q P H D Q “ 6 '		5.9±4.7	4.6±2.4	0.111
2 S H U D W L R Q W L P H P L Q X W H V P H D Q “ 6 '		340.7±76.9	335.6±68.8	0.796
, Q W U D R S H U D W L Y H E O R R G O R V V P / P H D Q “ 6 '		1136.6±1213.4	672.7±751.5	0.045
6 P D O O E R Z H O U H V H F W L R Q	< H V No			0.002
Colon resection	< H V No			
Pelvic peritonectomy	< H V No			0.001
Appendectomy	< H V No			0.018
Tumor resection from liver Glisson’s capsule	< H V No			0.038
Tumor resection from omentum minus	< H V No			0.039

7DEOH FRQWLQXHG		
Tumor resection from Morrison's pouch	< H V No	0.015
Tumor resection from colon serosa	< H V No	0.036
Ileostomy	< H V No	
Colostomy	< H V No	
Any extra-pulmonary complication	< H V No	
Intestinal anastomosis leakage	< H V No	0.006

$OO FRQFXUUHQW VXUJLFDO SURFHGXUHV DQG H[WUD SXOPRQDU\ FRPSOLFDWLRQV ZHUH DQDO\]HG RQO\
[a]2QH ERUGHUOLQH PXFLQRXV WXPRU DQG V\QFKURQL]HG FDQFHUV ZHUH H[FOXGHG IURP WKH DQDO\VLV
[b])LYH V\QFKURQL]HG FDQFHUV ZHUH H[FOXGHG IURP WKH DQDO\VLV
[c]2QO\ RYDULDQ WXEDO SHULWRQHDO HSLWKHOLDO FDQFHUV VXEMHFWHG WR SULPDU\ F\WRUHGXFWLRQ VX

7DEOH Independent predictors of pulmonary morbidity

,QGHSHQGHQW SUHGLFWRUV RI SXOPRQDU\ [illegible]	[illegible]	[illegible]	p
7UDQVGLDSKUDJPDWLF WKRUDFRWRP\	[illegible]	[illegible]	0.016
&RORQ UHVHFWLRQ SHUIRUPHG YHUVXV QRW	[illegible]	[illegible]	
,OHRVWRP\ SHUIRUPHG YHUVXV QRW	[illegible]	[illegible]	0.019
$Q\ H[WUD SXOPRQDU\ FRPSOLFDWLRQ	[illegible]	[illegible]	[illegible]

7DEOH Comparison of pulmonary complications in patients with and without transdiaphragmatic thoracotomy

3XOPRQDU\ FRPSOLFDWLRQ	1R WUDQVGLDSKUDJPDWLF WKRUDFRWRP\ JURXS Q	7UDQVGLDSKUDJPDWLF WKRUDFRWRP\ JURXS Q	p
Any kind of pulmonary complication	< H V No		0.004
Pleural effusion	< H V No		0.042
Pleural effusion, did not necessitate drainage	< H V No		0.812
Pleural effusion, necessitated drainage	< H V No		0.006
Pneumothorax	< H V No		0.002
Pneumonitis	< H V No		0.01
Atelectasis	< H V No		0.032
Pulmonary embolism	< H V No		!

7 D E O H Mean length of hospital stay, mean time from surgery to chemotherapy, and rate of postoperative intensive care

	/HQJWK RI KRVSLWDO VWD\ GD\V “ 6'	p	PHDQ FKHPRWKHUDS\ GD\V PHDQ “ 6'	p	3RVWRSHUDWLYH LQWHQVLYH FDUH XQLW Q		p
					Yes	No	
Pulmonary complication							
< H V	17.56±10.95		20.48±11.14	0.023			
No	10.61±7.42		16.63±9.56				
Transdiaphragmatic thoracotomy							
< H V	13.33±8.85	0.376	18.83±10.96	0.344			0.001
No	12.05±8.95		17.17±9.81				

6' 6WDQGDUG GHYLDWLRQ

patients had undergone diaphragm resection or had diaphragm perforation. Eleven of 43 patients developed ipsilateral effusions. Although 73% of patients who underwent diaphragm resection and had perforations developed ipsilateral effusions, statistical analysis did not show a significantly increased rate of ipsilateral effusions after diaphragm resection or diaphragm perforation. The small number of patients in the study group and relatively high rates of pleural effusion may have led to the absence of statistical significance. In our study, 20.7% of patients developed pleural effusions postoperatively. The rates of pleural effusion in patients without transdiaphragmatic thoracotomy and with transdiaphragmatic thoracotomy were 17.8% and 30.8%, respectively. Pleural effusion was more frequent among patients with transdiaphragmatic thoracotomy and it was statistically significant.

6 R O H \ P D Q L 0 compared 64 cases with diaphragmatic peritonectomy and 36 cases with pleurectomy with regard to pulmonary morbidity. The rates of pulmonary morbidity in the peritonectomy group and the pleurectomy group were 9.3% and 19%, respectively, and there was no significant difference S 7KH\ ZHUH DEOH WR VKRZ KLJKHU UDWHV RI SXOPRQDU\ morbidity after pleurectomy compared with peritonectomy, but they were unable to show a statistically significant difference due to the limited number of cases < H H compared 124 patients with diaphragmatic peritonectomy and 26 cases with full-thickness diaphragmatic resection with regard to pulmonary morbidity, and they showed that patients who underwent full-thickness diaphragmatic resection developed pleural effusion VLJQLILFDQWO\ PRUH IUHTXHQWO\ and significantly more frequent symptomatic pleural effusion UHTXLULQJ GUDLQDJH YZaparkiv et al. compared 79 patients who underwent diaphragmatic stripping and 33 patients who underwent diaphragmatic resection and showed that patients with diaphragmatic resection GHYHORSHG SOHXUDO HIIXVLRQ VLJQLILFDQWO\ PRUH IUHTXHQWO\ YHUVXV S

In the current study, we were able to identify transdiaphragmatic thoracotomy as an independent predictor of pulmonary morbidity after diaphragm surgery. To our knowledge, the present study is the largest case series evaluating pulmonary morbidity related to diaphragm surgery. We were able to show that patients with transdiaphragmatic thoracotomy developed pulmonary morbidity, pleural effusions, pleural effusions necessitating drainage, pneumothorax, pneumonitis, and atelectasis significantly more frequently than patients who underwent diaphragm surgery without transdiaphragmatic thoracotomy. In the current study, all the diaphragm surgery procedures and diaphragm repairment procedures were performed by gynecological oncologists and we think that diaphragm surgery procedures can be managed by experienced gynecological oncologists. A thorax surgeon should attend the operation when a pulmonary parenchymal resection is planned. 3UHRSHUDWLYH LPDJLQJ ZLWK WKRUD may help to predict cases with thorax and diaphragm involvement.

Eisenhauer et al. reported that ipsilateral pleural effusion was not associated with an increased length of hospital stay. Benedetti Panici et al. DQDO\]HG SDWLHQWV ovarian cancer. They performed diaphragm peritonectomy in 25 patients and diaphragm resections in 43 patients and reported that diaphragmatic resection was associated with significantly ORQJHU SRVWRSHUDWLYH KRVSLWDO VW S $FFRUGLQJ WR RXU GDWD GHYH morbidity was associated with longer hospital stay, longer time interval to chemotherapy, and a higher rate of postoperative intensive care. Patients with transdiaphragmatic thoracotomy needed postoperative intensive care more frequently than patients without transdiaphragmatic thoracotomy. Decreasing the rate of transdiaphragmatic thoracotomy among patients undergoing diaphragm surgery may help decrease postoperative intensive care admissions and therefore reduce postoperative care costs. Development of an extra-pulmonary complication, concurrent colon resections and ileostomy were also independent predictors of pulmonary morbidity. Among patients with concurrent colon resections and ileostomy, prolonged intravenous support and electrolyte imbalance may have contributed to higher rates of pleural effusions and pulmonary morbidity.

6WXG\ /LPLWDWLRQV

The retrospective design of the study and the absence of a patient group with advanced gynecological cancer that did not undergo diaphragm surgery are limitations of the current study. The high number of patients in the study, the competence in evaluating pulmonary complications separately, and identifying independent factors associated with pulmonary morbidity by PXOWLYDULDWH DQDO\]HV DUH DGYDQWDJHV RI WKH FXUUHQW VWXG\ 7R our knowledge, the present study is the largest case series evaluating pulmonary morbidity related to diaphragm surgery.

Conclusion

In conclusion, diaphragm surgery helps to enhance complete cytoreduction rates and therefore improves survival in advanced epithelial ovarian cancers and uterine corpus cancers. þW LV DVVRFLDWHG ZLWK KLJKHU UDWHV RI SXOPRQDU\ FRPSOLFDWLRQV Transdiaphragmatic thoracotomy is an independent predictor of pulmonary morbidity among patients who undergo diaphragm surgery. Avoiding accidental transdiaphragmatic thoracotomies with maximal attention may help decrease pulmonary morbidity rates and postoperative care costs. Potential benefits RI DOWHUQDWLYH VXUJLFDO WHFKQLTXHV H J XVLQJ VWDSOHU GHYLFHV preventing entry into the thorax cavity while performing full-thickness diaphragm resections should further be investigated.

(WKLFV

(WKLFV &RPPLWWHH $SSURYDO All procedures performed in this study were in accordance with the ethical standards of WKH LQVWLWXWLRQDO UHVHDUFK FRPPLWWHH DQG ZLWK WKH +HOVLQNL declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was received for WKLV VWXG\ DSSURYDO GDWH DQG QXPEHU (

,QIRUPHG &RQVHQW 6LJQHG LQIRUPHG FRQVHQW IRU DQRQ\PRXV publication of disease related information was obtained from each patient.

3HHU UHYLHZ Externally and internally peer- reviewed.

$XWKRUVKLS &RQWULEXWLRQV

&RQFHSW <' 'HVLJQ <' 'DWD &ROOHFWLRQ RU 3URFHVVLQJ 0 h <' 6$'d $QDO\VLV RU ,QWHUSUHWDWLRQ <' $. (GLWLQJ $. 1% *% 77 :ULWLQJ $. 1%

&RQIOLFW RI ,QWHUHVW The authors report no conflict of interest.

)LQDQFLDO 'LVFORVXUH Authors have no financial interests about the research.

References

%ULVWRZ 5(7RPDFFX] 56 $UPVWURQJ ')- 6XUYLYDO HIIHFW RI PD[LPDO F\WRUHGXFWLYH VXUJHU\ IRU DGYDQFHG RYDULDQ ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248-59.

&KL '6 (LVHQKDXHU (/ /DQJ - +XK - +DGGDG / $EX 5XVWXP 1 5 et al. What is the optimal goal of primary cytoreductive surgery IRU EXON\ VWDJH ,,,& HSLWKHOLDO RYDU Oncol 2006;103:559-64.

3. Papadia A, Morotti M. Diaphragmatic surgery during cytoreduction for primary or recurrent epithelial ovarian cancer: a review of the literature. Arch Gynecol Obstet 2013;287:733-41.

4. Benedetti Panici P, Di Donato V, Fischetti M, Casorelli A, Perniola G, Musella A, et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: analysis and management of complications in upper abdominal surgery. Gynecol Oncol 2015;137:406-11.

$OHWWL *' 'RZG\ 6& 3RGUDW] .& &OLE\ of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 2006;100:283-7.

$ODJNLR]LGLV , *URVVPDQ $ 7DQJ 1= :H * HW DO 6XUYLYDO LPSDFW RI F\WRUHGX advanced stage cancer of the uterine corpus: a retrospective cohort VWXG\ ,QW - 6XUJ

6RORPD] 8 0DW (HUHO 0/ 7XUDQ 9 (NLF III and -IV endometrial cancer: a single oncology centre review of 104 cases. J Obstet Gynaecol 2016;36:81-6.

8. Fanfani F, Fagotti A, Gallotta V, Ercoli A, Pacelli F, Costantini B, et al. Upper abdominal surgery in advanced and recurrent ovarian cancer: role of diaphragmatic surgery. Gynecol Oncol 2010;116:497-501.

(LVHQKDXHU (/ '·$QJHOLFD 0 $EX 5XVWX WR, Barakat RR, et al. Incidence and management of pleural effusions after diaphragm peritonectomy or resection for advanced Mullerian cancer. Gynecol Oncol 2006;103:871-7.

'HYROGHU . $PDQW) 1HYHQ 3 YDQ *RU I. Role of diaphragmatic surgery in 69 patients with ovarian carcinoma. Int J Gynecol Cancer 2008;18:363-8.

&KHUHDX (5RX]LHU 5 *RX\ 6)HUURQ * al. Morbidity of diaphragmatic surgery for advanced ovarian cancer: UHWURVSHFWLYH VWXG\ RI FDVHV (XU

%DVKLU 6 *HUDUGL 0$ *LXQWROL 5/ 0 6XUJLFDO WHFKQLTXH RI GLDSKUDJP IX trans-diaphragmatic decompression of pneumothorax during cytoreductive surgery for ovarian cancer. Gynecol Oncol 2010;119:255-8.

=DSDUGLHO , 3HLUHWWL 0 =DQDJQROR 9 F, et al. Diaphragmatic surgery during primary cytoreduction for advanced ovarian cancer: peritoneal stripping versus diaphragmatic resection. Int J Gynecol Cancer 2011;21:1698-703.

<H 6 +H 7 /LDQJ 6 &KHQ ; :X ; <DQJ + surgery and related complications in primary cytoreduction for advanced ovarian, tubal, and peritoneal carcinoma. BMC Cancer 2017;17:317.

6RO %´ PDQ 7 0DMG +)HUUDUL) 0DQHN 6 +DUGHUU HW DO 'LDSKUDJPDWLF SHUL resection with pleurectomy during Visceral-Peritoneal Debulking 93' LQ FRQVHFXWLYH SDWLHQWV ZLWK a surgical-histological analysis. Gynecol Oncol 2016;140:430-5.

*RX\ 6 &KHUHDX (&XVWRGLR $6 8]DQ & HW DO 6XUJLFDO SURFHGXUHV DQG PRUE in patients undergoing initial or interval debulking surgery for DGYDQFHG RYDULDQ DQG WXEDO FDQFHU - $P

'RZG\ 6& /RHZHQ 57 $OHWWL *)HLWR]D of outcomes and morbidity following diaphragmatic peritonectomy for women with ovarian carcinoma. Gynecol Oncol 2008;109:303-7.

Hemorrhagic corpus luteum: Clinical management update

+HPRUDMLN NRUSXV OXWHXP .OLQLN

0\NKDLOR 9 0HGYHGHY[1] $OHVVDQGUR 0DOYDVL[2] Sarah Gustapane[3] $QGUHD 7LQHOOL[4]

[1]Dnipropetrovsk Medical Academy of Health Ministry of Ukraine, Dnipropetrovsk, Ukrain

[2]Santa Maria Hospital, Gvm Care and Research, Clinic of Obstetrics and Gynaecology, Bari, Italy

[3]Veris Delli Ponti Hospital, Clinic of Obstetrics and Gynecology, Scorrano, Lecce, Italy

[4]Veris Delli Ponti Hospital, Chief of Clinic of Obstetrics and Gynecology, Scorrano, Lecce, Italy

$EVWUDFW

+HPRUUKDJLF FRUSXV OXWHXP +&/ LV DQ RYDULDQ F\VW IRUPHG DIWHU RYXODWLRQ D
+&/ UXSWXUH KDSSHQV D KHPRSHULWRQHXP UHVXOWV &OLQLFDO V\PSWRPV DUH PDLQO
is extensive and standard management is not defined. The authors elaborated a comparison of the differential diagnosis and therapeutic modalities from
ODSDURVFRSLF DSSURDFK WR QRQVXUJLFDO PHGLFDO RSWLRQV EHFDXVH KHPRUUKDJH
WKH GHYHORSPHQW RI +&/ WU\LQJ WR JLYH KRPRJHQHLW\ WR OLWHUDWXUH GDWD 7KH
LQWR PDQ\ WRSLFV 7KH ZDLW DQG VHH DWWLWXGH DYRLGV XQQHFHVVDU\ ODSDURVFRS
WUDQVIXVLRQ DQG DQWLELRWLF SURSK\OD[LV 6XUJLFDO WKHUDS\ RSHUDWLYH PDQ
ovarian wedge-shaped excision or oophorectomy. Prevention: the possibility to preserve fertility is essential, mainly in patients with bleeding disorders
XQGHUJRLQJ DQWLFRDJXODQW WKHUDS\ WKHUHIRUH WKH\ QHHG HVWUR SURJHVWLQLF
UHYLHZ ZLOO DLG SK\VLFLDQV LQ PDNLQJ DQ HDUO\ GLDJQRVLV RI +&/ WR DYRLG XQQH

.H\ZRUGV Corpus luteum, ovarian cyst, ectopic pregnancy, laparoscopy

Öz

+HPRUDMLN NRUSXV OXWHXP +./ \XPXUWODPDGDQ VRQUD ROXüDQ YH NRUSXV OXWH
NLVWLGLU +./ U•SW•U• PH\GDQD JHOGLÿLQGH KHPRSHULWRQHXP ROXüXU .OLQLN VHP
EDÿO×G×U $\×U×F× WDQ×V×QGD ELU oRN GXUXP YDU×U YH WDQ×PODQP×ü VWDQGDUW
VHoHQHNOHUH o•QN• +./·GHQ ND\QDNODQDQ NDQDPD JHQHOOLNOH NHQGL NHQGLQL V×
ELU NDU×üLODüW×UPDV×Q× \DSPDNWDODU <D]DUODU OLWHUDW•U YHULOHULQH KRPRMH
OLWHUDW•U YHULOHULQL DQDOL] HWWLOHU YH W×EEL \DNODü×P× ELUoRN DOW JUXED D
LQI•]\RQ WUDQVI•]\RQODU YH DQWLEL\RWLN SURILODNVLVL NXOODQDUDN JHUHNVL] O
\XPXUWDO×ÿ×Q NDPD üHNOLQGHNL HNVL]\RQX YH\D RRIHUHNWRPL üHNOLQGH ROPDO×G×
WHGDYL DODQ KDVWDODUGD |QHPOLGLU EX QHGHQOH \XPXUWODPD\× |QOHPHN YH EDü
LKWL\Do YDU×U %X GHUOHPH KHNLPOHUH +./·QLQ HUNHQ WHüKLVLQL NR\PDGD JHUHN

$QDKWDU .HOLPHOHU .RUSXV OXWHXP \XPXUWDO×N NLVWL HNWRSLN JHEHOLN ODSDUR

Introduction

Ovulation is a physiologic monthly event and may be rarely FRPSOLFDWHG E\ UXSWXUH RI WKH occurs at all stages of a woman's reproductive life. The &/ LV IRUPHG GXULQJ WKH OXWHDO SKDVH RI WKH 6SRQWDQHRXV EXW VHOI OLPLWLQJ EOHHGLQJ LV DQG ZKHQ EOHHGLQJ LV H[FHVVLYH

D KHPRUUKDJLF &/ F\VW ZKLFK PD\ U D UXSWXUHG &/ FDQ YDU\ IURP PLOG hemoperitoneum, leading the patient to shock and subsequent HPHUJHQF\ VXUJHU\ +HPRUUKDJLF FRU and bleeding are often triggered by exercise, coitus, trauma or a pelvic examination. Clinical symptoms are mainly due to peritoneal irritation by the blood effusion. The differential

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL 0\NKDLOR 9 0HGYHGHY 0'
'QLSURSHWURYVN 0HGLFDO $FDGHP\ RI +HDOWK 0LQLVWU\ RI 8NUDLQH 'QLSURSHWURYVN 8NUDLQH
Phone: +380677378117 (PDLO medvedev.mv@gmail.com 25&,' ,' orcid.org/0000-0002-0443-0572

5HFHLYHG *HOLü 7DULKL 19.04.2020 $FFHSWHG .DEXO 7DULKL 18.10.2020

diagnosis is extensive and includes ectopic pregnancy, adnexal torsion, neoplasm, and pelvic inflammatory disease. The actual incidence of HCL is unknown because it is often asymptomatic and escapes the attention of physicians. Hallatt et al. reported a higher prevalence in young women. Most ruptures occur during the secretory phase of the cycle. HCL is one of the differential diagnoses of acute abdomen in women of reproductive age. Although it can occur at any time of life, it is likely to develop in the early period after menarche. A significant correlation between coitus and rupture of the CL was described by [illegible] et al., showing a traumatic etiology in of patients. An increased frequency of HCL during pregnancy was also observed, with increased risk of spontaneous miscarriage.

The authors reviewed the clinical findings of HCL and elaborated a comparison of differential diagnosis and therapeutic modalities from the laparoscopic approach to nonsurgical, medical options.

In this investigation, we reviewed all data implicated with HCL development, such as age, race, heritage, reproductive factors, sex hormone, obesity, diet, smoking, physical activity, stress, talc use, and environmental and other factors. To perform the clinical research, the authors consulted the following scientific databases: PubMed, the Cochrane Library, Google Scholar, EMBASE, Science Citation index, The China Journal Full Text Database, Chinese Scientific Journals Full Text Database, Chinese Biomedical Literature Database, and the WANFANG database.

The following key terms were used to access the records: corpus luteum, corpus luteum rupture, bleeding, cyst, pregnancy, hemorrhagic corpus luteum, corpus luteum rupture. The authors reviewed all articles relating to the CL and problems related to the CL such as the onset and complications, the bleeding caused by the CL and the pharmacologic and surgical treatment. Randomized controlled studies were used when available; otherwise, literature that was the most relevant to the topic was used at the authors' discretion. Peer-reviewed articles regarding the CL and hemorrhage, sorted by relevance, were included for the aims of this work. Additional articles were identified from the references of retrieved papers. The aim of this extensive review was to provide information about the clinical and surgical data implicated with the development of HCL and its treatment modalities, trying to give homogeneity to literature data.

Pathophysiology and Risk Factors

According to Novak and Woodruff, bleeding does not normally occur from the stigma because it fills with fibrin. Ovulation is followed by a stage of proliferation or hyperemia, consisting of follicular cells collapse and luteinization, which is devoid of blood vessels. The lumen contains no blood. The stage of vascularization [...] the granulosa layer is penetrated by blood vessels that fill the cavity of CL. If the CL hematoma [...] intraperitoneal hemorrhage may occur, especially if a woman's clotting mechanisms are depressed by anticoagulant therapy or congenital bleeding disorders. In this study, we focused exactly on this type of HCL hemorrhagic cys[t] [...] extro preponderance.

Many studies observed a higher pr[...] ovary.

Aggarwal et al. reported a dextro prepon[derance] [...] of patients.

The study of Tang et al. reported a right prevalence of 81.25%, and proposed that the right preponderance was the result of a different venous architecture causing higher venous pressure in the right ovary [...] rupture [...] ovary in of patients.

According to some authors, the presence of the rectosigmoid colon protects the left ovary from trauma, especially during sexual intercourses.

Pain in the right iliac fossa may mimic acute appendicitis, and the same symptoms related to the left quadrant might be underestimated in many patients, and this may contribute to the increased right prevalence [...]

Fukuda et al. reported a greater ovulatory activity by the right ovary than the left ovary during [...]

Bleeding Disorders and Anticoagu[lant] [...]

Patients with bleeding disorders have a greater risk of extensive hemoperitoneum than patients with normal coagulation function, and the former often require surgery to stop the bleeding.

Many cases of hemoperitoneum have been reported in patients with von Willebrand disease type 1, 2A, 3, patients with afibrinogenemia, patients with G[...] thrombasthenia, patients with hemophilia A, hemophilia B, deficiency of factor X and factor XIII, and in patients receiving anticoagulant therapy for antiphospholipid antibody syndrome.

Hemorrhage from a ruptured CL cyst [...] any woman of reproductive age who is undergoing anticoagulant therapy because it is a potentially life-threatening complication. When ovarian enlargement and hemorrhagic effusion are detected, anticoagulant therapy should be stopped.

In women with known bleeding disorders or receiving anticoagulant therapy, HCL ruptu[re] [...] in the presence of lower quadrant abdominal pain.

Complete coagulation screening is essential for the early identification of patients with bleeding disorders; anamnesis, anticoagulant therapy, and family history can provide important information.

The ovulation [...] should be suppressed with either a low-dose oral contraceptive pill or gonadotropin-releasing hormone analogs.

&OLQLFDO $VSHFWV

5XSWXUHG RI &/ PD\ EH DVVRFLDWHG ZLWK WKH sudden onset of lower abdominal pain. The pain often begins during strenuous physical activity, such as exercise or sexual intercourse, often lasting less than 24 hours.

6\PSWRPV VWDUW LQ D WKLUG RI SDWLHQWV ZLWK LQWHUPLWWHQW FUDPS preceding the acute pain, due to hemoperitoneum resulting from the rupture .

The cramps are caused by the luteal cavity distension due to the intracystic bleeding and the pain can range from a diffuse tenderness to acute abdomen when the rupture and the consequent hemoperitoneum occurs; even a small peritoneal effusion is large enough to cause real acute abdomen. Other symptoms may include nausea and vomiting caused by visceral reaction due to peritoneal irritation, vaginal bleeding, weakness, hypotension, syncope, and cardiovascular collapse. Visceral pain can also be related to emotional signs such as marked anxiety and autonomic signs such as pallor, sweating, nausea, vomiting, bradycardia or tachycardia. These signs further amplify the symptoms caused by bleeding.

Barel et al. reported abdominal pain as a prevalent and constant symptom in all patients; 10.7% also had fever, 13% had nausea and vomiting, and 4% showed urinary disorders.

It is worth mentioning that it is not always clinically possible to differentiate hemorrhagic cyst and ruptured hemorrhagic cyst.

,Q PDQ\ FDVHV RI 5&/ SDWLHQWV UHSRUW DEGRPLQDO SDLQ and a moderate amount of free fluid in the abdominal cavity could be a normal finding in the postovulatory period. For this UHDVRQ ZH GLVFXVV ERWK FRQGLWLRQV WRJHWKHU LQ WKLV article.

Diagnosis

A physical examination of the abdomen and vagina is critical in the first evaluation of the patient. Accurate diagnosis depends on the clinical presentation, the results of tests, and the index of suspicion. A negative pregnancy test is important to exclude ruptured ectopic pregnancy.

6RPH GLDJQRVWLF WHVWV DUH QHHGHG UHTXLUHV DQ XOWUDVRXQG [DPLQDWLRQ WKH &/ DQG WKH DEGRPLQDO SDLQ a complete blood count, blood clotting tests, and an evaluation of inflammatory markers.

/DERUDWRU\ 7HVWV

For a patient's hemostasis evaluation, the following parameters should be evaluated:

‡ 3URWKURPELQ WLPH 37 7KLV LV XVHG WR DVVHVV WKH H[WULQVLF pathway of coagulation. PT is longer in cases of factor VII, X, V, II, and fibrinogen deficiency, and it is essential to evaluate the hepatic synthesis of coagulation factors and vitamin K status, as well as for monitoring anticoagulant therapy.

‡ $FWLYDWHG SDUWLDO WKURPERSODVWLQ WLPH 37 7KLV LV used to evaluate factors of the intrinsic and common pathway of coagulation and to monitor therapy with unfractionated heparin; it could be longer in cases of a shortage of one of the intrinsic pathway factors, or in the presence of antiphospholipid syndrome.

• Fibrinogen: This is reduced in case of liver diseases, CID, and massive transfusions, and is increased during inflammation.

‡ :KLWH EORRG FHOO observed that elevated : % & SHU P/ ZDV UHODWHG WR WK presentation and its value regresses with resolution

‡ +HPRJORELQ +JE DQG KHPDWRFULW decrease progressively and proportionally to the amount of SHULWRQHDO HIIXVLRQ 0RQLWRULQJ essential to assess the development of blood loss to evaluate the possibility for emergency surgery.

• Platelets: generally indicated to investigate the presence of possible thrombocytopenia or thrombocytopathy in patients ZLWK DQ +&/ ZLWKRXW D KLVWRU\ R anticoagulant therapy.

7KH KXPDQ FKRULRQLF JRQDGRWURSL K&* LV GHWHFWDEOH LQ EORRG WKUR four weeks of amenorrhea, and in the urine from the sixth and seventh weeks of gestation age. Beta-hCG is essential to identify pregnant patients and in making a differential diagnosis with extrauterine pregnancy or intrauterine gestation.

,PDJLQJ 8OWUDVRXQG

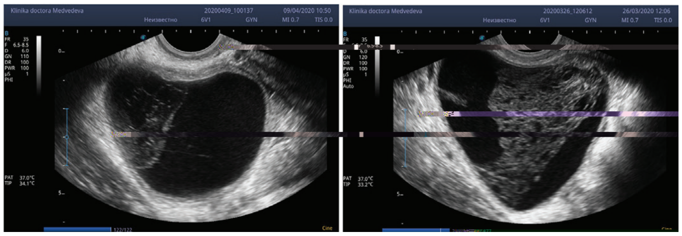
The sonographic appearance of a hemorrhagic ovarian cyst can KDV D NH\ UROH LQ WKH +&/ GLDJQRVL pattern depending on the formation and lysis of the clot 8VXDOO\ +&/ DSSHDUV DV D URXQG R diameter of 3.0-3.5 cm, with well-defined, regular and thin ZDOOV)LJXUH

Primarily, the clot forms like a fine fibrin network in the central cavity; subsequently, the coagulum in the cavity forms an RUJDQL]HG UHWLFXODU VWUXFWXUH becomes "corpus albicans," which is not always visible with ultrasound.

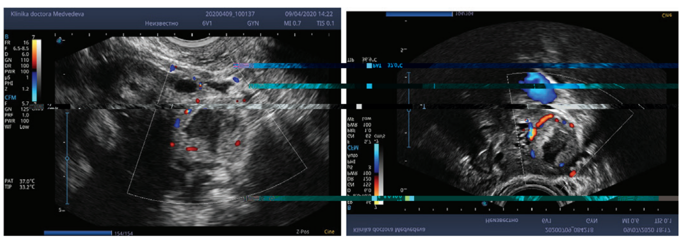
7KH LQWHUQDO HFKRJHQLFLW\ and interdigitations forming a "complex mass", entering into the differential diagnosis from ovarian neoplasm.

)RU WKLV UHDVRQ GRSSOHU +& DQG WKH JUH although there is always one posterior acoustic enhancement that allows to distinguish it from a solid lesion.

Ding et al. observed 104 cases of hemorrhagic ovarian cyst, GHVFULELQJ IRXU GLIIHUHQW 86 SDWW dense echo pattern, 24.0% showed a mixed pattern, 28.8% showed a sponge-like pattern and 27.0% showed a cystic SDWWHUQ 7KH\ DOVR REVHUYHG D ULQ high velocity and low resistance without internal blood flow in RI FDVHV)LJXUH



)LJXUH Typical sonographic features of a corpus luteum cyst with hemorrhagic content



)LJXUH 'RSSOHU IHDWXUHV RI &/&: ULQJ RI ILUH

have been well defined.

Tamura et al. LQYHVWLJDWHG WKH FKDQJHV LQ &/ EORRG IORZ during the luteal phase and early pregnancy. The relatively high UHVLVWDQFH LQGH[5, GXULQJ WKH ODWH IROOLFXODU SKDVH GHFOLQHG with progression towards the luteal phase. By the mid-luteal SKDVH WKH 5, ZDV ORZ LQGLFDWLQJ D KLJK EORRG IORZ WR WKH &/ There was an increase in RI and therefore a reduction in the EORRG IORZ RQ UHJUHVVLRQ RI WKH &/ ,Q ZRPHQ ZLWK OXWHDO SKDVH defects, the RI was significantly higher, indicating a decrease in blood flow. During pregnancy, the RI remains at the low mid-luteal phase level for the first 7-8 weeks and then increases once WKH &/ UHJUHVVHV

$Q DEGRPLQDO RU WUDQVYDJLQDO 86 FDQ DOVR VKRZ KHPRUUKDJLF effusion into the abdominal cavity, especially at the lowest points such as the pouch of Douglas, the vesico-uterine pouch, DQG WKH LOLDF IRVVDH +HPRUUKDJLF HIIXVLRQ FDQ DOVR EH REVHUYHG in the Morrison pouch and the paracolic lodges. The amount of effusion can vary from minimal to massive bleeding.

Examination of endometrium reveals a secretory pattern during the luteal phase and indicates an active production of progesterone.

Although ultrasonography is superior to computed tomography &7 IRU PDNLQJ WKH GLDJQRVLV WKH DSSHDUDQFH RI KHPRUUKDJLF cysts on CT scans depends on the age of the clot: blood from an acute hemorrhage has a high attenuation value, whereas blood from a previous hemorrhage has an attenuation value approaching that of water. In an acute setting, CT typically demonstrates a cystic adnexal mass with areas of high attenuation in the intramural and intracystic sites. +HPRSHULWRQHXP PD\ DOVR EH SUHVHQW ZLWK KLJK DWWHQXDWLRQ clot and blood accumulating in the pelvis. The pretreatment CT scan for ruptured corpus luteal cysts can suggest the necessity of surgical treatment based on image findings

'LIIHUHQWLDO 'LDJQRVLV

There are several pathologies that need a differential diagnosis ZLWK +&/ 7KH SHOYLF SDLQ LV W\SL disorders, such as ectopic pregnancy, PID, ovarian torsion, and several non-gynecologic diseases such as appendicitis, gastroenteritis, cystitis, and other urinary tract disorders Recently, a case of ruptured hemorrhagic ovarian cyst presenting an incarcerated inguinal hernia in an adult female was reported .

7KH 86 GLIIHUHQWLDO GLDJQRVLV EHW masses and complex malignant lesions is necessary. Bleeding may be generally due to the rupture of an ectopic pregnancy, an infiltrating neoplastic disease, vascular diseases and traumas. Clinical history and anamnesis of patients are very important for a differential diagnosis. In the event of a positive pregnancy test, the physician must investigate other nonspecific clinical ILQGLQJV RI DQ HFWRSLF SUHJQDQF\ cervical motion tenderness, a palpable adnexal mass and uterine VSRWWLQJ 7KH HDUOLHVW DSSHDUD occurs in the sixth week after the last period. Peritoneal signs are indicative of intraperitoneal blood collection. Usually, the pain is alternating and spasmodic, followed by intervals free of symptoms .

In most extrauterine pregnancies beta-hCG production is lower, the endometrium response is not stable, and spotting is common . In 70% of ectopic pregnancies, the beta-hCG levels rise more slowly, reaching a plateau and even showing a decrease in serum levels. An abnormal beta-hCG pattern is highly suggestive of an ectopic gestation or a no longer intact gestation. Besides the unconventional rise in beta-hCG levels compared with normal pregnancies, ectopic pregnancy can be differentiated from a spontaneous abortion by a slower decrease in serum titer . In a normally developing pregnancy, beta-hCG levels double every 1.5 days in the first 5 weeks of a regular gestation.

:LWK D VHUXP EHWD K&* OHYHO RI FKRULRQLF VDF FDQ EH GHWHFWHG E presenting a double echogenic ring around a hypoechoic gestational sac called “comet sign”. Conversely, in patients with EHWD K&* RI P,8 P/ DQG PRUH DQ YLVXDOL]HG E\ 796 ZLWK VSHFLILFDWL indirect proof of ectopic pregnancy.

The “tubal Ring” is a classic sonographic sign of ectopic pregnancy, represented by a hyperechogenic thick wall with anechoic content; only rarely it is possible to detect the \RON VDF ZKLFK LV RIWHQ FRQIXVHG Another significant sign of ectopic pregnancy is the “ring of fire”. Observed using the color Doppler, which is caused by YDVFXODUL]DWLRQ RI WKH SODFHQWD 7KLV VLJQ ZDV KRZHYHU DWWULEXWHG WKH YDVFXODUL]DWLRQ. Therefore, these signs are not clear enough to differentiate an ectopic pregnancy from D &/)UDWHOOL HW DO observed that the hyperechoic walls of the

"tubal ring" of ectopic pregnancy reflected the hyperechoic area observed in intrauterine pregnancies at the initial stage, formed by the fusion of the trophoblast and the decidua. In several patients with ectopic pregnancy, the "tubal ring" has higher echogenicity than ovarian parenchyma and endometrium, and the walls of the CL show the same echogenicity, often appearing isoechoic or more often hypoechoic.

Visualization of the characteristic CL blood flow may aid in the diagnosis of ectopic pregnancy because about 85% of all ectopic pregnancies are found on the same side as the CL. This explains why in the majority of cases with proven ectopic pregnancy luteal flow is detected ipsilaterally of the ectopic pregnancy. Luteal color or power Doppler flow may be used as a guide while searching for an ectopic pregnancy and could be called the ‘lighthouse effect’ of CL which directs the investigator t the color Doppler signals of the ectopic pregnancy.

Vidakovic et al. reported a case of a ruptured CL cyst in early pregnancy with the authors suspecting an ectopic pregnancy, but after surgery which confirmed HCL a normal intrauterine pregnancy was found.

Torsion of the ovarian pedicle is also one of the most common complications of ovarian neoformations.

It usually occurs suddenly and can also affect normal adnexa, frequently the right adnexa. Venous stasis caused by torsion of the pedicle, like in the case of pelvic varices with the increase of vein blood pressure, can result in ovarian edema associated with HCL as shown by Beyth et al. The prevalent symptom is abdominal pain as in the HCL and the abdomen appears slightly treatable and tense. Color Doppler US is diagnostic if it shows the reduction or absence of blood flow.

Cysts presenting rapid growth may break due to abnormal vascularity in some parts of the wall.

If the cyst contains blood, differential diagnosis with rupture of HCL becomes particularly difficult. Endometriomas may increase in size in every menstrual cycle and rarely break with acute abdomen and spreading content, with the dissemination of endometrial tissue into the peritoneal cavity. US is the fir line imaging technique for diagnosis. Endometriomas can have a variety of US appearances. The classic endometriosis cyst has been described as a homogeneous, hypoechoic focal lesion within the ovary; the majority of the endometriomas show diffuse low-level internal echoes, multilocularity and hyperechoic foci in the wall.

The differential diagnosis between HCL and [illegible] is based on the US reevaluation as well as the US appearance after the menstrual event, or at 4-6 weeks.

The disappearance or regression of a previously observed cyst is indicative of CL while the persistence [illegible] of endometriosis cysts.

In cases of PID, patients show inflammation signs such as fever, severe pain, and increased WBCs and other inflammatory markers; these signs are found only rarely in case of HCL.

In cases of PID, US examination of tubo-ovarian a will usually show a complex adnexal structure, with increased vascular flow compared with endometriosis cysts, with thick walls and internal pus-like echoes with cellular debris. During transvaginal examinations, patients may exhibit tenderness over the area of the fluid collection.

Classically, appendicitis diagnosis is based on symptoms, findings in a physical examination such as positive Blumberg sign, symptoms of acute abdomen, and severe leukocytosis. Acute abdomen and leukocytosis may both occur in case of HCL, but more often it is just a mi muscle contracture and a modest increase in leukocytes levels. US [illegible] show an increase o appendix edema, both typical of an inflammatory state. If diagnostic doubt persists and the clinical symptoms appear in evolution, further imaging exa performing a diagnostic laparoscopy are indicated.

Corpus Luteum of Pregnancy

The CL of pregnancy is simply the accompanies conception. It is most prominent early in pregnancy and is critical to sustaining gestation in the first 8 weeks when the maximum progesterone secretion occurs. As pregnancy evolves, the CL grad negligible role in the final two trimesters.

With routine ultrasonographic examination during the first trimester, the discovery of an ovarian cyst has become relatively common at the beginning of pregnancy.

Most unilocular and anechoic ovarian cysts with thin borders during the first trimester are C present after the end of the first trimester. Except in case of complications, surgery should be avoided. The complications of these cysts are represented mainly by torsion, intracystic bleeding, and rupture. Adnexal torsion is frequently associated with ovarian stimulation for in vitro fertilization or masses, mainly of functional origin. Operative laparoscopy has become increasingly common in pregnant women over the past decade.

Emergency surgery during the first trimester for complications of an ovarian cyst, especially before the ninth week of amenorrhea, is associated with a high rate of abortion. In the second part of pregnancy, fetal morbidity with prematurity caused by emergency surgery is considerable. The ideal period for scheduled surgery is probably the beginning of the second trimester, when the risk of abortion [illegible]

A primary ovarian pregnancy is usually confused with tubal pregnancy, ruptured CL cyst, HCL, an

This case presents the clinical and the histologic findings of a [illegible] the contralateral ovary.

Advances in laparoscopic technology and surgical techniques have overcome the technical difficulty of an enlarged gravid uterus.

It certainly seems that progesterone may still play an important role postoperatively in the first trimester if surgery involves the DGQH[D DQG RU &/ +RZHYHU E\ WKH VHFRQG WULPHVWHU WKH SODFHQWD takes over the role of producing progesterone to support the pregnancy.

5XSWXUHG &/ F\VW RI SUHJQDQF\ ZLWK PDVVLYH KHPRSHULWRQHXP is a rare but life-threatening disorder that can occur suddenly. Ovarian conservative treatment should be laparoscopic if the patient's condition permits it.

7KHUDS\

2QFH WKH GLDJQRVLV RI KHPRUUKDJLF &/ ZLWK KHPRSHULWRQHXP has been confirmed, it is necessary to establish a therapy. The GHFLVLRQ DERXW WKH WUHDWPHQW RI &/ LQFOXGHV WKH ´ZDLW DQG see" option, with a continuous follow-up of clinical, laboratory SDUDPHWHUV DQG 86 GHWHFWLRQ In most cases, keeping patients under observation and waiting for the remission of symptoms is enough. In rare cases, surgery may be required to stop bleeding because hemodynamic LQVWDELOLW\ DQG GHWHULRUDWLRQ RI FOLQLFDO VWDWXV FDQ RFFXU 6XU management should be laparoscopic.

An article published in 1984, in which 173 surgical cases were DQDO\]HG LW ZDV FRQFOXGHG WKDW LQ PRVW FDVHV D FRUUHFW SUH surgical diagnosis allowed the avoidance of surgery. +R HW al. showed that the use of surgery was significantly higher LQ WKH V FRPSDUHG ZLWK -DQXDU\ DQG 'HFHPEHU FOLQLFDO PDQLIHVWDWLRQV RI +&/ in the 1980s.

:DLW DQG VHH $WWLWXGH

With the improvement of diagnostic tools over time, physicians have increasingly opted for a wait-and-see approach. Most cases RI UXSWXUHG &/ F\VWV ZLWK PRGHUDWH KHPRSHULWRQHXP FDQ EH treated conservatively .

During the observation period, it is important to continuously PRQLWRU 86 SHOYLF FKDQJHV KHPDWRFULW DQG WKH V\PSWRPV reported by the patient.

The acute pain often subsides within the first 24 hours, and failure to improve could be a sign of worsening. Thus, during the observation period, it is recommended to perform another 86 HYDOXDWLRQ DQG UHSHDW WKH SDWLHQW¶V EORRG WHVWV ZLWK VLJQV RI DQHPLD IDLQWLQJ DVWKHQLD

,I +JE YDOXHV DUH VWDEOH RU DUH PDLQWDLQHG DERYH PJ G/ DQG LI D 86 HYDOXDWLRQ LV FRPSDWLEOH ZLWK VPDOO &/ WUHDWPHQW LV QRW indicated.

,I WKH V\PSWRPV GLVDSSHDU DQG 86 IHDWXUHV DQG +JE YDOXHV DUH unchanged, the patient can be discharged the same day with the recommendation of returning to the hospital immediately if pelvic pain or signs of anemia appear, or with the indication to be periodically followed by a general practitioner.

Pelvic U6 LV DOVR UHFRPPHQGHG DIWHU the clinical symptoms, preferably at the end of the following menstrual period.

UXJ 7KHUDS\

During the observation periods, physicians may prescribe drug therapy and supportive care; this, however, does not improve the outcome of the disease.

$QWLILEULQRO\WLF

Tranexamic acid is one of the most widely used drugs in this category. Tranexamic acid is a synthetic derivative of the amino acid lysine, which exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. There are no clear indications for antifibrinolytic treatment, but we know from a few trials that systemic tranexamic acid administered at the outset for surgery reduces intraoperative blood loss, and if it is administered within 3 KRXUV RI DQ\ LQMXU\ LW VLJQLILFDQW

$QDOJHVLFV

They are used on patients' request to relieve painful symptoms, but pain does not always recede after the administration of these drugs.

6XSSRUWLYH WKHUDSLHV

/LTXLG LQIXVLRQ LV FHUWDLQO\ D XV volume mass and prevent a drop blood pressure. Glucose-ZHUH VLPLODU ZLWK WKRVH REVHUYHG fasting in case of surgical treatment requirement.

7UDQVIXVLRQV

6RPHWLPHV EORRG WUDQVIXVLRQ LV Q DQG +FW DUH VLJQLILFDQWO\ UHGXFHG In cases of patients with bleeding disorders undergoing DQWLFRDJXODQW WKHUDS\ DGPLQLVW vitamin K may be useful to replenish the missing coagulation factors .

$QWLELRWLF 3URSK\OD[LV

Antibiotic prophylaxis is given to prevent bacterial superinfection of the pelvic effusion, which could result in real septic peritonitis. Antibiotic prophylaxis is conducted with broad-spectrum antibiotics active against the most common germs responsible for peritonitis. Prescription of antibiotics is made on an individual basis because the literature is lacking any evidence of their use in case of infection absence.

6XUJLFDO WUHDWPHQW

6XUJLFDO WUHDWPHQW ZDV LQ WKH the first choice and consisted mainly of a laparotomy with oophorectomy. With the advent of laparoscopy, a minimally invasive approach is preferred to laparotomy, which however remains the first-choice method in the event of cardiovascular collapse .

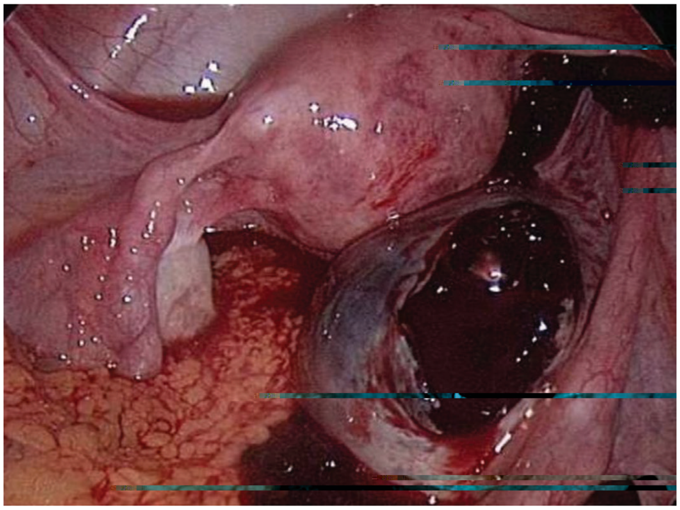


Figure 3. Laparoscopic view of ruptured CLC

/DSDURVFRS\ DQG /DSDURWRP\

/DSDURVFRS\ LV WKH SUHIHUUHG VXUJLFDO DSSURDFK EHFDXVH LW UHVXOWV LQ OHVV PRUELGLW\ WKDQ ODSDURWRP\ )LJXUH known that the laparoscopy has several advantages compared with laparotomy, which has been replaced almost completely in gynecology during the last years

The first and most important advantage of laparoscopy is the type of incision, which is minimally invasive compared with laparotomic transverse incisions.

7KH KRVSLWDOL]DWLRQ RI WKH SDWLHQW LV UHGXFHG ZLWK ODSDURVFRS\ FRPSDUHG ZLWK ODSDURWRP\ “ operative pain is significantly reduced

Complications risks are lower in laparoscopy, which however is more operator dependent.

In the event of massive hemoperitoneum, autologous blood transfusions from blood recovered from the peritoneal cavity should also be considered, even with the laparoscopic technique .

$ OLPLWDWLRQ RI WKH ODSDURVFRSLF WHFKQLTXH LV WKH VL]H RI WKH F\VW LI LW H[FHHGV WKH GLDPHWHU VL]H RI FP WKH LQGLFDWLRQ WR ODSDURVFRS\ LV OLPLWHG WR WKH VXUJHRQV H[SHULHQFH WKLV HYHQW KRZHYHU TXLWH UDUH LQ FDVHV RI +&/

During laparoscopy, three kinds of surgical options can be used:

‡ &\VWHFWRP\ RU HQXFOHDWLRQ RI RYDULDQ F\VWV OXWHXPHFWRP\

The technique is preferable because it allows the preservation of ovarian function.

• Ovarian wedge-shaped excision.

• Oophorectomy or ovariectomy: this was the preferred technique in the past and resulted in the total loss of the ovary, often accompanied by loss of the ipsilateral fallopian tube.

:RPHQ ZLWK &RQJHQLWDO RU $FTXLUHG %OHHGLQJ 'LVRUGHUV

Women receiving anticoagulant therapy or with congenital disorders of the coagulation system have a higher risk of UXSWXUHG &/ F\VWV 6XUJLFDO WUHD in this category of patients. There is still not enough evidence to support a surgical or expectant approach. According to some published case series, conservative treatment is the dominant trend in carefully selected patients with coagulopathies.

In summary, the observational approach in hemodynamically stable patients could be the first choice option in most cases. There are no data comparing these two strategies in this patient population, but if there are no concerns about ongoing brisk bleeding or infection or malignancy, the risks of surgery are not warranted. In cases of continuing bleeding or the decision of a patient to choose active management, a laparoscopic approach should be suggested with ovary-sparing surgery, using minimal energy.

2XWFRPHV

There are scant data regarding the outcomes of ruptured ovarian cysts. Available studies include:

• In series of women with a ruptured ovarian cyst and hematoperitoneum, 15 of 78 were managed surgically 3DWLHQWV ZKR XQGHUZHQW VXUJHU\ K RYHU KRXUV YV J G/ DQG KDG WKDQ WKRVH PDQDJHG FRQVHUYDWLYH

‡ ,Q DQRWKHU VHULHV RI ZRPHQ ZLW were managed with surgery and the remainder was managed with observation the study did not give rates of surgical complications, transfusions or recurrence.

3UHYHQWLRQ RI 5HFXUUHQFH

There are no known methods to prevent rupture of an existing ovarian cyst, except for surgical drainage or removal of the cyst. Patients with bleeding disorders or undergoing anticoagulant therapy have a higher risk of recurrence. Regular follow-up FDQ PLQLPL]H WKH ULVNV 7KHVH SDW with a higher risk of decreased ovarian function and adhesion formation, which consequently contributes to reduced fertility rates.

Thus, the possibility of preserving a future pregnancy is essential and patients need drugs such as estro-progestinics or *Q5+ DQDORJXHV WR SUHYHQW RYXODWLRQ investigated the effects of OCs on follicular cyst development and ovulation. In general, current OCs resulted in the development of fewer follicular and correspondingly lutein cysts

Conclusion

This review focuses on the pathophysiology, clinical SUHVHQWDWLRQ GLDJQRVLV DQG WUH patients with bleeding disorders or pregnancy complicated by &/ F\VWV

5XSWXUH RI &/ LV D FRPPRQ RFFXU reproductive age. Management is based upon patient characteristics, including the severity of symptoms, whether there is hemodynamic instability &XUUHQWO\ 86 LV WKH JROG VWDQGDUG WHFKQLTXH LQ known to simulate several medical, surgical, and gynecologic

conditions that cause acute abdomen. The most important is ectopic pregnancy.

The "tubal ring" is a classic sonographic sign of ectopic pregnancy.

Beta-hCG is essential for identifying pregnant patients and making a differential diagnosis with extrauterine pregnancy and LQWUDXWHULQH JHVWDWLRQ RU &/

Observation is an adequate option in hemodynamically stable patients, without severe abdominal pain and in the presence RI D VPDOO DPRXQW RI SHOYLF IOXLG GHWHFWHG E\ 86 :KHQ a large amount of fluid is observed and/or in the presence of severe abdominal pain laparoscopy should be performed on admission. Direct laparotomy is mandatory in cases of circulatory collapse.

7KH GHFLVLRQ RQ WKH WUHDWPHQW RI &/ LQFOXGHV WKH "ZDLW DQG see" option with a continuous follow-up of clinical, laboratory SDUDPHWHUV DQG 86 GHWHFWLRQ

During observation periods, drug therapy and supportive care are suggested. A careful pre-surgical diagnosis can often avoid the need for surgery.

6XUJHU\ PD\ EH UDUHO\ UHTXLUHG WR VWRS EOHHGLQJ EHFDXVH hemodynamic instability and deterioration of clinical status can occur.

Patients with bleeding disorders or undergoing anticoagulant therapy have a higher risk of recurrence and often undergo surgery, with a higher risk of decreased ovarian function and fertility rates.

7KLV DUWLFOH SURYLGHV DQ RYHUYLHZ RI +&/ ZLWK D IRFXV RQ helping physicians to identify the clinical signs and sonographic features early, to quickly diagnose this condition, to choose the appropriate treatment for their patient, and to prevent recurrent episodes.

(WKLFV

3HHU UHYLHZ Externally and internally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV Design: A.T., Data Collection or Processing: A.T., Analysis or ,QWHUSUHWDWLRQ 0 9 0 /LWHUDWXUH 6HDUFK 0 9 0 Writing: M.V.M.

&RQIOLFW RI ,QWHUHVW No conflict of interest was declared by the authors.

)LQDQFLDO 'LVFORVXUH The authors declared that this study received no financial support.

References

+DOODWW -* 6WHHOH &+ -U 6Q\GHU 0 5XSWXUH RI FRUSXV OXWHXP ZLWK hemoperitoneum: a study of 173 surgical cases. Am J Obset Gynecol 1984;149:5-9.

*XSWD 1 'DGKZDO 9 'HND ' -DLQ 6. 0LWWDO 6 &RUSXV OXWHXP hemorrhage: rare complication of congenital and acquired coagulation abnormalities. J Obstet Gynaecol 2007;33:376-80.

$JJDUZDO $ *RHO 3 :DQFKX 0 0DOKRWUD 5XSWXUHG FRUSXV OXWHXP corpus luteum with hemoperitoneum. J Obstet Gynecol Ind 2004;54:488-90.

4. Novak ER, Woodruff JD. Gynecologic and Obstetric Pathology. 7th HGLWLRQ YRO 3KLODGHOSKLD :% 6DXQGHUV

7DQJ /& &KR +. &KDQ 6< :RQJ 9& 'H[WUDO SUHGRPLQDQFH RI corpus luteum rupture: a clinical study. J Reprod Med 1985;30:764-8.

+R :. :DQJ <) :X ++ 7VDL +' &KHQ 7+ &KHQ 0 5XSWXUHG corpus luteum with hemoperitoneum: case characteristics and demographic changes over time. Taiwan J Obstet Gynecol 2009;48:108-12.

)XNXGD 0)XNXGD . $QGHUVHQ &< %\VNRY / 5LJKW VLGHG SUHGRPLQDQFH of human ovulation in natural cycles correlated with age and DFKLHYHPHQW RI SUHJQDQF\ +XP 5HSURG

%RWWLQL (3DUHWL), 0DUL ' 0DQQXFFL 3 Prevention of hemoperitoneum during ovulation by oral contraceptives in women with type III von Willebrand disease and DILEULQRJHQHPLD &DVH UHSRUWV +DHPDWRORJLFD

0HVFKHQJLHVHU 66 $OEHUWR 0) 6DOYL• Recurrent haemoperitoneum in a mild von Willebrand's disease combined with a storage pool deficit. Blood Coagul Fibrinolysis 2001;12:207-9.

*KRVK . 0RKDQW\ ' 3DWKDUH $9 -LMLQD) Recurrent haemoperitoneum in a female patient with type III von Willebrand's disease responded to administration of oral contraceptive. +DHPRSKLOLD

*RPH] $ /XFLD -) 3HUHOOD 0 $JXLOODU & +HPRSHULWRQHXP caused by haemorrhagic corpus luteum in a patient with type 3 von :LOOHEUDQG·V GLVHDVH +DHPRSKLOLD

*UHHU ,$ /RZH *' :DONHU --)RUEHV &' 0DQDJHPHQW RI EOHHGLQJ in obstetrics and gynaecology in patients with congenital coagulopathies. Br J Obstet Gynaecol 1991;98:909-18.

13. Jarvis RR, Olsen ME. Type I von Willebrand's disease presenting as recurrent corpus hemorrhagicum. Obstet Gynecol 2002;99:887-8.

7HU]LF 0 /LNLF , 3LOLF , %LOD - .QH]HYLF 0 6XFFHVVIXO management of massive hematoperitoneum caused by ovulation in a patient with severe form of von Willebrand disease--a case report. Clin Exp Obstet Gynecol 2012;39:537-40.

&HWLQND\D 6(3DEXFFX (* 2]PHQ % 'RNPH] % 5HFXUUHQW hemoperitoneum due to ovulation as a clinical sign in congenital DILEULQRJHQHPLD $FWD 2EVWHW *\QHFRO 6FDQG

16. Castman G, Ruggeri M, Rodeghiero F. Congenital afibrinogenemia: successful prevention of recurrent hemoperitoneum during RYXODWLRQ E\ RUDO FRQWUDFHSWLYH $P - +HPDWRO

17. Koussi A, Economou M, Athanasiou-Metaxa M. Intra-abdominal hemorrhage due to a ruptured corpus luteum cyst in a girl whit congenital afibrinogenemia. Eur J Pediatr 2001;160:196.

18. O'Brien PM, DiMichele DM, Walterhouse DO. Management of an acute hemorrhagic ovarian cyst in a female patient whit hemophilia $ - 3HGLDWU +HPDWRO 2QFRO

'DIRSRXORV . *DOD]LRV * *HRUJDGDNLV * D, Plakopoulos A, et al. Two episodes of hemoperitoneum from luteal cyst rupture in a patient with congenital factor X deficiency. Gynecol Obstet Invest 2003;55:114-5.

.KDPDVKWD 0$ &XDGUDGR 0- 0XMLF) 7D\ORU '$ 6WHSQLNRYD GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995;332:993-7.

<DPDKDPL /< GH $XDUMR '% 6LOYD &$ % 6HYHUH KHPRUUKDJLF FRUSXV OXWHXP F

&DVWHOOLQR * &XDGUDGR 0- *RGIUH\ 7 GR. Characteristics of patients with antiphospholipid syndrome

with major bleeding after oral anticoagulant
Dis 2001;60:527-30.
Payne JH, Maclean RM, Hampton KK, Baxter AJ,
Hemoperitoneum associated with ovulation in women with
bleeding disorders: the case for conservative management and the
role of the contraceptive pill. Haemophilia
Barel O, Smorgick N, Pansky M, Schneider, Halperin R. Clinical
and laboratory presentation of hemorrhagic corpus luteum. J
Gynecol Surg
Nemoto Y, Ishihara K, Sekiya T, Konishi H, Araki T. Ultrasonographic
and clinical appearance of hemorrhagic ovarian cyst diagnosed by
transvaginal scan. J Nippon Med Sch
Takasaki A, Tamura H, Taniguchi K, Asada H, Taketani T,
Matsuoka A, et al. Luteal blood flow and luteal function. J Ovarian
Res 2009;2:1.
Valentin L. Imaging in gynecology. Best Pract Res Clin Obstet
Gynaecol 2006;20:881-906.
Swire MN, Castro Aragon I, Levine D. Various sonographic
appearances of the hemorrhagic corpus luteum cyst. Ultrasound Q
2004;20:45-58.
Jain KA. Sonographic spectrum of hemorrhagic ovarian cysts. J
Ultrasound Med 2002;21:879-86.
30. Parson AK. Imaging the human corpus luteum. J Ultrasound Med
2001;20:811-9.
Spinelli C, Di Giacomo M, Mucci N, Massart F. Hemorrhagic corpus
luteum cysts: an unusual problem for pediatric surgeons. J Pediatr
Adolesc Gynecol 2009;22:163-7.
32. Patel MD, Feldstein VA, Filly RA. The likelihood ratio of sonographic
findings for the diagnosis of hemorrhagic ovarian cysts. J Ultrasound
Med 2005;24:607-14.
Yoffe N, Bronshtein M, Brandes J, Blumenfeld Z. Hemorrhagic
ovarian cyst detection by transvaginal sonography: the great
imitator. Gynecol Endocrinol 1991;5:123-9.
Ding Z, Zhang D, Ying W, Wang J. Sonographic value in diagnosis
of hemorrhagic ovarian cysts. Eur J Gynaecol Oncol 2010;31:87-9.
Glock JL, Blackman JA, Badger GJ, Brumsted JR. Prognostic
significance of morphologic changes of the corpus luteum by
transvaginal ultrasound in early pregnancy monitoring. Obstet
Gynecol 1995;85:37-41.
Durfee SM, Frates MC. Sonographic characteristics of the corpus
luteum of pregnancy. J Clin Ultrasound 1999;27:55-9.
Zalud I, Kurjak A. The assessment of luteal blood flow in pregnant
and non-pregnant women by transvaginal color Doppler. J Perinat
Med 1990;18:215-21.
Bonde AA, Korngold EK, Foster BR, Fung AW, Sohaey R, Pettersson
DR, et al. Radiological appearances of corpus luteum cysts and their
imaging mimics. Abdom Radiol 2016;41:2270-82.
Tamura H, Takasaki A, Taniguchi K, Matsuoka A, Shimamura
Sugino N. Changes in blood flow impedance of the human corpus
luteum throughout the luteal phase and during early pregnancy.
Fertil Steril
Lee MS, Moon MH, Woo H, Sung CK, Jeon HW, Lee TS. Ruptured
corpus luteal cyst: prediction of clinical outcomeswith CT. Korean J
Radiol 2017;18:607-14.
Liu X, Song L, Wang J, Liu Q, Liu Y, Zhang X. Diagnostic utility of
CT in differentiating between ruptured ovarian corpus luteal cyst
and ruptured ectopic pregnancy with hemorrhage. J Ovarian Res
2018;11:5.
Badawy SZ. Etiology and management of [illegible]
reproductive years. J Gynecol Surg
[illegible]
appendicitis. Bangladesh Med J 2008;37:66-7.
[illegible]wicz R. Hemorrhagic corpus
gastroenteritis. Am J Emerg Med 2002;20:133.
Jategaonkar PA, Yadav SP. Ruptured
presenting as an incarcerated inguinal hernia in an adult female:
a rare clinical scenario of a common surgical emergency. Case Rep
Emerg Med 2013;2013:925694.
Hucke J, Füllers U. Extrauterine Sch
2005;38:535-52.
Alkatout I, Honemeyer U, Strauss A, T
et al. Clinical diagnosis and treatment of ectopic pregnancy. Obstet
Gynecol Surv
Lozeau AM, Potter B. Diagnosis and
pregnancy. Am Fam Physician 2005;72:1707-14.
Nezhat C, Nezhat FR, Luciano AA, et al
Nezhat C, Nezhat FR, Luciano AA, Siegle
CH, editors. Operative Gynecologic
Techniques. New York: McGraw Hill
Kadar N, Romero R. Serial human ch
measurements in ectopic pregnancy. Am J Obstet Gynecol
1988;158:1239-40.
Fritz MA, Guo SM. Doubling time of huma
hCG in early normal pregnancy rela
and gestational age. Fertil Steril
52. Brennan DF. Ectopic pregnancy part I: clinical and laboratory
diagnosis. Acad Emerg Med 1995;2:1081-9.
Stein MW, Ricci ZJ, Novak L, Robertsv
Sonographic comparison of the tubal
the corpus luteum. J Ultrasound Med 2004;23:57-62.
Frates MC, Visweswaran A, Laing FC, Co
corpus luteum echogenicities: a useful differentiating characteristic.
J Ultrasound Med 2001;20:27-31.
Blaivas M, Lyon M. Reliability of ad
distinguishing possible ectopic pregnancy from corpus luteum
cysts. J Ultrasound Med 2005;24:599-603.
Kupesic S. Ectopic pregnancy. In: Kurja
Donald School Textbook of Ultrasoun
Jaypee Brothers Medical Publishers; 2008. p. 230-43.
Honemeyer U. Primary care in obstetr
for advanced ultrasound. Donald Sch
2009;3:61-74.
Seeber BE, Barnhart KT. Suspected
Gynecol 2006;107:399-413.
59. Vidaković S, Dokić, Vilendečić Z, Maravić MD. Ruptured corpus
luteum cyst in early pregnancy: a ca
2013;141:689-92.
Beyth Y, Klein Z, Tepper R, Weinstein
corpus luteum is associated with ovarian edema. J Pediat Adolesc
Gynecol 2006;19:325-7.
Velcani A, Conklin P, Specht N. Son
ovarian abscess mimicking an endometrioma and review of cystic
adnexal masses. J Radiol Case Rep 2010;4:9-17.
Alcázar JL, León M, Galván R, Guerriero
content using mean gray value for discriminating endometrioma
from other unilocular cysts in premenopausal women. Ultrasound
Obstet Gynecol 2010;35:228-32.
Sergent F, Verspyck E, Marpeau L, Mana
during pregnancy. Presse Med 2003;32:1039-45.
Shakur H, Roberts I, Bautista R, Cab
et al. Effects of tranexamic acid on death, vascular occlusive

events, and blood transfusion in trauma patients with significant KDHPRUUKDJH &5$6+ D UDQGRPLVHG SODFHER FRQWUROOHG WULDO /DQFHW

&KHQ / 'LQJ - +XD . &RPSDUDWLYH DQDO\VLV RI ODSDURVFRS\ YHUVXV laparotomy in the management of ovarian cyst during pregnancy. J Obstet Gynaecol Res 2014;40:763-9.

.LP -+ /HH 60 /HH -+ -R <5 0RRQ 0+ 6KLQ - HW DO 6XFFHVVIXO conservative management of ruptured ovarian cysts with KHPRSHULWRQHXP LQ KHDOWK\ ZRPHQ 3/R6 2QH H

5D]LHO $ 5RQ (O 5 3DQVN\ 0 $ULHOL 6 %XNRYVN\ , *ROGPDQ -$ &XUUHQW management of ruptured corpus luteum. Eur J Obstet Gynecol Reprod Biol 1993;50:77-81.

7HQJ 6: 7VHQJ -< &KDQJ &. /L &7 &KHQ <- :DQJ 3+ Comparison of laparoscopy and laparatomy in managing hemodynamically stable patient whit ruptured corpus OXWHXP ZLWK KHPRSHULWRQHXP - $P $VVRF *\QHFRO /DSDURVF 2003;10:474-7.

<DPDGD 7 2NDPRWR < .DVDPDWVX + 7VXGD <DPDGD 2 .DWD\DPD 6 DXWRORJXV EORRG WUDQVIXVLRQ IRU from ectopic pregnancy or ovarian bleeding laparoscopic VXUJHU\ -6/6

%XSWD $ *XSWD 6 0DQDNWDOD 8 *XSWD 0 6 &XUUHQW Conservative management of corpus luteum haemorrhage in patients on anticoagulation: a report of three cases and review of literature. Arch Gynecol Obstet 2015;291:427-31.

Review / Derleme

DOI: 10.4274/tjod.galenos.2020.39225
Turk J Obstet Gynecol 2020;17:310-313

Adenoid cystic carcinoma of Bartholin's gland diagnosed after lung lobectomy: Review of the literature and a case presentation

6HJPHQWDO DNFLÿHU OREHNWRPL VR
%DUWKROLQ NDQVHUL /LWHUDWÕU GH

6HGD ýDKLQ $NHU[1], &HYULH \H &DQ[2], ...]UDW[1], 2UWDo

[1]Ankara University Faculty of Medicine, Department of Gynecologic Oncology, Ankara, Turkey
[2]Ankara University Faculty of Medicine, Department of Pathology, Ankara, Turkey

Abstract

%DUWKROLQ·V JODQG ZDV ILUVW LGHQWLILHG LQ KXPDQ IHPDOH LQ E\ &DVSDU %DUW
PXFLQRXV DFLQL WKH GXFW LV SUHGRPLQDQWO\ WUDQVLWLRQDO HSLWKHOLXP DQG W
LV DQ XQFRPPRQ QHRSODVP $GHQRLG F\VWLF FDUFLQRPD $&& RI EDUWKROLQ JODQG F
DOO EDUWKROLQ JODQG PDOLJQDQFLHV $&& RI WKH %DUWKROLQ·V JODQG LV FKDUDFWH
6R GLVWDQW PHWDVWDVLV KDV EHHQ IRXQG LQ RQO\ D IHZ FDVHV WR WKH OXQJV OLYH
\HDUV IROORZ XS DQG SUHVHQWHG ZLWK D OXQJ PHWDVWDVLV
.H\ZRUGV $GHQRLG F\VWLF FDUFLQRPD RI WKH %DUWKROLQ·V JODQG YXOYDU FDQFHU

Öz

%DUWKROLQ EH]L \×O×QGD &DVSDU %DUWKROLQ WDUDI×QGDQ NDG×Q JHQLWDO DQD
P•VLQ|] NDQDO WUDQVLV\RQHO YH RULILV VNXDP|] HSLWHOOH NDSO×G×U 3ULPHU ED
NDUVLQRP LVH oRN QDGLU J|U•OPHNWH YH EDUWKROLQ NDQVHUOHULQ ·LQL ROXüWXU
YH \DYDü E•\•PH SDWHUQL QHGHQL\OH UHN•UUHQV YH X]DN PHWDVWD] X]XQ YDNLW DOD
D] KDVWDGD UDVWODQPDNWDG×U %L] \×OO×N KDVWDO×NV×] WDNLS VRQUDV× DNFLÿHU
$QDKWDU .HOLPHOHU Adenoid kistik Bartholin karsinomu, vulvar kanser, Bartholin bezi karsinomu

Introduction

7KH %DUWKROLQ JODQG ZDV ILUVW LGHQWLILHG LQ WKH KXPDQ IHPDOH ERG\ LQ E\ &DVSDU %DUWKROLQ. The main function of the Bartholin gland is to secrete mucus to provide vaginal and vulvar lubrication. Each Bartholin gland is approximately 0.5 cm in size and drains mucous into a duct 2.5 cm long. The ducts open onto the vulvar vestibule at the four and HLJKW R·FORFN SRVLWLRQV RQ HDFK VLGH RI WKH YDJLQDO RULILFH. The Bartholin gland has different epithelial types: the body is mucinous acini, the duct is transitional epithelium, and the orifice is squamous epithelium. 3ULPDU\ FDUFLQRPD RI WKH Bartholin gland is an uncommon neoplasm. Bartholin gland FDUFLQRPD %*& FRPSULVHV DSSUR[LPDWHO\ YXOYDU FDUFLQRPDV DQG RI IHPDOH %*& KDV PDQ\ KLVWRORJLF VXEW\SHV: adenocarcinoma, squamous, adenosquamous, transitional cell carcinoma, and adenoid F\VWLF FDUFLQRPD $&&. Adenocarcinomas and squamous FHOO FDUFLQRPDV HDFK DFFRXQW IRU adenosquamous carcinomas account IRU DSSUR[LPDWHO\ %*&V $&& RI %*& LV D UDUH YDULDQW Bartholin gland malignancies and the first documentation of $&& ZDV LGHQWLILHG LQ .OHLQ ... WR GDWH RQO\ SDWLHQWV KDYH EHHQ GHVFULEHG ... JODQG LV FKDUDFWHUL]HG E\ VORZ JUR

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL 6HGD ýDKLQ $NHU 0'
Ankara University Faculty of Medicine, Department of Gynecologic Oncology, Ankara, Turkey
3KRQH +90 544 692 65 38 (PDLO drsedasahinaker@hotmail.com 25&,' ,' orcid.org/0000-0001-6192-5726
5HFHLYHG *HOLü 7DULKL 12.03.2020 $FFHSWHG .DEXO 7DULKL 18.07.2020

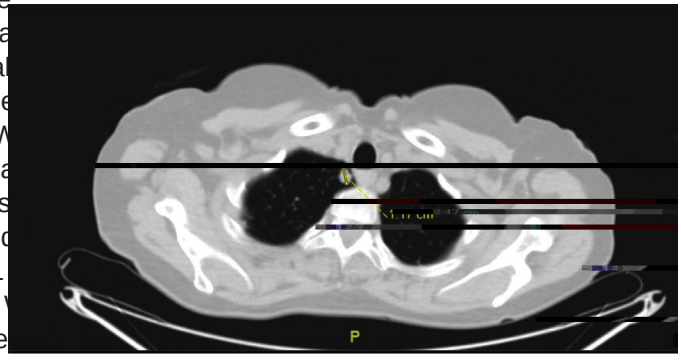
metastases can take a long period. Only in rare cases are distant metastasis seen in the lungs, liver, bone, and brain. We present a case of ACC in a woman who presented with lung metastasis after four years of follow-up.

&DVH 3UHVHQWDWLRQ

,Q 6HSWHPEHU D \HDU ROG JUDYLGLW\ SDULW\ menopausal women presented with a palpable mass and vulval pain of the left Bartholin's gland area. Under general anesthesia, the left Bartholin's gland was excised with a Bartholin gland cyst prediagnosis. A pathologic examination revealed an ACC of the Bartholin gland, the tumor continued at the positive edge of surgery with negative perineural invasion. The unexpected malignant lesion was diagnosed and a scientific study was conducted for metastatic disease. Chest, abdomen, and pelvis F RPSXWHG WRPRJUDSK\ &7 VFDQV VKRZHG QR PHWDVWDWLF disease. Then the patient underwent hemivulvectomy with left inguinofemoral lymph node dissection. After surgery, the pathology result showed a tumor on one side of the surgica margin and positive perineural invasion. The inguinofemora lymph nodes were collected, all of which were tumor-free. The SDWLHQW UHFHLYHG QR DGMXYDQW WKH patient regularly and who showed no recurrence over a 4-yea period. Forty-nine months after the surgery, she had ches pain and cough symptoms. A thorax CT scan was performed which showed a right upper lung lesion in diameter of 1.2*1.1 FP)LJXUH ,Q 6HSWHPEHU left pulmonary wedge resection. The diagnosis was clarifie with pathologic results. It showed a lung metastasis of ACC with no tumor in lymph nodes and margins are negative)LJXUH $ SDWKRORJ\ H[DPLQDWLRQ VKRZHG FROXPQV RI FHOOV arranged concentrically around gland-like spaces filled with HRVLQRSKLOLF SHULRGLF DFLG 6FK the examination showed the characteristic tumor proliferation in a cribriform pattern composed of nests, hence, the presenc of ACC metastasis. Two years earlier, when the first ACC wa diagnosed, it showed similar speciality and was clarified with immunohistochemical characteristics. Tumour cells were ZLGHO\ SRVLWLYH ZLWK 60$ &' D ZLWK &. DQG FDOSRQLQ)LJXUH free with 56 months of follow-up and stable disease.

Discussion

In 1864, Klob was the first to describe BGC. It has various types such as adenocarcinoma, squamous, adenosquamo transitional cell carcinoma, and ACC. Ten to fifteen percen of patients have ACC, which is histologically similar to adenocarcinoma of the salivary glands. ACC of the Bartholin gland is extremely rare. Only 80 cases have been reporte in the literature . Common symptoms are a painless mass pruritus, dyspareunia, burning sensation, vulvar pain, and abnormal bleeding. Initial misdiagnosis or delayed diagnosis may occur in up to 50% of patients, with incorrect diagnoses of Bartholin cysts or abscesses. The most frequent symptoms is a progressive enlargement or swelling in the vulva; the patients often experience pain, which is probably due to tumor involvement of nerves In our case, the patient was misdiagnosed as having a Bartholin cyst and underwent Bartholin gland excision. The patient underwent reexcision and inguinofemoral lymphadenectomy because of incomplete surgery and margins with the tumor. The Bartholin gland was excised for the primary treatment. In women aged over 40 years diagnosed with Bartholin cysts, fine needle aspiration cytology is to exclude malignancy recommended. The incidence of Bartholin gland tumors is highest among women in their 60s. The incidence of BGC in one series was 0.023 per 100,000 woman-years in premenopausal women and 0.114 per 100,000 woman-years in postmenopausal women; however, ACC of the Bartholin gland shows a different age predisposition. ACC can be shown from the late 20s. ACC of the Bartholin's gland

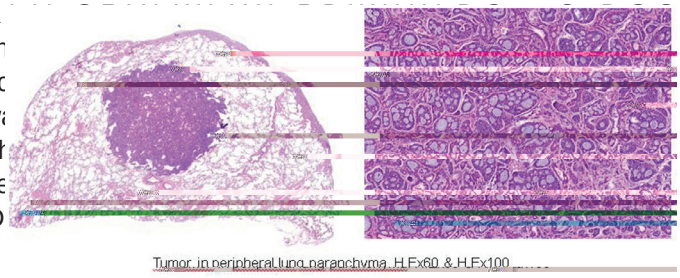


WKH

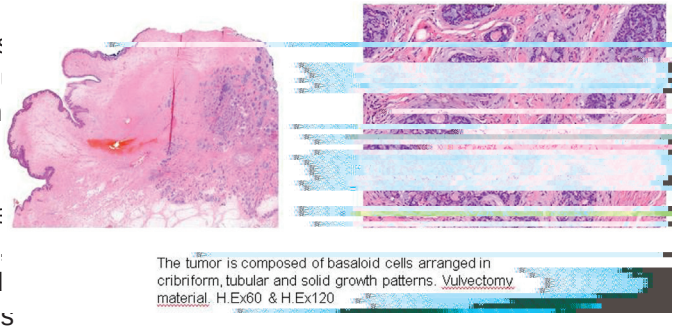
)LJXUH CT scan showed right upper lung lesion in diameter o 1.2*1.2 cm

CT: Computed tomography

LWLR



)LJXUH Tumor in peripheral lung paranchyma



)LJXUH Tumor in vulvectomy material

shares classic histologic features with ACC of the salivary gland. The tumor is composed of uniform, small cells arranged in FRUGV DQG QHVWV ZLWK D FULEULI filled with an amphophilic or eosinophilic acellular basement membrane-like material. The tumor must be located in an appropriate anatomic location. Most tumors have perineural invasion, which is thought to contribute to its high local recurrence rate. $&& RI WKH %DUWKROLQ JODQG LV FKDUDFWHUL]HG by slow growth, local recurrence, and distant metastases by intravascular spread may occur over a long period. Distant metastasis of ACC is not common, it is very rare in the lung, brain, liver, and bone. Alsan et al. showed the most prevalent distant metastasis of ACC site was lungs, followed by liver, and rarely bone. Our patient had a distant metastasis after 4 years of follow-up.

Optimal surgical treatment for ACC of the Bartholin gland is not identified with guidelines. Radical vulvectomy ± inguinal lymphadenectomy and simple excision can both be performed. 7KH PRVW LPSRUWDQW SRLQW LV WR DFKLHYH D WXPRU IUHH PDUJLQ <DQJ et al. showed 68.9% of patients who had a simple excision had recurrence rate. Patients who underwent radical vulvectomy had a 42.9% recurrence rate; resection margins in the radical vulvectomy group were positive in 30% of the patients. The SRVLWLYH PDUJLQ UDWH ZDV LQ WKH VLPSOH H[FLVLRQ JURXS +VX et al. presented two ACCs of Bartholin gland origin with lung metastasis; the first patient had a positive margin in pathologic H[DPLQDWLRQ DQG UHFHLYHG SRVWRSHUDWLYH DGMXYDQW H[WHUQDO EHDP UDGLRWKHUDS\ DQG GLVWDQW PHWDVWDVLV was found 42 months after the radiotherapy. The other patient ZKR KDG WXPRU IUHH PDUJLQV KDG QR DGMXYDQW WUHDWPHQW)LIW\ QLQH PRQWKV DIWHU WKH VXUJHU\ VKH KDG OXQJ PHWDVWDVHV <RRQ et al. presented 5 cases of ACC of the Bartholin gland. Two had lung metastases. In the first case, a 54-year-old woman had right-side radical local excision + ipsilateral inguinal lymph QRGH GLVVHFWLRQ DGMXYDQ UDGLRWKHUDS\ 5HVHFWLRQ PDUJLQV DQG SHULQHXUDO LQYDVLRQ ZHUH SRVLWLYH twice 7 and 8 months later and underwent metastasectomy ZLWK VXEVHTXHQW FKHPRWKHUDS\ for the first metastasis and metastasectomy only for the second metastasis. After 71 months' follow-up, she had stable disease. The second case was a 60-year-old woman who had left-side UDGLFDO ORFDO H[FLVLRQ DQG QR DGMXYDQW WKHUDS\ PDUJLQV DQG SHULQHXUDO LQYDVLRQ UHFXUUHQFH DQG GLVWDO PHWDVWDVHV WKH ORFDO PHWDVWDVLV ZDV UHPRYHG 71.18 and 189 months after surgery and complete excision of the pulmonary lesion was not possible because of the number DQG VL]H RI WKH OHVLRQV 7KH SD DGMXYDQW WKHUDS\ 5HVHFWLRQ ZHUH SRVLWLYH /RFDO SHOYLF UH OXQJ RFFXUUHG LQ WKH SDWLHQW /XQJ PHWDVWDVHV ZHUH DW

and complete excision of pulmonary lesion was not possible EHFDXVH WKH QXPEHU DQG WKH VL]H R After 224 months' follow-up, she had progressive disease. ,Q RXU FDVH cases, the patient had positive margins in pathologic examination, rHFHLYHG QR D treatment; she had lung metastases 49 months after surgery, and after 56 months follow-up, she has stable disease. When the distant metastasis was evaluated, it seemed to be related to margin positivity and perineural invasion. ACC of Bartholin's gland is a slow-growing tumor, long-term survival is excellent according to Copeland et al. The 5-year progress-free interval is 47% and the 5-year survival rate is 71%. They are 38% and 50%, respectively, at 10 years, and 13% and 51% at 15 years. According to these results, it has been suggested to use 10- to 15-year-survival rates rather than 5-year survival rates for ACC of the Bartholin's gland. The patient of BG-ACC metastasis RI ,QJXLQDO O\PSK QRGH WDNH SODFH occurs, it is ipsilateral to the primary tumor. In our case, there was no lymph node metastasis. In the literature, the effect of lymphadenectomy on survival and prognosis is controversial. There is little information on the treatment of metastasis and the management depends on the location. In literature, there are no data to support chemotherapy to prevent distant metastasis. If a distant metastasis exists, chemotherapy treatment alternatives such as chlorambucil-adriamycin, methotrexate-dactinomycin, cyclophosphamide-adriamycin-cisplatin or cyclophosphamide can be used. Various treatment modalities, including radiotherapy, may produce tumor regression. Publications have HPSKDVL]HG SRRU RXWFRPHV LQ SDW margins even when treated with radiotherapy. A prospective UDQGRPL]HG VWXG\ FDQ SURYLGH WKH deciding the optimal treatment. Due to the rarity of ACC of the Bartolin gland, we can obtain data from reviews and large series. ACC of Bartholin's gland is a rare, vulvar malignancy with unpredictable biologic behavior. Physicians have to suspect it in women aged over 40 years with persistent Bartholin's gland masses. There is no consensus on the treatment and the treatment modality must be tailored according to each patient. Radical local excision or radical vulvectomy ± lymphadenectomy seems to be the most suitable treatment. Positive surgical margins are a very important factor related to UHFXUUHQFH 6XUJHU\ UDGLRWKHUDS can be used for recurrence. Follow-up of ACC of the Bartholin gland has to be for a long period due its slow growth behavior.

(WKLFV

3HHU UHYLHZ Externally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV

&RQIOLFW RI ,QWHUHVW No conflict of interest the authors.

)LQDQFLDO 'LVFORVXUH The authors declared that this study received no financial support

References

&KDPOLDQ '/ 7D\ORU +% 3ULPDU\ FDUFLQRPD RI %DUWKROLQ·V JODQG $ report of 24 patients. Obstet Gynecol 1972;39:489e94.
+HOOHU '6 %HDQ 6 /HVLRQV RI WKH %DUWKROLQ JODQG D UHYLHZ - /RZ Genit Tract Dis 2014;18:351.
1DWLRQDO &DQFHU ,QVWLWXWH &DQFHU 6WDW)DFWV 9XOYDU &DQFHU KWWSV VHHU FDQFHU JRY VWDWIDFWV KWPO YXOYD KWPO
'XQQ 6 $GHQRLG F\VWLF FDUFLQRPD RI %DUWKROLQ·V JODQG D UHYLHZ RI WKH OLWHUDWXUH DQG UHSRUW RI D SDWLHQW $FWD 2EVWHW *\QHFRO 6FDQG 1995;74:78-80.
&UXP &3 0F&OXJJDJH :* +HUULQJWRQ &6 5HJDXHU 6 :LONLQVRQ EJ. Tumours of the Vulva: Epithelial tumors. In: Kurman RJ, &DUFDQJLX 0/ +HUULQJWRQ &6 <RXQJ 5+ HGLWRUV :+2 &ODVVLILFDWLRQ RI 7XPRXUV RI)HPDOH 5HSURGXFWLYH 2UJDQV /\RQ International Agency for Research on Cancer; 2014.p.237-8.
/ySH] 9DUHOD (2OLYD (0F,QW\UH -))XOOHU $) 3ULPDU\ WUHDWPHQW of Bar-tholin's gland carcinoma with radiation and chemoradiation: a report onten consecutive cases. Int J Gynecol Cancer 2007;17:661-7.
.ORE -0 3DWKRORJLVFKH $QDWRPLH GHU :HLEOLFKHQ 6H[XDORUJDQH Wein, 1864.
$OVDQ &, 9LQK +XQJ 9 (UHQ) $EDFLRJOX &% $GHQRLG F\VWLF carcinoma of the Bartholin's gland: case report and systematic review of the literature. Eur J Gynaecol Oncol 2011;32:567-72.
0LQFKJUXE 6 :LOH\ (/ 9XLWFK) $OEHUUH variant of adenoid cystic carcinoma of the Bartholin's gland. Am J Clin Pathol 1994;101:204-8.
10. Frable WJ, Goplerud DR. Adenoid cystic carcinoma of Bartholin's gland diagnosis by aspiration biopsy. Acta Cytol 1975;19:152-3.
11. Visco AG, Del Priore G. Postmenopausal bartholin gland enlargement: a hospital-based cancer risk assessment. Obstet Gynecol 1996;87:286-90.
'L 'RQDWR 9 &DVRUHOOL $ %DUGKL $ 9HOOD %DUWKROLQ JODQG FDQFHU &ULW 5HY
1DVX . .DZDQR < 7DNDL 1 .DVKLPD . 0 Cystic Carcinoma of Bartholin's Gland. Gynecol Obstet Invest 2005;59:54-8.
<DQJ 6< /HH -: .LP :6 -XQJ ./ /HH 6- /H cystic carcinoma of the Bartholin's gland: report of two cases and UHYLHZ RI WKH OLWHUDW•UH *\QHFRO 2QF
+VX 67 :DQJ 5& /X &+ .H <0 &KHQ <7 Report of two cases of adenoid cystic carcinoma of Bartholin's gland and review of literature. Taiwan J Obstet Gynecol 2013;52:113-6.
<RRQ * .LP +6 /HH << .LP 7- &KRL &+ 6F of clinical outcomes of patients with adenoid cystic carcinoma of Bartholin glands. Int J Clin Exp Pathol 2015;8:5688-94.
&RSHODQG /- 6QHLJH 1 *HUVKHQVRQ '0 & 6HVNO -& $GHQRLG F\VWLF FDUFLQRP Gynecol 1986;67:115-20.
6PLWK /& /DQH 1 5DQNRZ 50 &\OLQGU FDUFLQRPD $P - 6XUJ

Turk J Obstet Gynecol 2020;17:314-317

Severe ovarian hyperstimulation syndrome and gonadotropin-releasing hormone agonist trigger in patients with hypogonadotropic hypogonadism: A report of two cases

+LSRJRQDGRWURSLN KLSRJRQDGL]P K KLSHUVWLP•ODV\RQ VHQGURPX YH JR DJRQLVWL\OH WULJJHU þNL ROJX VX

$OL 6DPL[1] U)E•Q]GD[2] *G)HWPD[3] ×ÐH bQHS 8PD\ 5E\•D] 'HYHHU

[1]Novafertil IVF Center, Clinict of Obstetrics and Gynecology, Konya Turkey
[2]%DKoHüHKLU 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 2EVWHWULFV DQ
[3]Necmettin Erbakan University Faculty of Medicine, Department of Obstetrics and Gynecology, Konya, Turkey
[4].Ro 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH þVWDQEXO 7XUNH\
[5]6×WN× .RoPDQ 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 2EVWHWULFV D

$EVWUDFW

2YDULDQ +\SHUVWLPXODWLRQ V\QGURPH 2+66 LV D UDUH FRQGLWLRQ LQ SDWLHQWV Z K\SRJRQDGLVP DUH UHSRUWHG D UDUH FDVH RI VHYHUH 2+66 DQG D FDVH RI SUHYHQ respectively. The first case was a 31-year-old patient. In vitro IHUWLOL]DWLRQ ,9) WUHDWPHQW ZDV SHUIRUPHG Z 7KH ILUVW SDWLHQW ZDV GLDJQRVHG DV KDYLQJ VHYHUH 2+66 RQ WKH QLQWK GD\ DIW IOXLG ZHUH DVSLUDWHG IURP KHU DEGRPHQ 7KH VHFRQG FDVH ZDV D \HDU ROG DQG *Q5+ DJRQLVW VWLPXODWLRQ WHVW ZDV SHUIRUPHG EHIRUH ,9) WUHDWPHQW $IWHU W ZHUH UHWULHYHG IURP WKH RYDULHV DQG 2+66 GLG QRW RFFXU $OWKRXJK VHYHUH 2+ D *Q5+ VWLPXODWLRQ WHVW LV SHUIRUPHG EHIRUH RYDULDQ VWLPXODWLRQ 2+66 FDQ hypogonadotropic hypogonadism.
.H\ZRUGV $57 IUHH]H DOO *Q5+ DJRQLVW WULJJHU K\SRJRQDGRWURSLF K\SRJRQDGLV

Öz

2YHU +LSHUVWLP•ODV\RQ VHQGURPX 2+66 KLSRJRQDGRWURSLN KLSRJRQDGL]P KDVWDO KRUPRQ *Q5+ DJRQLVW WULJJHUL\OH 2+66 HQJHOOHQPLü KLSRJRQDGRWURSLN KLSRJR NHn] vitro IHUWLOL]DV\RQ ,9) WHGDYLVL X\JXODQP×ü DQFDN ROJXGD RYHU KLSHUVWLP•O GRNX]XQFX J•QGH üLGGHWOL 2+66 WDQ×V× NRQXOGX +DVWDQHGH J•Q NDOG× YH EDW LQIHUWLO KDVWD\G× +Lo ,9) WHGDYLVL J|UHPHPLüWL ,9) WHGDYLVLQGHQ |QFH *Q5+ DJ DJRQLVW WULJJHUL \DS×OG× 7RSODQDQ RRVLWH UDüPHQ 2+66 PH\GDQD JHOPHPLüW ROPDNOD ELUOLNWH JHOLüHELOLU (ÿHU KLSRJRQDGRWURSLN KLSRJRQDGL]P KDVWDODU \HULQH *Q5+ DJRQLVW WULJJHU \DS×ODELOLU YH 2+66 |QOHQHELOLU
$QDKWDU .HOLPHOHU $57 IUH]H DOO *Q5+ DJRQLVW WULJJHU K\SRJRQDGRWURSLF K\

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL $OL 6DPL *•UE•] 0'
Novafertil IVF Center, Clinict of Obstetrics and Gynecology, Konya Turkey
Phone: +90 533 553 04 42 (PDLO DOLVDPLJXUEX]#KRWPDLO FRP 25&,' ,' orcid.org/0000-0001-7747-3074
5HFHLYHG *HOLü 7DULKL 15.07.2020 $FFHSWHG .DEXO 7DULKL 16.10.2020

Introduction

+\SRJRQDGRWURSLF K\SRJRQDGLVP ++ LV D SXEHUW\ GHOD\ DQG amenorrhea-causing disorder due to deficiency of gonadotropins DQG VH[VWHURLGV LQ WKH FLUFXODWLRQ ,QGLYLGXDOV ZLWK ++ KDYH defects either in the secretion of the gonadotropin-releasing KRUPRQH *Q5+ IURP K\SRWKDODPXV RU *Q5+ UHFHSWRUV LQ the hypophysis. Ovaries are not stimulated depending on the GHILFLHQF\ RI JRQDGRWURSLQV WKXV LQIHUWLOLW\ IROORZV LQ ++ 6WLPXODWLRQ ZLWK H[RJHQ JRQDGRWURSLQV LV FUXFLDO IRU treatment because folliculogenesis and ovulation are defective LQ SDWLHQWV ZLWK ++ +XPDQ FKRULRQLF JRQDGRWURSLQ K&* LQMHFWLRQ LV PDQGDWRU\ WR PDWXUH RRF\WHV LQ FRQWUROOHG RYDULDQ VWLPXODWLRQ EHFDXVH WKH OXWHLQL]LQJ KRUPRQH /+ SHDN GRHV not exist in these patients

2YDULDQ +\SHUVWLPXODWLRQ V\QGURPH 2+66 LV WKH PRVW serious, life-threatening, iatrogenic complication of assisted UHSURGXFWLYH WHFKQRORJ\ $57 F\FOHV +&* LV WKH PDMRU PROHFXOH WKDW WULJJHUV 2+66 Therefore, to prevent and PDQDJH 2+66 *Q5+ DJRQLVWV KDYH EHHQ VWDUWHG WR EH XVHG for final oocyte maturation. As a result, a segmented approach LQFOXGLQJ *Q5+ DJRQLVW WULJJHULQJ SOXV IUHH]LQJ RI DOO HPEU\RV ZDV UHFRPPHQGHG IRU WKH FRPSOHWH SUHYHQWLRQ RI 2+66 especially for patients with an extreme ovarian response

,Q JHQHUDO 2+66 LV QRW FRPPRQ LQ SDWLHQWV ZLWK ++ DQG hCG is the primary choice for oocyte maturation +RZHYHU LQ VRPH SDWLHQWV ZLWK ++ D K\SHU UHVSRQVH PD\ RFFXU and hCG triggering might be a life-threatening event in these SDWLHQWV 7KH H[DFW SDWKRORJ\ LQ SDWLHQWV ZLWK ++ PD\ EH UHODWHG to pituitary receptors or hypothalamus, and a patient with ++ PD\ QRW UHVSRQG WR *Q5+ agonists efficiently. Therefore, WKHRUHWLFDOO\ *Q5+ DJRQLVWV DUH QRW UHFRPPHQGHG WR EH XVHG IRU WULJJHULQJ RRF\WH PDWXUDWLRQ LQ SDWLHQWV ZLWK ++

,Q WKH IROORZLQJ DUWLFOH ++ DQG DJRQLVW WULJJHU ZLOO EH GLVFXVVHG FRQVLGHULQJ WZR SDWLHQWV ZLWK ++ ,Q WKH ILUVW FDVH VHYHUH 2+66 ZDV VHHQ LQ WKH VHFRQG SRWHQWLDO 2+66 GHYHORSPHQW was prevented using a *Q5+ DJRQLVW WULJJHU

Case Reports

The patients were treated in Novafertil In vitro)HUWLOL]DWLRQ ,9) &HQWHU .RQ\D 7XUNH\ ,QVWLWXWLRQDO UHYLHZ ERDUG DSSURYDO ZDV JLYHQ DQG ,5% ZULWWHQ consent was obtained from the patients.

In 2013, a 31-year-old patient presented to our IVF center with V\PSWRPV RI SULPDU\ DPHQRUUKHD DQG VHFRQGDU\ LQIHUWLOLW\ 6KH was married for 11 years and had undergone a right salpingo-RRSKRUHFWRP\ GXH WR D GHUPRLG F\VW DW WKH DJH RI 6KH XQGHUZHQW LQWUDXWHULQH LQVHPLQDWLRQ ,8, WUHDWPHQW WKUHH WLPHV with hMG and IVF treatment three times. These trials resulted in one early period miscarriage and one healthy birth. The patient KDG QHYHU GHYHORSHG 2+66 LQ DQ\ VWHS RI WKH WUHDWPHQWV 7R UHJXODWH KHU PHQVWUXDO F\FOHV VKH XVHG FRQMXJDWHG HVWURJHQV SURJHVWHURQH 3 FRPELQDWLRQ 3UHPSDN & WDEOHWV GDLO\ 7KH SDWLHQW RWKHU WKDQ D QRUPDO XWHUXV DQG DQ HQODUJHG OHIW RYDU\ ZLWK D IROOL

were observed on the left ovarium, whereas the right ovarium was not monitored. In a previously taken hysterosalpingogram, the cavity and left tubal transition were normal; however, the ULJKW WXED ZDV QRW PRQLWRUHG +HU ERG\ PDVV LQGH[ZDV 24 kg/m². The basal characteristics of the patient are illustrated in 7DEOH +HU EORRG DQDO\VLV UHVXOWV SODWHOHWV KHPRJORELQ +J +FW 2Q WKH ILUVW WUHDWPHQW F\FOH 3 U ZDV WULJJHUHG LQ PHQVWUXDO F\FOH RYDULDQ VWLPXODWLRQ ZLWK ,8 K0* 0HQRJRQ)HUULQJ 7 dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was triggered using 5000 IU urinary hCG 3UHJQ\O DPS 06 7XUNH\ 7R DYRLG 2+66 /+ SHDN GRHV PHGLFDWHG ZLWK FDEHUJROLQH after the trigger day. Transvaginal ultrasound-guided aspiration was performed 36 hours later. Two embryos, each grade 1, ZHUH WUDQVIHUUHG DQG WKUHH JUDGH third day following LQWUDF\WRSODVPLF VSHUP IVF outcomes are shown in Table 2. On the embryo transfer (7 GD\ KHU :%& +JE DQG +FW YDOXH

On the 9th day following ET, she consulted our IVF center due WR DEGRPLQDO GLVWHQWLRQ VZHOOLQJ enlarged and abdominal fluid was observed on examination. +HU EORRG DQDO\VLV UHVXOWV :%& +FW ZHUH 16.2, and beta-hCG: 61.7. Accordingly, she was accepted as KDYLQJ ODWH 2+66 DQG ZDV KRVSLWDOL]HG 6KH VWD\HG LQ KRVSLWDO IRU GD\V 50,550 cc paracentesis fluid was aspirated; in total, 20% 100 cc human albumin and 0.9% NaCl was given 27 times, and hydroxyethyl starch was administered every day. The patient was discharged from hospital on the 13th week of the pregnancy and she gave birth to a healthy girl via cesarean section.

A 26-year-old woman consulted our IVF center with symptoms RI SULPDU\ DPHQRUUKHD DQG SULPDU\ for 3 years. In her history, it was remarkable that she responded insufficiently to clomiphene citrate and had no menstruation after medroxyprogesterone acetate was administered; therefore,

7DEOH Clinical characteristic of two patients with hypogonadotropic hypogonadism

	Case 1 2+66	Case 2 *Q5+ $J WU
$JH <HDUV	31	26
%0, NJ P	24	30.1
%DVDO VHUXP)6+ P,8 P/	1	0.9
%DVDO VHUXP /+ P,8 P/	0.15	0.73
%DVDO VHUXP (VWUDGLRO SJ P/	28.6	20
%DVDO VHUXP 76+ P,8 P/	2.28	1.43
%DVDO VHUXP 3URODFWLQ QJ P/		

2+66 2YDULDQ +\SHUVWLPXODWLRQ V\QGURPH *Q5+ *RQDGRWURSLQ UHOHDVLQJ KRUPRQH %0, %RG\ PDVV LQGH[ )6+)ROOLFOH VWLPXODWLQJ KRUPRQH /+ 76+ 7K\URLG VWLPXODWLQJ KRUPRQH

+0* ZDV XVHG XQWLO XQLWV IRU
ZLWKLQ DQ ,8, SODQ +RZHYHU QR
the patient. When she was examined, it was determined that she had a small uterus and thin endometrium. Moreover,
PDQ\ VPDOO DQWUDO IROOLFOHV ZHUH
EDVDO FKDUDFWHULVWLFV DUH VXPP
WUHDWPHQW D WULDO RI *Q5+ DQD
DQG PJ WULSWRUHOLQ *RQDSHS
administered subcutaneously. After triggering, in the first and
VHFRQG KRXUV /+ OHYHOV ZHUH
6WLPXODWLRQ ZDV VWDUWHG ZLWK
7XUNH\ RQ WKH VDPH GD\ ZLWKRXW
Follicle growth, as well as estradiol levels, were followed and gonadotropin doses were arranged according to the response.
:KHQ DW OHDVW WKUHH OHDGLQJ IR
were developed, oocyte maturation was triggered with 0.2 mg triptorelin. Thirty-two oocytes were retrieved 36 hours
DIWHU WKH WULSWRUHOLQ LQMHFWL
is presented in Table 2. Following the first menstruation, she received hormone replacement therapy. One good quality embryo was transferred after the second menstruation using
(KHPLK\GUDWH (VWURIHP PJ 1R
thawing protocol. This procedure resulted in pregnancy. At the time of writing, the patient was in her 13th week of pregnancy.

7DEOH *In vitro* IHUWLOL]DWLRQ RXWFRPHV RI JRQDGRWURSLQ ... hypogonadotropic hypogonadism

	Case 1 2+66	Case 2 *Q5+ $J WU
'D\V RI VWLPXODWLRQ GD\	13	21
*RQDGRWURSLQ VWDUW GRVH ,8	300	225
7RWDO JRQDGRWURSLQ GRVH ,8	3150	6825
(VWUDGLRO RQ WULJJHU GD\ SJ P/	5695	7797
1R RI RRF\WHV UHWULHYHG Q	10	32
1R RI RRF\WHV WKDW PDWXUHG Q	7	23
1R RI IHUWLOL]HG RRF\WHV Q	6	19
1R RI WUDQVIHUUHG HPEU\RV Q	2	1
1R RI FU\RSUHVHUYHG HPEU\RV Q	3	12

2+66 2YDULDQ +\SHUVWLPXODWLRQ V\QGURPH *Q5+ *RQDGRWURSLQ UHOHDVLQJ KRUPRQH

Discussion

,Q SDWLHQWV ZLWK ++ WKH DLP RI
single pregnancy through monofollicular development with stimulation and coitus or IUI. When ovulation induction and/
RU ,8, IDLOV RU DGGLWLRQDO SDW
RU ROLJRVSHUPLD DFFRPSDQLHV
warranted. The ILUVW SDWLHQW KDG VHYHUH
had a single ovary. In the second case, response to stimulation was received over a long period and finally, an excessive ovarian

UHVSRQVH GHYHORSHG VR WKH HPEU\RV ZHUH
SUHVHQWHG ZDV SUHIHUUHG IURP *Q5+ D
the first day of treatment.
A fresh embryo was transferred to the first patient according to
UXOH ,9) VWDWHG RQ HFRQRPLF
DOWKRXJK 2+66 GHYHORSHG
ZLWK HPEU\R WUDQVIHU
recovery duration lasting until the 18th week of the pregnancy.
,QWHUHVWLQJO\ VKH KDG D YHU\ VHY
DQG D VLQJOH YLDEOH RYDU\
was aspirated via repeated paracentesis. If the ET was cancelled,
2+66 ZRXOG QRW KDYH GHYHORSHG
WR UHFRQVLGHU WKH PDQDJHPHQW
response to controlled ovarian stimulation.
3DWLHQWV ZLWK ++ DUH GLIILFXOW
from the point of ovarian stimulation. Although the patients have the same clinical findings, their response to ovarian stimulation may be hyper, normal or poor. Both ovaries can be
YLVXDOL]HG DV K\SRSODVLF LQ XOWUD
counting antral follicles is quite challenging. The prediction of the response to gonadotropins is challenging because the exact number of antral follicles cannot be identified and the levels of gonadotropins are below normal ranges $0+ RQO\ UHIOHF
WKH JURZLQJ IROOLFXODU SRRO
conditions that cause a permanent or sustained interruption
RI JRQDGRWURSLQ ZKLFK PD\ OHDG
7KHUHIRUH $0+ LV QRW D SURSHU
SDWLHQWV ZLWK ++ ZKLFK PD\ XQGHU
reserve. Determining the ovarian response before treatment is vital to provide acceptable rates of pregnancy with minimal adverse effects. Unfortunately, there is no reliable indicator for
RYDULDQ UHVSRQVH LQ SDWLHQWV ZLWK
A high dose and long duration are needed during stimulation,
ZKLFK LQFUHDVHV WKH ULVN RI 2+66 E
and doubt of developing poor-response. It was stated that the ovarian stimulation duration could range from 12 to 54 days
On the other hand, despite the application of a high dose,
2+66 GHYHORSPHQW LV TXLWH UDUH L
2+66 RFFXUV WKH FOLQLFDO FRQGLWLRQ
in our first case.
Kuroda et al. WUDQVIHUUHG D VLQJOH IUR]H
DOO VWUDWHJ\ WR SDWLHQWV ZLWK ++
fresh cycle on endometrial receptivity. They wanted to prevent a decreased response; therefore, the final oocyte was maturated
ZLWK K&* DIWHU FRQVLGHULQJ WKH
SUHYLRXV ,9) F\FOHV 7KH\ GLG QRW
LQ WKHLU VWXGLHV 'HVSLWH XVLQJ
study, Kuroda et al. GLG QRW HPSOR\ *Q5+ ZK
WULJJHU DJHQW EHFDXVH RI WKH
of a decreased response with agonist triggering.
7KH 2+66 ULVN ZDV HVWLPDWHG
SHDN OHYHOV DIWHU D *Q5+ DJRQLVW
YDOXHV IRU /+ RU)6+ SHDN KDYH EHH

the peak equal or more than twofold is considered sufficient for maturation. This test would show a problem either with SLWXLWDU\ *Q5+ UHFHSWRUV RU ZLWK *Q5+ SURGXFWLRQ LQ WKH K\SRWKDODPXV ,I WKH FRQGLWLRQ LV FDXVHG E\ SLWXLWDU\ *Q5+ UHFHSWRUV /+ DQG)6+ OHYHOV ZLOO QRW LQFUHDVH FDXVHG E\ *Q5+ SURGXFWLRQ JRQDGRWURSLQ OHYHOV ZLOO LQFUHDVH)XUWKHUPRUH HYHQ LQ ZRPHQ ZLWK *Q5+ UHFHSWRU PXWDWLRQV gonadotropin levels were detected to be increased like healthy controls in a previous study :RPHQ FDUU\LQJ *Q5+ UHFHSWRU mutations were indicated to ovulate either spontaneously or LQ UHVSRQVH WR SXOVDWLOH *Q5+ DGPLQLVWUDWLRQ YLD D SRUWDEOH pump .

In our second case, it was planned to start the stimulation with high-dose gonadotropin because her BMI was high and no response was obtained despite long-term gonadotropin use in WKH SUHYLRXV ,8, F\FOH 7KH SRVVLELOLW\ RI WULJJHULQJ ZLWK *Q5+ DJRQLVW ZDV FRQVLGHUHG GXH WR WKH triggering was performed knowing that the patient would UHVSRQG EHFDXVH WKH /+ LQFUHPHQW ZDV REVHUYHG GD\ RI WKH *Q5+ VWLPXODWLRQ WHVW 7KXV 2+66 GHYHORSPHQW was prevented and a healthy pregnancy was acquired in the VHFRQG FDVH ,I /+ UHVSRQVH FDQQRW EH REWDLQHG DIWHU D *Q5+ VWLPXODWLRQ WHVW FRPELQHG XVH RI PHWKRGV LV VXJJHVWHG

(DUO\ RU ODWH 2+66 FDQ GHYHORS LQ SDWLHQWV ZLWK ++ 6HYHUH 2+66 FDQ EH SUHYHQWHG ZLWK *Q5+ DJRQLVW WULJJHULQJ LQVWHDG RI K&* WULJJHULQJ LQ SDWLHQWV ZLWK ++ ZLWK D K\SHU UHVSRQVH 7KH XVH RI D *Q5+ VWLPXODWLRQ WHVW ZLOO EH YHU\ KHOSIXO IRU WKH VHOHFWLRQ RI SDWLHQWV ZKR ZLOO UHVSRQG WR *Q5+ DJRQLVW triggering before controlled ovarian stimulation cycles in SDWLHQWV ZLWK ++

$FNQRZOHGJHPHQWV

We would like to thank the staff at the Novafertil IVF Center and all staff in the department of obstetrics and gynecology of Necmettin Erbakan University because of their disciplined and careful work.

(WKLFV

,QIRUPHG &RQVHQW Written informed consent was obtained from the patients.

3HHU UHYLHZ Externally and internally peer-reviewed.

$XWKRUVKLS &RQWULEXWLRQV

6XUJLFDO DQG 0HGLFDO 3UDFWLFHV R.D., Concept: $ 6 R.D., Design: R.D., Data Collection or Processing: F.K., Z.U.G., Analysis or Interpretation: $ 6 /LWHUDWXUH 6HDUFK F.K., Z.U.G., Writing: Z.U.G., R.D.

&RQIOLFW RI ,QWHUHVW The authors declare no conflict of interest.

)LQDQFLDO 'LVFORVXUH The authors declared that this study received no financial support.

References

)UDLHWWD 5 =\OEHUVWHMQ '6 (VWHY K\SRJRQDGLVP 0HYLVLWHG &OLQLFV 6DP 8.
<LOGL] * ,QFL)HUGDQ *H[... 5 Comparision of reproductive outcome of the women with hypogonadotropic hypogonadism and tubal factor infertility. Clin Exp Obstet Gynecol 2010;37:120-2.
+XPDLGDQ 3 4XDUWDUROR - 3DSDQLNRO K\SHUVWLPXODWLRQ V\QGURPH JXLGDQF 2010;94:389-400.
'HPLUKLVVDU 6 3RUWDEOH SXPS ... VHJPHQWDWLRQ RI ,9) WUHDWPHQW +XP 5
*DR < <X % 0DR - :DQJ ; 1LH 0 :X ; $V techniques with congenital hypogonadotropic hypogonadism patients: a systematic review and meta-analysis. BMC Endocr Disord 2018;18:85.
(QJPDQQ / %HQDGLYD & +XPDLGDQ 3 *Q5+ DJRQLVW WULJJHULQJ LQ 6:27 DQDO\VLV 5HSURG %LRPHG 2QOLQH
<LOPD] 6 2]JX (UGLQF $6 <XPXVDN 2 % <LOPD] 1 7KH UHSURGXFWLYH RXW K\SRJRQDGRWURSLF K\SRJRQDGLVP XQGH 6\VW %LRO 5HSURG 0HG
7UDQ 1 &KHGUDV 0, 5RVHQ 0 7KH UR KRUPRQH $0+ DV D 2+66 SUHYHQWLRQ Metab 2011;96:3609-14.
3DSDQLNRODRX 7DUODW]LV 7DPL]KDUDYL 0 5HGG\ 1 of assisted reproductive technology cycle in patients with K\SRJRQDGRWURSLF K\SRJRQDGLVP - +X 50.
/HY\ 7 2UYLHWR 5 +RPEXUJ 5 3HOHJ ' 6HYHUH RYDULDQ K\SHUVWLPXODWLRQ V oestrogen concentrations in a hypogonadotrophic, hypogonadal SDWLHQW +XP 5HSURG
8OXJ 8 %HQ 6KORPR , 7RVXQ 6 (UGHQ +) The reproductive performance of women with hypogonadotropic K\SRJRQDGLVP LQ DQ LQ YLWUR IHUWLOL program. J Assist Reprod Genet 2005;22:167-71.
-LDQJ 67 .XDQJ <3 5HVHDUFK SURJUHVV WHFKQLTXHV IRU K\SRJRQDGRWURSLF K\S 'LHU <LNH 'D[XH ;XHEDR %LDQML 6KL
.XURGD . (]RH . .DWR . <DEXXFKL $ 6 HW DO ,QIHUWLOLW\ WUHDWPHQW VWUD all embryos and single vitrified-warmed embryo transfer during KRUPRQDO UHSODFHPHQW F\FOH IRU LQ with hypogonadotropic hypogonadism. J Obstet Gynaecol Res 2018;44:922-8.
6XQ 4+ =KHQJ < =KDQJ ;/ 0X <0 5ROH UHOHDVLQJ +RUPRQH 6WLPXODWLRQ 7HVW Deficiency in Both Males and Females with Delayed Puberty. Chin 0HG - (QJO
0DLRQH /)qYUH $ 1HWWRUH ,& 0DQLOD HW DO 6LPLODULWLHV DQG GLIIHUHQFHV women with congenital hypogonadotrophic hypogonadism caused E\ *Q5+5 PXWDWLRQV DQG ZRPHQ ZLWK SU +XP 5HSURG

'2, WMRG JDOH Qos.2020
Turk J Obstet Gynecol 2020;17:318-319

Rectus abdominis muscle with different abdominal pathologies: A cite to myofascial trigger point

)DUNO× DEGRPLQDO SDWRORMLOHUOH 0L\RIDV\DO WHWLN QRNWD\D ELU DW×

)DWLK %DÿF×HU

%LUXQL 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 3K\VLFDO 0HGLFLQH D

Keywords: Rectus abdominis muscle, primary dysmenorrhea, myofascial pain syndrome
Anahtar Kelimeler: 5HNWXV DEGRPLQLV NDV× SULPHU GLVPHQRUH PL\RIDV\DO WHWLN QRNWD

'HDU (GLWRU

I read the article, “Relation between uterine morphology and the severity of primary dysmenorrhea” with interest. Although the etiologic factors in primary dysmenorrhea are covered in the article, the role of muscle structures in etiology is not mentied. In this article, we would like to discuss the rectus abdominis PXVFOH DQG LWV P\RIDVFLDO WULJJHU SRLQW 07U3 another underdiagnosed cause of primary dysmenorrhea and abdominal wall pain.

The rectus abdominis muscle extends from the pubic symphysis and tubercle as a beam and ends at the anterolateral aspect of the xiphoid process and superiorly in three fragments of the costal cartilages of the ribs 5-7. The rectus abdominis PXVFOH IDFLOLWDWHV IOH[LRQ RI WKH WUXQN DQG VWDELOL]HV WKH pelvis. Contributing to the increased abdominal pressure with other abdominal muscles, it also plays a role in micturition, defecation, vomiting, and childbirth. MTrPs of the rectus abdominis muscle have been associated with pathologies such as pain in the abdominal wall and primary dysmenorrhea [1].

Primary dysmenorrhea is a frequently encountered condition that reduces the quality of life of the patient and considerably impacts the economy of the healthcare system. Primary dysmenorrhea is a recurrent, cramping pain in the lower abdomen occurring during menstruation without any pelvic pathology. Medical treatments, yoga, pilates and stretching exercises, massage techniques for soft tissues, and invasive approaches can be used to treat primary dysmenorrhea. According to the literature, * DXEHFD * LODGLQL HW DO administered placebo-controlled dry needle treatment for MTrP of the rectus abdominis muscle in SDWLHQWV ZLWK SULPDU\ G\VPHQRUUH / LX SHUIRUPHG ORFDO DQHVWKHWLF LQ MTrPs of the rectus abdominis and oblique muscles in patients with primary dysmenorrhea.

As observed by physicians, abdominal pain has been most frequently associated with intraabdominal pathologies. Therefore, numerous consultations and tests are required, and abdominal surgeries are occasionally performed, although the necessity thereof is debatable. When patients cannot find a remedy for their pain, they visit various clinics for examinations, and certain patients are considered to have psychiatric disorders. In fact, MTrP of the rectus abdominis muscle causes abdominal wall pain. Muscolino EJ detected the MTrP of the rectus abdominis muscle in a patient with Crohn’s disease who had a complex history of medical treatments and clinical courses. A stretching exercise program for the relevant muscle was used to treat this patient.

7KH GLDJQRVLV RI 07U3 LV XQGHU UHF DQ H[DPLQDWLRQ WKH SRVVLELOLW\ muscle should be considered. MTrPs of the rectus abdominis and related muscles can have different clinical manifestations. These patients should be thoroughly evaluated and appropriate WUHDWPHQW PRGDOLWLHV VKRXOG EH

$GGUHVV IRU &RUUHVSRQGHQFH <D]×üPD $GUHVL)DWLK %DÿF×HU 0'
%LUXQL 8QLYHUVLW\ )DFXOW\ RI 0HGLFLQH 'HSDUWPHQW RI 3K\VLFDO 0HGLFLQH DQG 5HKDELOLWDWLRQ þVWD
Phone: +90 544 242 90 42 (PDLO bagcier_42@hotmail.com 25&,' orcid.org/0000-0002-6103-7873
5HFHLYHG *HOLü 7DULKL 30.09.2020 $FFHSWHG .DEXO 7DULKL 01.11.2020

controlled studies with a long-term follow-up are required in this field.

(WKLFV

3HHU UHYLHZ Externally peer-reviewed

)LQDQFLDO 'LVFORVXUH The author declared that this study received no financial support.

References

ýHQW•UN ý 5HODWLRQ EHWZHHQ XWHULQH DUWHU\ EORRG IORZ DQG VHYHULW\ RI primary dysmenorrhea. Turk J Obstet Gynecol 2020;17:84-9.

0DTXLUULDLQ - *KLVL -3 .RNDOM $0 5HFW
LQ WHQQLV SOD\HUV %U - 6SRUWV 0HG
*DXEHFD *LODUUDQ] $)HUQiQGH] GH /DV
-5 6HRDQH 5XL] -0 &RPSDQ\ 3DORQpV $
Effectiveness of dry needling of rectus abdominis trigger points for the treatment of primary dysmenorrhoea: a randomised parallel-group trial. Acupunct Med 2018;36:302-10.

4. Muscolino JE. Abdominal wall trigger point case study. J Bodyw Mov Ther 2013;17:151-6.

+XDQJ 40 /LX / :HW QHHGOLQJ RI P\RID abdominal muscles for treatment of primary dysmenorrhoea. Acupunct Med 2014;32:346-9.

2020 Referee Index

2020 Author Index

2020 Author Index

2020 Author Index